



## CLINICAL IMPLICATIONS OF RENIN-ANGIOTENSIN SYESTEM IN MAMMALS

Syeda Wajiha Khalid and Sikander Ali\*

Institute of Industrial Biotechnology, GC University Lahore, Pakistan

\*Corresponding author: [alisbiotech@yahoo.com](mailto:alisbiotech@yahoo.com)

### Abstract

Renin is a proteolytic enzyme that is primarily produced by the juxtaglomerular cells of the kidney that is encoded by the REN gene. Angiotensin (Ang) II is locally produced in the kidney. The Angiotensin II is an active peptide and it constricts the blood vessels due to which blood pressure increases. The renin-angiotensin system altogether acts as a hormonal system in regulating the blood pressure and water or osmotic balance of the system. The renin-angiotensin system in collaboration with aldosterone is known as the Renin-angiotensin aldosterone system as it regulates various activities in the body and its function as a hormone system. There are many clinical implications of the renin-angiotensin system, some of them are documented in this review, that include controlling hypertension and stress, chronic kidney diseases, cardiovascular diseases, central nervous system disorders and memory facilitation.

### INTRODUCTION

Renin is a proteolytic enzyme that is primarily produced by the juxtaglomerular cells of the kidney that is encoded by the REN gene which is present on chromosome 1q32. Apart from kidney it also occurs in other organs e.g. in brain where it is associated in the control of numerous activities (Auronet *al.*, 2014). It is also the enzyme that is involved in the catalysis, in the first step of the activation pathway of angiotensinogen to angiotensin I, and gene mutation in it is related to renal tubular dysgenesis, hyperproreninemia and hyperuricemic nephropathy.

Angiotensin (Ang) II is locally produced in the kidney by a well-established method, any local effects of this locally produced Ang-II and any interference in this process is supposed to trigger significant renal effects of the blockers of renin-angiotensin system which is also abbreviated to as RAS (Matusaka *et al.*, 2012). Recent studies revealed that the use of infusions of 125I-labelled angiotensins at renal tissue sites allows considerable uptake of the circulating 125I-Ang II thus helping in the detection of 125I-Ang at points that considerably do not affect the blood pressure the tissue levels at steady-state paralleled to the steady-state plasma levels, approximately four to five times, of 125I-Ang II. Thus the renin-angiotensin system altogether acts as a hormonal system in regulating the blood pressure and water or osmotic balance of the system (Cousin *et al.*, 2009). The renin-angiotensin system in collaboration with aldosterone is also referred to as the Renin-angiotensin aldosterone system abbreviated as RAAS, due to its regulation of various activities in the body and its function as a hormone system.

## Mechanism of action of Renin-Angiotensin Aldosterone System

During the shortage of the renal blood supply, the juxtaglomerular cells of the kidney activates the prorenin receptor which secretes the renin directly into the blood circulation (Jeunemaitre, 2008). The renin of the plasma then brings about the conversion of Angiotensinogen (from liver) to Angiotensin I (Bader *et al.*, 2012). The conversion of Angiotensin I to Angiotensin II then takes place with the aid of an enzyme i.e. Angiotensin-converting enzyme referred to as ACE, this enzyme is produced in the lungs (Demurtaset *al.* & Lu *et al.*, 2013). The Angiotensin II is an active peptide and it constricts the blood vessels due to which blood pressure increases. The stimulus from Angiotensin II brings about the secretion of the aldosterone hormone from the adrenal cortex, which further increases the blood pressure, as it causes the increase in the reabsorption of sodium and water in the blood by the kidney tubules.

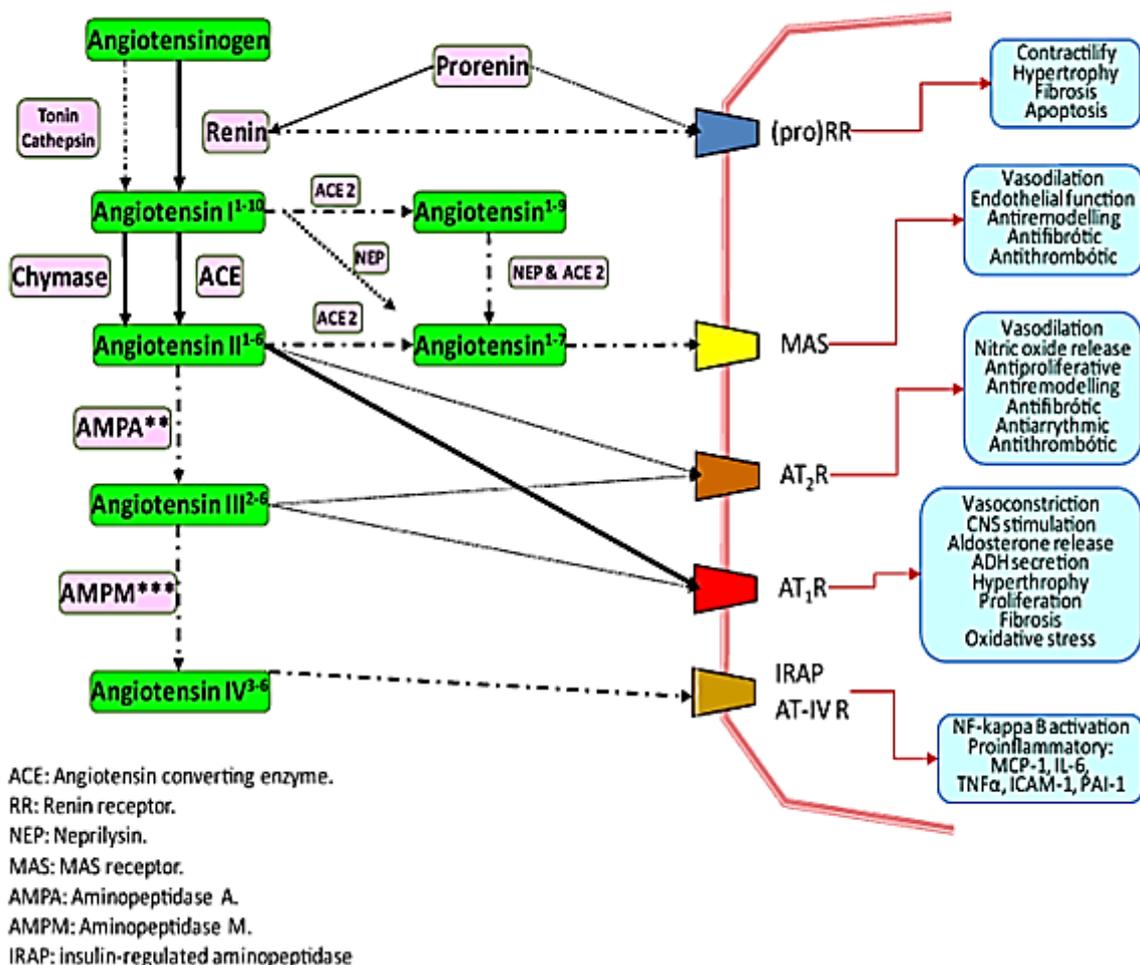


Fig. 1. The renin-angiotensin aldosterone system (Macia-Heras *et al.*, 2012).

## Clinical implications

There are many clinical implications of the renin-angiotensin system in the body. There is a clear-cut evidence of this showing an important role for the tissue angiotensin systems in the indication of cardiovascular diseases and also in their structural remodelling (Auronet *al.*, 2014). The synthesis of aldosterone regulated by cardiac tissue is a well-known example of a renin-aldosterone system existence in the heart. Moreover many of these have therapeutic implications, and also more specifically the blockers of the angiotensin receptors as well as the inhibitors of the angiotensin converting- enzyme.

**Table 1: Role of Renin-Angiotensin system in clinical disorders (Wright *et al.*, 2013).**

Clinical disorder	Treatment Strategy	Response	Bibliography
Cerebroprotection	AngIV administered to rats and gerbils	Facilitated cerebral blood flow and protected against ischemia	Faure <i>et al.</i> ,(2006)
Depression	ACE inhibitors administered to AD patients	Reduced depressive symptoms	Isingriniet <i>al.</i> ,(2009)
Diabetes	ARBs administered to type 1 diabetic patients	Protected against end organ damage	Chen <i>et al.</i> ,(2008)
Memory facilitation	AT4 receptor agonist in rats	Facilitated long-term potentiation Improved spatial memory	Davis <i>et al.</i> ,(2006)
Stress	Candesartan blockade of AT1 receptors in rats	Prevented AT1 receptor binding in anterior pituitary, adrenal and PVN, also reduced elevations of pituitary ACTH and adrenal corticosterone	Nishimura <i>et al.</i> ,(2000)

### Hypertension

Worldwide almost 972 million people are affected by hypertension, and it is ranked second to diabetes which is the leading cause of ESRD i.e. end stage renal disease. The angiotensin II plays a key role in its systemic synthesis through renin-angiotensin system by regulating the systemic arterial pressure. It further acts on the smooth vascular muscles directly, it being acting as a strong vasoconstrictor (Advani *et al.*, 2009). Furthermore, it then affects the cardiac rate as well as the contractility by the action on the sympathetic nervous system. The angiotensin II also changes the renal sodium as well as water absorption by its capability of stimulating the zona-glomerulosa cells in the adrenal cortex to synthesis and secretion of the aldosterone (Takahashi *et al.*, 2011). In addition, it increases the thirst and also stimulates the release of the antidiuretic hormone (Barri, 2008). Thus the angiotensin II is believed to play key role in the acute as well as the chronic regulation of the blood pressure through the regulation of the systemic endocrine system.

A strong neurohormone that controls the systematic arterial pressure, the angiotensin II also has an effect on the structure and function of the vascular system through the autocrine and the paracrine effects of the local synthesis that is particularly tissue-based (Dahmet *et al.*, 2006). This alternative synthesis pathway of the angiotensin II is catalysed in the tissues through the enzymes for instance cathepsin G, chymase and the chymostatin-sensitive angiotensin II generating enzyme.

Thus this production of angiotensin II has a significant role in the remodelling of the cardiovascular diseases (Gonzalez *et al.*, 2013). These alternate up-regulating pathways then

occurs through the turbulence, stretch and the stress in the blood vessels. Common processes in the myocardium and the glomeruli of the kidney may then lead to the remodelling the targeted organs, consequently leading to the organ dysfunction (Santos *et al.*, 2012). Moreover, the angiotensin II may then enhance the receptor density and also the sensitivity for the additional factors that then modulate the growth of the smooth vascular muscle for instance the fibroblasts, i.e. in the transformation of the growth factor  $\beta$ -1, and also the growth factors derived from the platelets, and also in some other growth factors that are insulin-like. Additionally, the atherosclerosis may also be related to the excessive angiotensin II effects on the walls of the vessel, which consequently causes the cells of the smooth muscles to grow and migrate. It then also causes the activation of the macrophages, as well as enhances the aggregation of the platelets. The angiotensin II then stimulates the inhibitor 1 of the plasminogen activator which then directly leads to the endothelial dysfunction. In addition some other effects are also postulated by the angiotensin II on the vascular structure that then stimulates the atherogenesis, which also includes the blockage of the apoptosis, the rise in oxidative stress, and also the promotion of the migration and adhesion of the leukocytes, as well as the thrombosis stimulation (Kamide *et al.*, 2014).

### Central Nervous System Control

The central nervous system plays the main role in the regulation of the key functions of the circulatory system by controlling the sympathetic and parasympathetic nervous systems, the reflex action of the baroreceptor and the release of the pituitary hormone. Some immunoreactive materials like Digoxin and ouabain were found in the hypothalamic nuclei more than twenty years ago, they were believed to localize the paraventricular nuclei along with supraoptic nuclei and nerve fibres of the circumventricular organs, they were thought to be affecting the electrolyte balance as well as the blood pressure, and their turnover rate was supposed to be increasing with the increase in the sodium intake (Fletcher *et al.*, 2010). It was observed that as the intake of ouabain is the cause of an increase in the blood pressure due to the activation of sympathetic nervous system, so a factor known as the endogenous digitalis-like factor abbreviated as EDLF was then believed to be regulating the functions of the cardiovascular system that are related to brain, especially after sodium intake (Giese *et al.*, 2014). After the experiments carried out especially in rats, it was discovered that the mechanism of ouabain function in the brain particularly involves the sodium ions, the renin-angiotensin-aldosterone system RAAS and the epithelial sodium channels, and all of these are thus due to the effect of loading the sodium. The experimentation basically include the rat fed with high sodium level, which was then fed to the rats, which activated the ENaCs due to the elevated levels of sodium in the cerebrospinal fluid. These activated ENaCs then increase the sodium intracellularly, especially in the neurons which then consequently activates the RAAS, it then releases the EDLF factor in the brain, thereby increasing the sympathetic nervous system. This RAAS stimulates the oxidative stress inside the brain, which further activates the RAAS and augments the sympathetic nervous system outflow. In the peripheral origin the angiotensin II and the aldosterone act inside the brain so as to activate this flow increasing sympathetic cascade and thus consequently leads to the hypertension (Zhang *et al.*, 2004; Viazzi *et al.*, 2013). Thus, from the brain the Na<sup>+</sup>-ENaC-EDLF axis then activates the sympathetic flow and has a significant role in the secondary hypertension.

### Memory Utilization

The renin-angiotensin system (RAS) of the brain has a significant role in the learning process and memory development. The RAS components of the brain have been identified that can serve as a target for the cure of the neurodegenerative disorders e.g. Alzheimer's disease (Auron *et al.*, 2014). New findings propose that memory could be enhanced by the role of Ang II and is basically thought to occur by the inter-conversion of Ang II to AngIV, this is the peptide

that acts as an agonist at the subtype of AT<sub>4</sub> receptor which provides the cognitive facility. This theory gives the notion that the blockers of the angiotensin (ARBs) are responsible for enhancing memory, but still it lays underneath to yet to be proved that might be the blockage of the receptor AT<sub>1</sub> subtype that allows the conversion of the Ang II in excess to the Ang IV (Nishimura *et al.*, 2000). This suggests that the ACE inhibitors increase the cognitive ability, that results in greater amount of Ang I to be converted into Ang I-9 and finally to Ang III, Ang IV and Ang 3-7. This is how the mechanism of cognitive facilitation acts.

### **The ovarian renin-angiotensin-aldosterone system**

The latest organ-related functions of angiotensin II have been described recently, that are specific in action. The significance of the secretory epithelial function in many of these tissues containing the component parts of the reproductive system are also known. The basic source of the angiotensin II is the reproductive system itself, and also there is a substantial evidence to propose that there is a distinct functional renin-angiotensin aldosterone system inside the ovary and the uterus. The two basic types of the angiotensin II receptors are known as angiotensin-receptor I and angiotensin-receptor II, with respect to their sensitivity to the angiotensin II antagonists. Nevertheless, the existence of the angiotensin II receptors in the female and male reproductive organs shows the diversity of roles that are not related to their main functions. The renin-angiotensin-aldosterone system is a chief element of maintaining the sodium balance in the body especially during pregnancy (Siragy *et al.*, 2010). Recently, the methods involving RT-PCR have discovered that the angiotensinogen transcription within the smooth muscles of the spiral arteries of the decidua, that is a specific allele of that gene that may be related to the hypertension during pregnancy and also in the preeclampsia (Sjolie *et al.*, 2011). The activity played by renin in the plasma and the aldosterone levels during the normal and the hypertensive pregnancy had been investigated, which were found to be increasing gradually during all the three trimesters of a normotensive pregnancy. In the hypertensive women the plasma renin activity was found out to remain unaltered during the three trimesters of the pregnancy. But the aldosterone levels of the plasma however, were increased progressively, during the pregnancy in relatively all the three trimesters. Nevertheless, the aldosterone levels were considerably less than those during the normotensive pregnancy (Song *et al.*, 2013). This increase in the plasma aldosterone levels were pointed out despite the unchanged levels of renin. Further innovative work in the investigation of the renin-aldosterone system in the pathogenesis of hypertension during pregnancy is needed.

### **Insulin resistance**

Angiotensin II and insulin are considered as the key hormones in controlling the hemodynamic, homeostasis and metabolic pathways. Modern studies have proposed that the pathways of the Angiotensin II and insulin especially the signal transduction pathways, share numerous downstream effectors (Aydin *et al.*, 2005; Liu, 2007). The two hormones are very important Ang II and insulin, which control the hemodynamic and metabolic homeostasis, respectively (Alberti *et al.*, 2005). Current studies suggest that insulin and Ang II signal transduction pathways tend to share many downstream effectors that take part at many different levels (Goossens, 2012). When the circulating insulin binds to its receptor the signalling insulin is initiated.

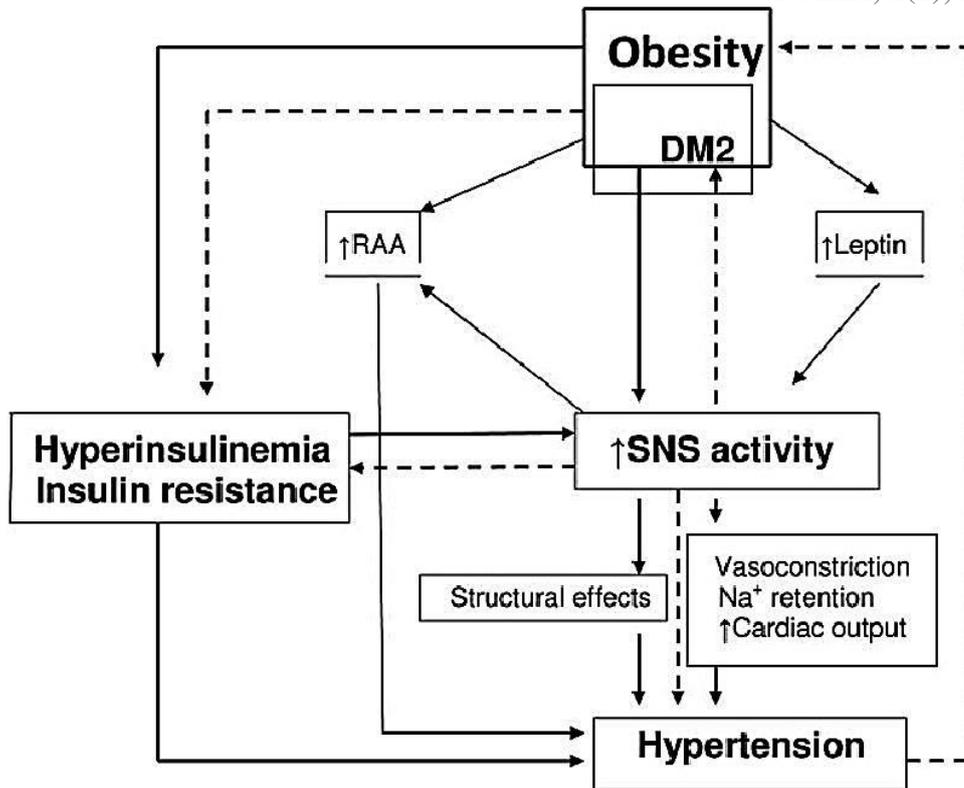


Fig. 2. The mechanism of Renin-Angiotensin system in insulin resistance (Masuo *et al.*, 2011).

The insulin receptor tends to be a tyrosine kinase that is a heterotetramer in nature, this insulin when binds brings about a quick autophosphorylation of tyrosine that will activate the kinase receptor and will permit a momentary interaction with the IRS-I (Kim *et al.*, 2006). The phosphorylated IRS-I tyrosine interacts with P13K would result in the activation of Akt phosphorylation and P13K, which initiates Glut-4 translocation in the sarcolemma to assist in the uptake of glucose and resultantly nothing is produced within the endothelium that could bring about the vasorelaxation (Schulman *et al.*, 2009; Zhou *et al.*, 2012). Technically, the upregulation of Renin-Angiotensin system occurs due to the insulin resistance, which increases the pathogenicity of the heart failure, hypertension, and atherosclerosis (Filippo *et al.*, 2010). Deaths caused by renal and cardiovascular diseases are decreased due to the inhibition by RAS, and also inhibits the frequency of the onset of type II diabetes (Underwood *et al.*, 2013).

### Chronic kidney diseases

The renin angiotensin aldosterone system controls the renal activities related to vasomotor, it also controls the salt and water balance at optimum level, as well as regulates the tissue growth within the kidneys (Yosypiv, 2014). Due to these reasons it is also involved in the pathophysiology of the kidney disorders. If the renin angiotensin system is activated it would enhance the systemic hypertension as well as the glomerular capillary hypertension, which has the potential to stimulate hemodynamic injury in the glomerulus and the vascular epithelium (Brewster *et al.*, 2004). Additionally, the proinflammatory and profibrotic functions of the Ang II and aldosterone can also cause potential kidney damage. Many unfortunate effects related to the Ang II seems to occur due to its binding with the type 1 receptor (Susantitaphong *et al.*, 2013). Similarly, aldosterone also seems to stimulate renal injury when it binds to the receptor in the kidney. So through all this, it can be concluded that the inhibitors of this cascade could minimize the development of chronic kidney diseases (Madsen *et al.*, 2010). Some of the agents that can affect this cascade include the ACE inhibitors, blockers of the angiotensin receptors and the antagonists of the aldosterone receptor (Viazziet *et al.*, 2013).

Some of the factors of the renal progression and microalbuminuria include age, blood pressure, male gender, dyslipidemia, smoking, obesity, and the background of the cardiovascular diseases (Atkins *et al.*, 2005; Shastri *et al.*, 2011). There is a great deal of inter-individual diversity amongst pharmacological reactions as well as the renoprotection that suggests the probable function of the genetic components (Coresh *et al.*, 2007; Kunz *et al.*, 2008). Similarly, it was observed that AGT and the ACE genetic variants that are functional, will control the chances of the microalbuminuria that are deliberated by the increase in the blood pressure in common population, but the treatment is not available so far (Leoncini, 2010).

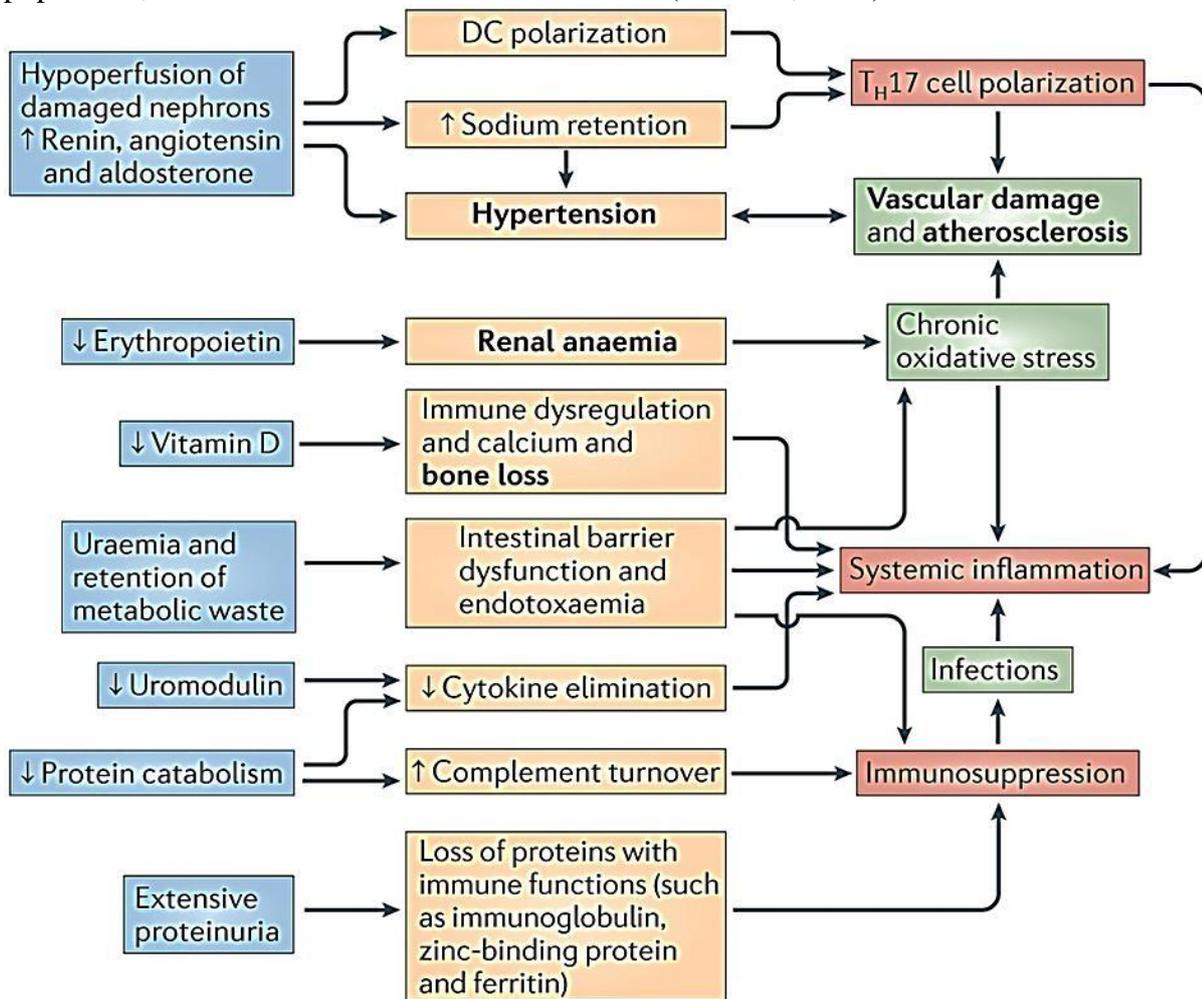


Fig. 3. The layout of Renin-Angiotensin System in Chronic kidney diseases and its effects on immunity (Kurtset *et al.*, 2013).

### Cardiovascular control

The marginal RAS is considered to be two-fold system that consists of flowing angiotensin and the RASs of the local tissues. This system gives rise to a cardiovascular functionality which acts as a stimulus upon the heart, and causes an increase in the vascular resistance. This enhanced vascular resistance arises because of direct action on the smooth vascular muscles and the subsidiary action through the brain that results in the arousal of the sympathetic nervous system, the secretion of the potent vasopressin i.e. a vasoconstrictor, and the blockage of the reflex baroreceptor (Lastra *et al.*, 2010). Lately, it has been observed that the constituents of the RAS are found within the vasculature, this is a very promising finding as it could lead to very finest pharmacological as well as physiological implications (Rader *et al.*, 2010).

The innovative finding of RAS constituents of the brain lead to the concept of an independent local RAS of brain. Substantial proof is now present that suggests the presence of two main

pathways of the brain that are angiotensinergic (Maione *et al.*, 2011). The forebrain passageway incorporates with the supraoptic, paraventricular, the intermediate proptic nuclei, and also the circumventricular organs. Another passageway connects with the medulla and the hypothalamus, and also with the solitary tract nucleus i.e. NTS. As the CVOs contain finest capillaries and are dispersed within the angiotensin receptors, activating these receptors by the angiotensins that are blood-borne, which is supposed to control the circuits of the central cardiovascular system. This system thus allows the communication between the central and the peripheral RASs. Provide that the AT1 subtype receptor binds with the Ang II and Ang III with almost equal affinity, and these ligands likely incite rise in blood pressure, levels of thirst, and vasopressin secretion, it had been hypothesized that Ang II and Ang III are equally potent to the AT1 receptor subtype, Ang II can be transformed into Ang III to onset the recetor subtype.

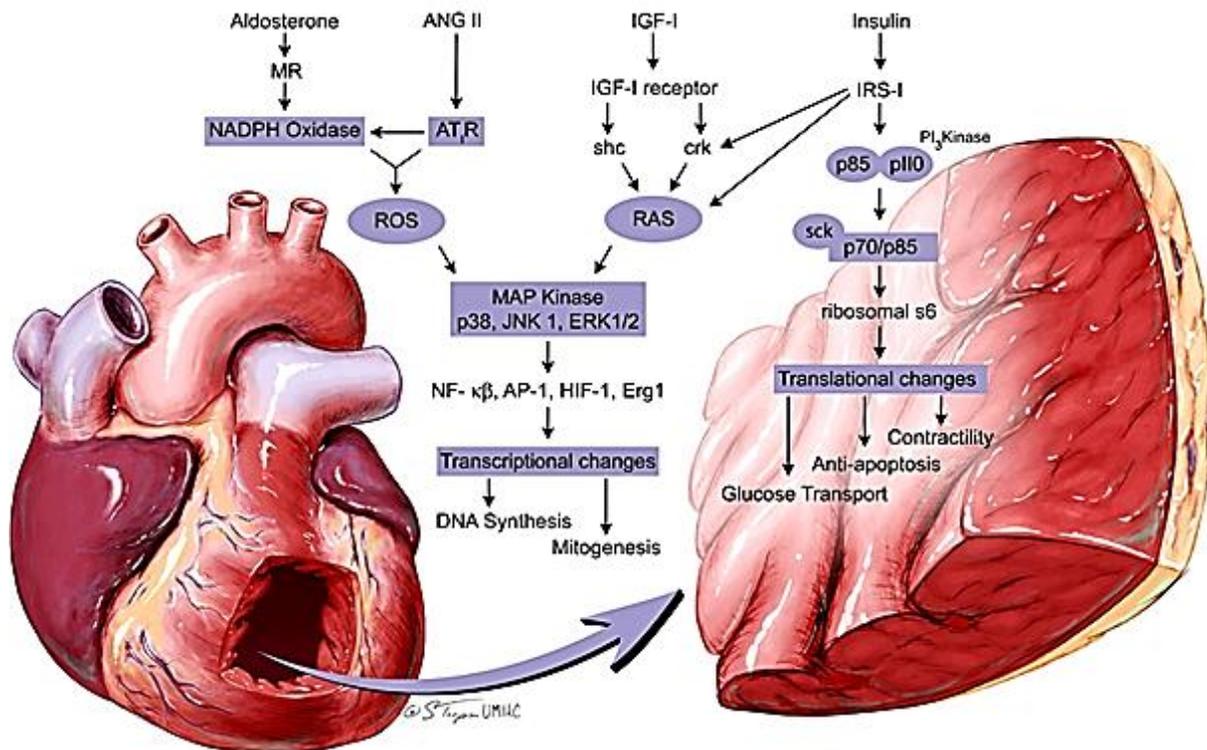


Fig. 4. The Renin- Angiotensin System mechanism in control of in cardiovascular diseases (Cooper *et al.*, 2007).

### ACE Inhibitors

The degradation of the bradykinin is blocked by the enzyme that transforms angiotensin, due to which effects of Ang II mediated by AT1R are opposed. Since alternative passageways are present that would cause the exit of the Ang II, The inhibition effect caused by the ACE only partly causes the reduction of the Ang II production (Reilly *et al.*, 1982; Staessen *et al.*, 2006). It had been proposed that the chief mechanism of ACE inhibitors is by the inhibition of the degradation pathway of bradykinin, as the Ang II levels in the plasma regulates the treatment of the ACE inhibitor (Wei *et al.*, 2010). Nevertheless, it doesn't suggest the production of Ang II within the tissues is not degraded by the inhibition due to the ACE enzyme (Raja *et al.*, 2008). In a case like this, the development of the Ang 1 to Ang 7 from the Ang II by another enzyme i.e. ACE 2 would be shortened due to which there would be a lesser amount of countering effect of the typical patho-physiological activities of the RAS mediated by the AT1 receptor through the activation of the Mas receptor by Ang 1-7. In addition, an enhanced production of the Ang 1-7 would occur in both the plasma and the tissues by the shifting of Ang I to produce Ang 1-7 through metabolic passageways for instance those that exist in the eye i.e. Neurolysin (Bertazzoli-Filho *et al.*, 2007). The inhibitors of the renin-angiotensin system,

including the inhibitors of the ACE (angiotensin converting enzyme) and the inhibitors of the Ang II receptor the ARBs (Robleset *al.*, 2013), as well as the inhibitors of the renin enzyme directly are found out to be helpful in the treatment of hypertension.

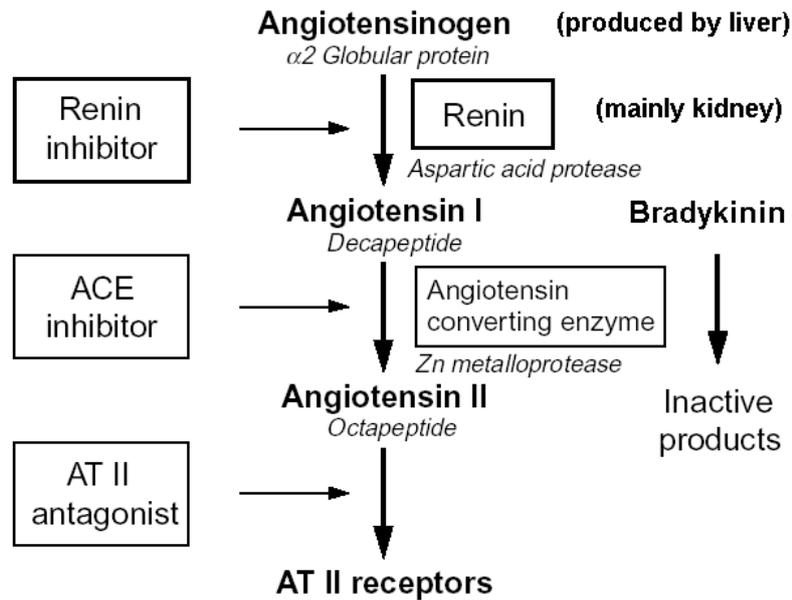


Fig. 5. The mechanism of Angiotensin converting enzyme inhibitors (Rahuel *et al.*, 2000).

## Conclusion

The renin-angiotensin system has a lot many clinical implications. It acts as a hormonal system in correlation with aldosterone, known as Renin-Angiotensin Aldosterone system, and is meant for controlling many vital functions within our body. It finds its applications in Nervous system, cardiovascular diseases, kidney problems, hypertension, liver disorders, and in memory utilization process, where it is meant to enhance the memory. It has been discovered from recent studies that the renin-angiotensin-aldosterone system is also a chief element of maintaining the sodium balance in the body especially during pregnancy. The renin-angiotensin system together with insulin also tends to control the hemodynamic and metabolic homeostasis. The up-regulation of Renin-Angiotensin system occurs due to the insulin resistance, which increases the pathogenicity of the heart failure, hypertension, and atherosclerosis. So this shows that the Renin-Angiotensin system has a lot many clinical implications in the mammalian systems. Similarly, the inhibitors of the renin-angiotensin system, the ACE inhibitors, and the inhibitors of the Ang II receptor the ARBs, and the inhibitors of the renin enzyme directly are also found out to be helpful in the treatment of hypertension.

It has been recently discovered that natural killer cells and the T-cells of the human immune system contain a functional renin-angiotensin system (Jurewicz *et al.*, 2007). This is quite beneficial in a sense that, as this system is functional in the leukocytes, and so are able to produce as well as deliver the Ang II at the sites of inflammation. As this chemotaxis is being increased by the Ang II, so it would automatically create a strong inflammation amplification system, which would certainly cause reduction in inflammation. This, directs towards the future prospects of the renin-angiotensin system.

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