Renin as a key enzyme for the integrity of various critical life-functions in the humans

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ABSTRACT

Renin Angiotensin System is the complex and old hormone system mainly involved in the regulation of blood pressure. Renin is released by kidney & acts on Angiotensinogen to produce Antiotensin 1 which is converted to Angiotensin II. This Angiotensin II binds to the cells through specific receptors i.e. AT1 and AT2 to perform its functions. Renin-angiotensin-aldosterone system maintains the amount of hormone angiotensin in body. Juxtaglomerular cells alongwith cAMP are involved in the release and storage of rennin. Function of JG-cells is opposite to release of calcium. A number of events regulating rennin include substances released to inhibit calcium, presence of adenylyl cyclase, phosphodiesterases & receptors for renin and gap junction along with calcium waves. In pathogenic conditions activity of RAAS components can cause diseases of kidney & heart. RAAS is helpful when Angiotensin ll liberates aldosterone and water & Na level in kidneys. Aliskiren, a rennin inhibitor can cause decrease in systolic blood pressure and plasma rennin. In the onset of diabetes, the activation of AngII pathway supports cell growth & its proliferation, apoptosis, oxidative stress generation etc and these all contributes in cardiac remodeling & accelerating atherosclerosis.

Keywords: Renin Angiotensin system, Juxtaglomerular cells, RAAS, ANgiotensin II, Aliskiren, Calcium, Kidney.

1. Introduction

The RAS (Renin Angiotensin System) is very old hormone system. It is very complicated regulatory system having a lot of distinguishable features. The main function of this system is in the maintaining the salt and blood volume as well as it is also involved in regulating adequate blood pressure (Montanni & Vile, 2004).When we talk about evolution, many animals and our ancestors faced the threats of low blood pressure and low blood volume due to the intake of low sodium diet, so they developed RAS mechanisms to maintain salt and water levels in the body. Renin is present in the form of prorenin which is an intracellular protein in the juxtaglomerular cells. Due to lower plasma sodium levels or low blood pressure, these cells convert prorenin to renin which then goes directly to the circulatory system. This plasma renin then acts on plasma protein angiotensinogen and convert it to a small peptide named as Angiotensin I (Lavoie & Sigmund, 2003). The major end product of this RAS i.e. angiotensin II play its role in the prevention of shrinkage of intravascular volume which may prove fatal. This angiotensin II along with the nervous system (sympathetic), play its role in the maintaining homeostasis by normalizing the changes in the pressure in arteries and fluids' volume to maintain sodium level. This system is also tangled in promoting the growth of vessels and heart and also makes the blood vessels sensitive to any kind of vasoconstrictor agents. However, this is one of the slowest actions performed by Renin Angiotensin System. Angiotensin II also play its role in the stimulation of secretion of aldosterone (Yee, Burns & Wijidicks, 2010). If RAS starts working abnormally, it results in the increased blood pressure. However, there are certain drugs available

which can control blood pressure (Solomon & Anavekar, 2005). An illustration of the molecular structure of renin enzyme is given in Figure 1.

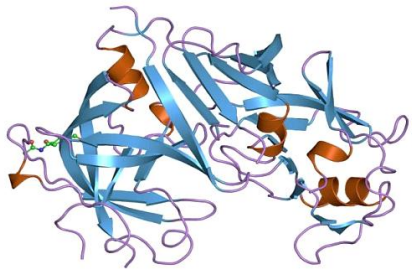

Figure 1. Molecular representation of renin.

The past of Renin-Angiotensin System is almost 100 years old. A physiologist named as Robert A. Tigerstedt (1853– 1923) did an experiment along with a medical student, Per Gustav Bergman. They injected the kidney cells of a rabbit into jugular vein of other rabbits known as "recipients" and observed the body changes. They observed that those extracts initiated raised blood pressure in recipient rabbits' vein. Form their experiments, they established a statement that kidney had a substance, pressor, (which causes an increased blood pressure rate by the constriction of blood vessels) a called it as Renin. They further experimented and stated that renin was found in the renal cortex and it generated the pressure response which did not involve intact nervous system (Basso & Terragno, 2001). After it, no experiment was done on it for several years. Harry Goldblatt who did an experiment on dogs and induced hypertension in them by clipping their renal arteries (Goldblatt et al., 1934) made further observations. He revived the interest in Renin Angiotensin System and in 1939 it was found that renin itself has not pressor action but there was an enzyme involved that acted on the protein, as a result a vasoconstrictor released which was then named as Angiotensin (Lavoie & Sigmund, 2003).

2. The Renin–Angiotensin Cascade.

As Renin-Angiotensin System remains neglected for years, it was then explained as follows. Renin is a proteolutic enzyme which is released by the kidney as a result of a certain stimulus. This enzyme is released in the circulatory system where it shows its action on a protein named as Angiotensinogen (AGT) and produces a small fragment of 10 amino acids called as Angiotensin I which is further transformed into angiotensin II by the working of an enzyme, Angiotensin Converting Enzyme (Lavoie & Sigmund, 2003). The location of that enzyme is usually on the surface of the vascular endothelial cells. Angiotensin II play its role in the constriction of arterioles which then results in the increase in blood pressure (Yee, Burns & Wijidicks, 2010). When the blood leaves from kidney and the liver, it passes from the lungs and hence the vascular endothelial cells of lungs convert angiotensin I to Angiotensin II. This Angiotensin II then binds to the cells via specific receptors to perform various actions. Four steps are to be made at this specific stage that are firstly, there are many other alternative pathways by which angiotensin I to II can be produced e.g. in place of renin, there, tonnin and cathepsin D, which is able to trigger the formation of Angiotensin I and in the same way, in place of ACE, trypsin and cathepsin G can play their role in the alteration of AngI to Ang II (Cogan, 1990).

However these alternative pathways are still unclear in human beings. Secondly, there are many other substrates present in the body other than Ang I on which ACE can act e.g. it can act on bradykinin, substance P & other minor peptides and as a result their degradation can be promoted. However, if ACE is blocked by specific inhibitors, it will not degrade bradykinin or substance P which will be accumulated in the cell and this result in a benefit in the body i.e. in the reduction of hypertension. These inhibitors also show some side effects like angioedema and cough. Thirdly, many angiotensin peptides are also present in body having their biological

activity. As already mentioned that Ang II is produced as a result of RAS, other enzymes may act on this AngII and cleave one or two amino acids at the terminal position and as a result Ang III and Ang IV are formed. Ang III and Ang IV are involved in the functionality of brain (Montanni & Ville, 2005). If the cleavage of Ang I occurs from the carboxyl terminal, Ang (1-7) is produced and is has role in vasodepression. These Ang (1-7) also act along with the ACE inhibitors and play their role in the reduction of hypertension. And finally, the components of RAS i.e. renin, AGT and ACE is present in many tissues. Kidney is the site of production of renin and AGT is produced in the liver from where they come to the circulatory pathways. However, these can be expressed nearby some specific tissues. That renin and AGT which are present in the circulatory system forms the systemic Renin Angiotensin System and those RAS components which are present locally inside the tissues forms the tissue Renin Angiotensin System (Cogan, 1990).

Local RAS works in many organs i.e heart, vascular walls, brain, kidneys, fats, pancreas and in reproductive organs also. For instance, the RAS present in brain and intrarenal RAS play their role in the maintenance of salt concentration and blood pressure. A flowsheet representation of Renin Angiotensin system is given in Figure 2.

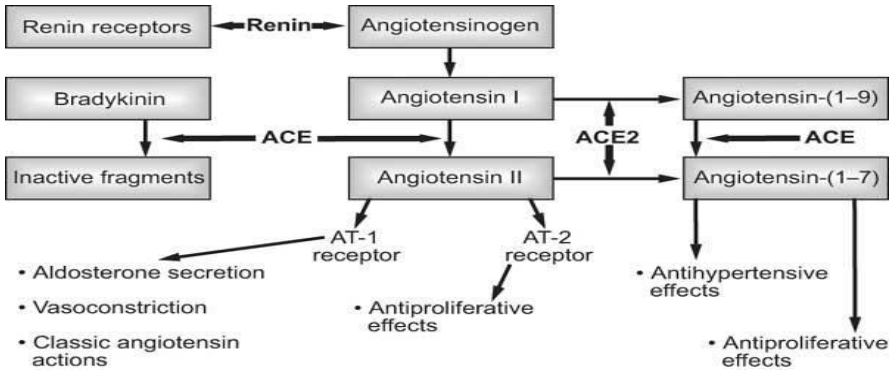

Figure 2. Flowsheet Representation of RAS

2.1. Specific receptors for Angiotensin II

Angiotensin II acts through specific receptors i.e. AT1 and AT2. In case of rodents, AT1 receptor exists in two isomeric forms called as AT1a and AT1b. These isotopes are however not found in humans and only AT1 type receptors are found. Other types of AT receptors found are AT4R and AT1-7R and they have their role in the mediation of other angiotensin types and intracellular receptors. Mostly, the important actions of angiotensin II i.e. contraction of vessels, maintenance of appropriate levels of sodium in the body, growth of cells and their proliferation, are mediated by AT1 receptors. These receptors can also be blocked by specific inhibitors named as sartans. The other type, AT2, is usually present on fetal tissues and their number varies time to time e.g. in postnatal period receptor number decreases and in case of any tissue rupture, their number increases. These At2 receptors are involved in dilation of vessels, differentiation of cells and apoptosis. One important action of AT2 receptors is in the compensating of the effects of Ang II that occurs because of the working f AT1 receptors (Cogan, 1990).

3. Role of calcium in renin secretion

Renin is an enzyme which is monogamous and is related to kidney development. Calcium is present in body fluids and is important in the secretion and release of this enzyme. Phenomenon of relaxation of muscles and their contraction is involved in the renin release. Basically calcium act as a signal molecule in its activation and the signal is released from the baroreceptor, macula densa, and neurohormonal pathways. Whenever there is release of calcium, according to its high or low level, the renin is released by various places in order to maintain the body (Fray, Lush Share, & Valentine, 1983). Along with calcium, level of NaCl is also involved, when its level is increased, the amount of adenosine is also increased which is released by macula densa cells near

kidney, this action results and acts on juxtaglomerular cells, which signals to increase the level of calcium and stop release of renin enzyme. So the enzyme is produced in case of low calcium in body (Churchill, Churchill, & Mcdonald, 1985).

There are different pathways but in neurohormonal pathway, a system called 0-adrenergic mechanism, which is stimulated and the will allow to secrete renin through a cAMP cascade cycle that will decrease calcium. And another system called alpha-adrenergic mechanism which will inhibit enzyme secretion when there is calcium level high. These systems are antagonistic and work oppositely (Hackenthal, Schwertschlag, & Taugner, 1983). As by the research scientist concluded that along with calcium, sodium is also responsible for its level, the renin secretion is also inhibited same way with sodium as for calcium. Macula densa cells also release sodium along with calcium, these two collectively inhibit renin, only calcium is not involved, this is done during the transport of NaCl outside the cell.

Angiotensin II is actually mediated by system I, that is active and involve I maintaining the renin level by its release. Angiotensin system II is not involved in renin production and transport but also carry out various other functions like vasoconstriction, amplification of sympathetic pathways, regulating blood pressure, sodium retention increase or decrease, cell growth regulation and promotion, aging, hypertension and maintenance of aldosterone level. It is also involved in targeting several diseases and in controlling heart failures as well (Lum, Shesely, Potter, & Beierwaltes, 2003).

3.1. JG cells (juxtaglomerular cells)

These cells are placed in front of afferent arteriole of nephron in kidney, before the glomerular part (Figure 3). These are also involved in maintaining and releasing certain enzymes and molecules.

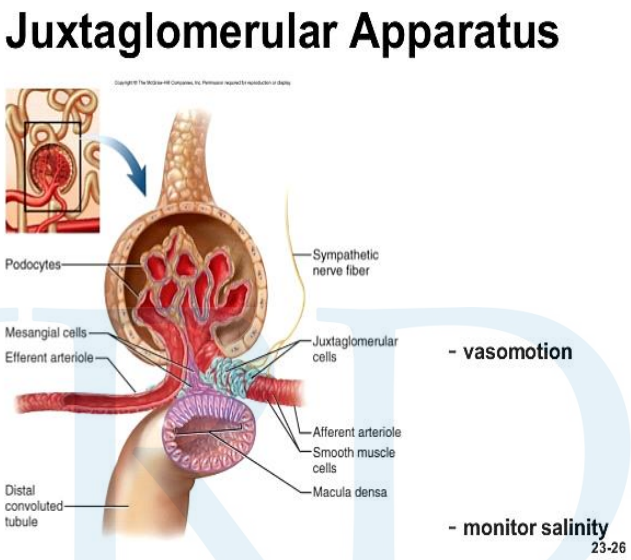

Figure 3. Juxtaglomerular Apparatus

Endothelial layer of tissues in present along with the side of lumen from where the renin is released, and on the opposite side there is a separating space which are responsible for separating these juxtaglomerular cells from macula cells. These macula cells (Fig 3) are present on terminal of TAL, which is called thick ascending limb; this is part of loop of Henle of nephron in kidney. The space between these cells is a region where the enzyme renin is released. As the renin is secreted the already released renin moves away, it is not collected I one place, due to its continuous movement a diffusion gradient is created and because of this gradients the renin

tends to move towards lumen. From lumen it goes to glomerular hylus mesangial cells and then interacts with the afferent arteriole (López, Pentz, Nomasa, Smithies, & Gomez 2004).

3.2. Macula densa cells

These cells are present on initial sides of both arterioles (Fig 3) and are closely contacted to the juxtaglomerular cells. These cells manufacture proteins which are needed to be transport outside the cell (Ryan, Coghlan, & Scoggins 1979).

3.3. Calcium channels

There are specific channels present for calcium release (Fig 4) and regulation which show electrical potential of JG cells. The coupling of these causes polarization, which effects release of calcium and renin. Depolarization can cause inhibition of renin and hyperpolarization may increase the amount of renin released (Churchill, & Churchill, 1982). KCl is responsible for regulating renin. If the depolarization is caused of potassium ions, this will improve signals to release the renin enzyme. Polarity plays ital. role in activation of angiotensin system and L-type calcium channels. Due to polarity and ion formation these channels are inhibited due to which the renin release is increased (Churchill, 1980). Along with this pathway the calcium is also released from endoplasmic reticulum, which also effects the renin secretion in cell (Schweda, & Kurtz, 2004). This calcium from endoplasmic reticulum is called store operated calcium because it is the stored form of Ca present in reticulum and is released in the form of depletion causing to increase in calcium level which is contacted to cation channel which is divalent inside plasma membrane; this situation will permit entrance of calcium from outside the cell as well. Store

operated-calcium-channels differ from the voltage gated L-Type channel. Renin release id again inhibited if Ca from these channels is produced (Schweda, Riegger, Kurtz, & Krämer, 2000).

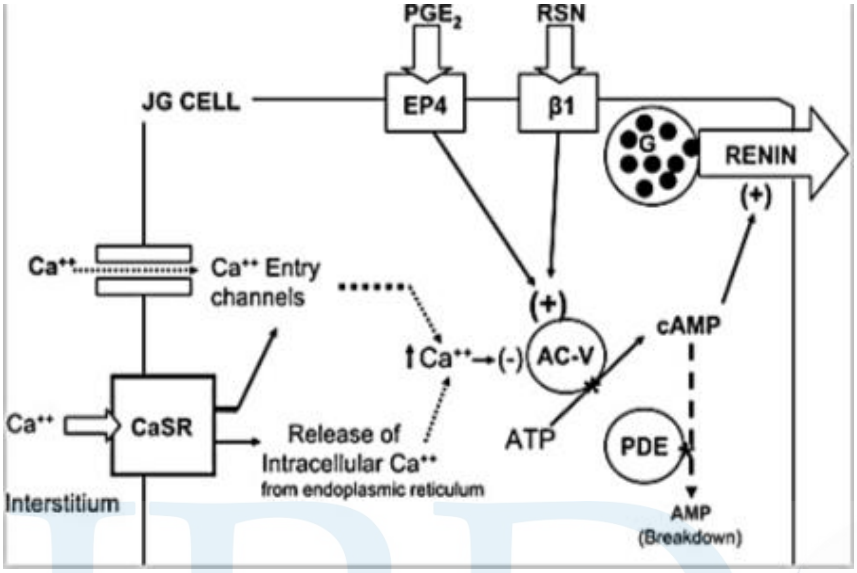

Figure 4. Calcium Channels involved in Renin Secretion

3.4. Receptor Mediated Calcium Mobilization

Negative feedback inhibition of this enzyme was presented by Arthur Vander in 1965 (Vander, & Geelhoed, 1965). His work has been confirmed by other scientists as well like Vandongen and Pert. Due to presence of calcium outside the cell the angiotensin system can inhibited. This angiotensin system II is responsible for the increase of Ca inside the cell by vasoconstriction (Ruan, & Arendshorst, 1996). Other hormones like vasopressin etc. also show this behaviour of coupling which will inhibit Ca level from JG cells; this system has receptor mediated response as well. These receptors may increase intracellular level of Ca due to activation of angiotensin system which may activate the negative feedback to decrease these levels by suppressing renin or calcium (Zhuo, Ohishi, & Mendelsohn, 1999).

3.5. cAMP signalling pathway

This pathway is basically involved in exocytosis of renin. This is basically involved in stimulation of regulation of renin by sympathetic nerves which act by β1-adrenoreceptors, which binds to neurotransmitter in L-Type Ca channels (Hackenthal, Paul, Ganten, & Taugner, 1990). cAMP along with sodium chloride plays important role in its pathways and activation and inactivation of renin. It is also affected by adenylyl cyclase activity which has almost 9 isoforms, these are activated by level of calcium in body low levels of calcium can cause inhibition of two forms of adenylyl cyclase due to which cAMP is more synthesized and more renin is released by JG cells (Ortiz, Ortiz, Harding, Garvin, & Beierwaltes, 2007).

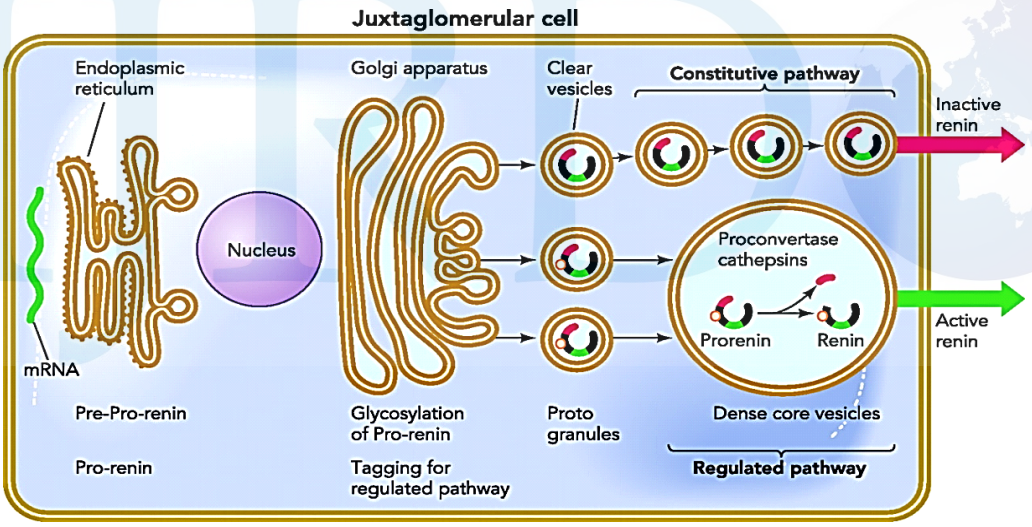

Figure 5. Pathways showing release of active and inactive renin.

Constituted and regulated pathways (Fig 5) are adopted by body according to the several body conditions and due to that active or inactive renin may be produced. Fig 5 shows mechanism inside the cell where endoplasmic plays its role in its secretion.

4. Pathophysiological roles of renin–angiotensin system in GIT

The renin angiotensin system (RAS) is used to regulate and maintain physiology of heart and kidney. It is homeostatic pathway, can also regulate gastrointestinal tract.

4.1. Function & localisation of RAS in GIT

There are mainly two types of receptors present in cells. Both angiotensin receptors (1 & 2) are found in small vessels of muscularis propria, epithelial cells of tissues and myenteric plexus. AT1R is located to the epithelial brush border (Ewert, Spak, Olbers, Johnsson, Edebo, & Fandriks, 2006). In small intestine the mRNA of renin is localised (Seo, Fukamizu, Saito, & Murakami, 1991). Angiotensin II is also present in crypt and crypt-villus junction epithelial cells, in the rat brush border and in propria as well as in muscularis mucosa and the sub mucosal blood vessels and muscularis propria (Nagata, Kato, Kuwasako, & Kitamura, 2010).

In colon, this enzyme is not been that much studied; there are limited publications on it. But in colon renin can be found in its epithelium, mesenchymal cells, walls and mucosa (Hirasawa, Sato, Hosoda, Yamamoto, & Hanai, 2001). Angiotensin renin system 1 was also found in macrophages, myoblasts myofibroblasts and mucosal vessel walls. On other way the angiotensin system 2 was detected in mesenchymal cells. Angiotensin converting enzymes were also observed in different regions of surface of epithelium and in mesenteric microvascular walls along with submucosal mesenchymal cells and lamina propria. Angiotensinogen mRNA was isolated from homogenised rat colon but it is not found in human colon.

Components of this RAS are present in the mucosal lining of gastric antrum and in the body of healthy adults. These were also detected in gastric epithelium in basal surface. System 1 was found specifically in endothelium. Both of these renin and angiotensinogen are present in

lamina propria mesenchymal cells along with vascular endothelial cells (Carl, Gräntzdörffer, Lendeckel, Ebert, & Röcken, 2009). By other studies it was also found that angiotensin converting enzymes were seen in mucin secreting cells and chief cells. Stomach wall is composed of both longitudinal and circular muscles and there in-vitro examination shows that system II of angiotensin exist in them along with some receptors on myocytes (Cullen, Ephgrave, Broadhurst, & Booth, 1994).

5. Role of Pathogens in (RAAS) Renin Angiotensin Aldosterone System

The RAAS is a significant provider in regulating blood pressure, salt balance, tissue growth and water. It acts as circulating endocrine system as well as tissue-autocrine system (Fig 6), mostly in kidney, brain and heart. Kidneys release rennin in circulating system and convert the angiotensinogen to angiotensin I and is further changed into angiotensin II by the activity of ACE (angiotensin-converting enzyme). Angiotensinogen enzyme is mostly produced in liver (Osswald, 1984). In the presence of pathophysiological conditions, activity of the components of RAAS in tissues may lead to the pathogenicity of renal & cardiovascular diseases Ryan, G. B., (Coghlan, & Scoggins, 1979). Furthermore, enzymes such as chymostatin-sensitive angiotensin II-generating enzyme in tissues may lead to synthesis of angiotensin II, shown in figure d (Vander, & Geelhoed, 1965).

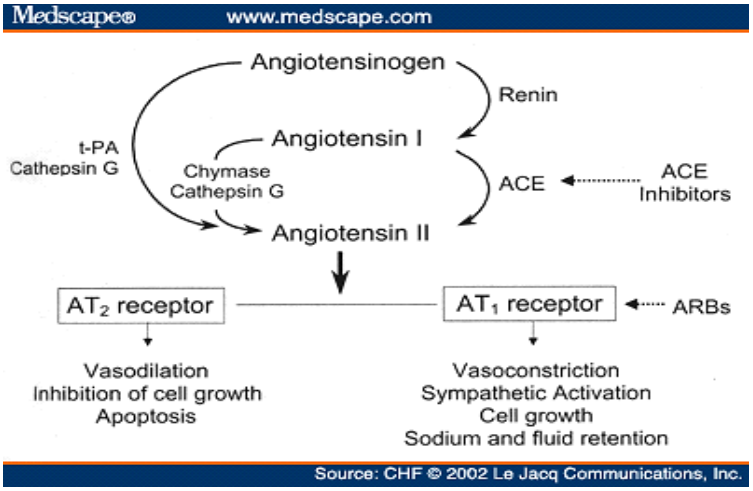

Figure 6. Role and pathways of angiotensin II formation and its receptors

Inflammatory cells also considered as biochemically compatible in contributing for the enhancement in angiotensin II.

6. Role of angiotensin II

Angiotensin II is the main effector peptide of the RAAS. It is a powerful vasoconstrictor which is responsible to trigger the liberation of aldosterone and causes the kidneys to increase the preservation of Na (sodium) and H_2O. This increases the level of blood and sustains normal blood pressure in any hypotensive situation. Additionally, angiotensin II has a various actions that are related to the renal and cardiovascular pathology. It is also involved in vascular remodeling by the activation of signal transduction pathways which helps in promotion of cell growth, fibrosis and inflammation events (Nagata, Kato, Kuwasako, & Kitamura, 2010). Its role in different cells is shown in figure 7.

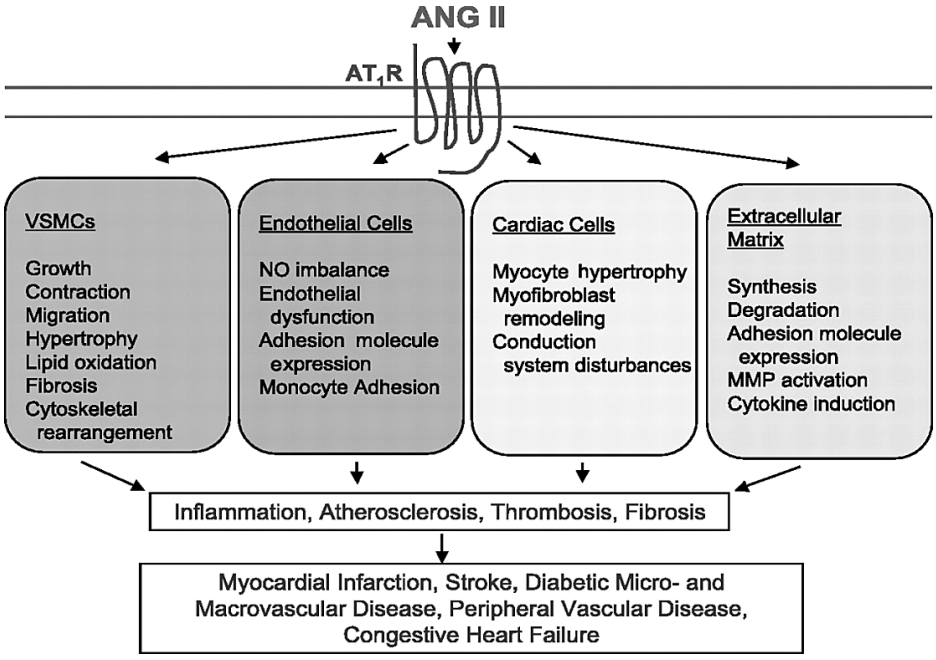

Figure 7. Different Roles of Angiotensin System II.

6.1. Aldosterone and Low level Renin in Hypertension

Aldosterone is the most important mineralo-corticoid hormone that is secretion of the adrenal cortex. Recognizing mineralo-corticoid receptors in heart, brain and vasculature has set the theory that aldosterone could mediate its harmful effects in the above mentioned target organs directly (Rocha, *et al*., 2002). Also there is indication of the biosynthetic localization of aldosterone in these tissues (Duprez, Buyzere, Rietzschel, & Clement, 2000). These increasingly evidences says that aldosterone can act through genomic mechanisms as well as non-genomic mechanisms. Aldosterone is also helpful in the cardiac and vascular remodeling and inflammation (Struthers, 2004). Inhibition of plasma renin levels is repeatedly encountered in patients suffering from hypertension. Low plasma renin concentration is also one of the distinguishing characteristics of the primary aldosteronism, but the occurrence of this particular disorder in the common hypertensive inhabitants is now supposed to be pretty little. Therefore,

the method for renin control in the huge mass of patients with low renin hypertension (LRH) has remained vague and divisive (Deykin, Balko, & Spark, 1972).

Increased preservation of Na ions or decreased excretion of Na by the kidneys due to the GRK4 proteins (G Protein-Coupled Receptor Kinase 4) leads to the fall in Na retention, renin and aldosterone level. Along with these genetic factors some environmental factors also interplay their role for creating "the perfect storm" in the development of hypertension as shown in figure 8 (Rayner & Ramesar, 2015).

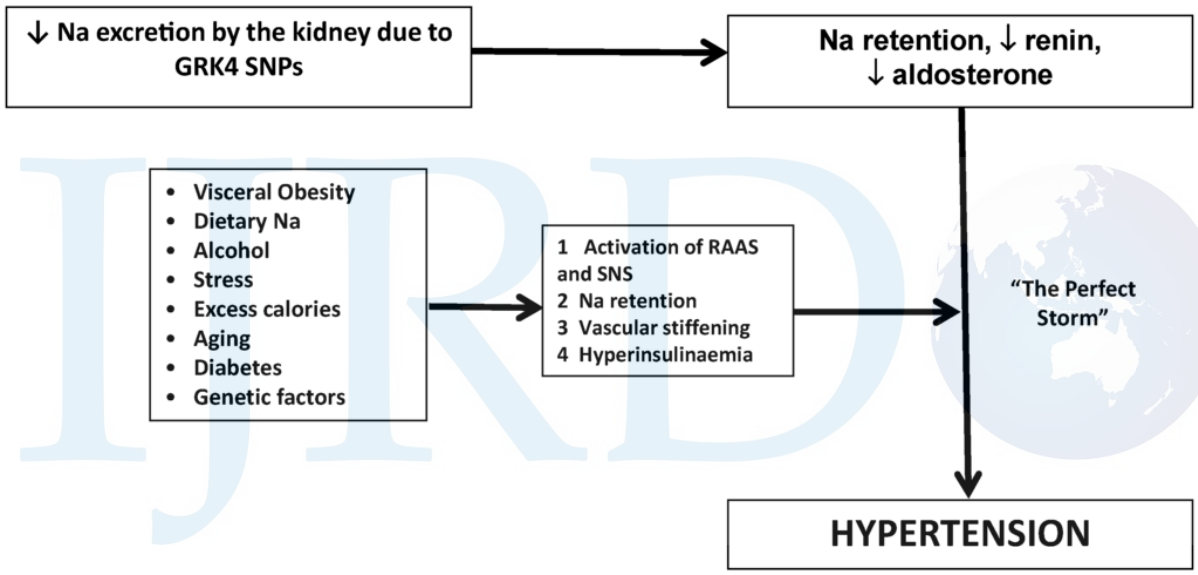

Figure 8. Development of hypertension.

7. Blockade of RAAS

The blocking of RAAS helps in the protection against the cardiovascular events and thus helps in reducing mortality. Pharmacologic disturbance of this system is likely to happen at the 5 main sites: release of rennin from juxtaglomerular cells, cleavage of angiotensinogen by renin catalysis, conversion of angiotensin I to II by ACE, binding of ang II to AT1 receptor and the binding of aldosterone to mineralo-corticoid receptor (Fiordaliso, *et al.*, 2006). RAAS blockade

can also have a bang on the untimely mechanisms of vascular diseases like non-functioning of endothelial & vascular remodeling (Figure 9).

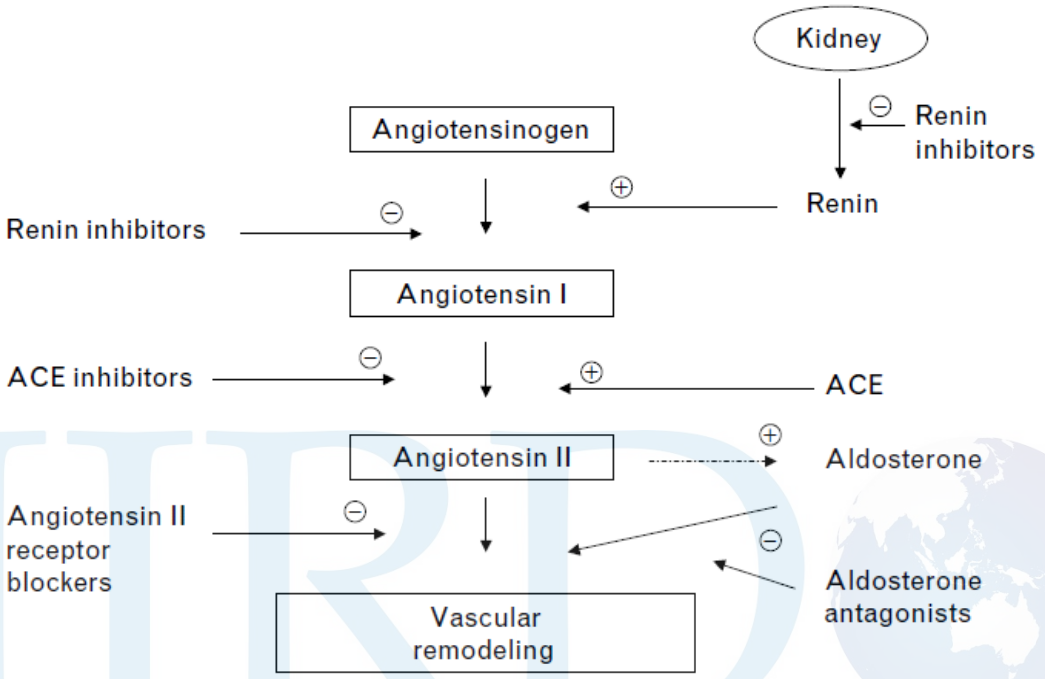

Figure 9. Agents blocking the RAAS at several points

Diabetes mellitus is known as one of the most common reason of the ESRD (end-stage renal disease) Worldwide. The Renin Angiotensin Aldosterone System activation links diabetes to cardiovascular disease. Currently RAAS is picturized as an extremely complex pathway which triggers a series of actions leading to the cardiovascular disease on its overstimulation. This system is not only present in the circulation having specific hemodynamic effects, but it is also found at the tissue level showing non-hemodynamic effects. Its activation occurs in the heart failure, and the activation of ACE enzyme or Angiotensin II contributes to both atherosclerosis and cardiac injuries (Wollert, 1999). As compare to the general individuals patients suffering from diabetes have a higher probability of cardiovascular mortality (Grundy, *et al.*, 1999). As we

know that diabetes is linked with the accelerated atherosclerosis which affects the coronaries increasing the risk of heart failure and myocardial infarction. In contrast, it can also prove causative for the diabetic cardio-myopathy (Rubler, *et al.,* 1972). RAAS antagonism has significance in the decrease of cardiovascular complication which clearly demonstrates that diabetes-induced RAAS activation helps considerably to diabetic cardiovascular diseases (Yusuf, Sleight, Bosch, Davies, & Dagenais, 2000). In the onset of diabetes, the activation of AngII pathway can support the cell growth and its proliferation, apoptosis; inflammation, oxidative stress generation and fibrosis, and these all are contributing to the cardiac remodeling and accelerating atherosclerosis. This can be overturned or decreased by the RAAS blockade (Fiordaliso, *et al.,* 2006).

8. ALISKIREN; The Renin Inhibitor

There are a number of renin inhibitors that were developed in the past decades, but the poor bioavailability, low potency and short duration of action caused the failure to discover a clinically useful drug (Gradman, *et al.,* 2005). Aliskiren is the rennin inhibitor that represented a class of non-peptide, orally active renin inhibitors. Chemical structure of aliskiren is shown in figure 10.

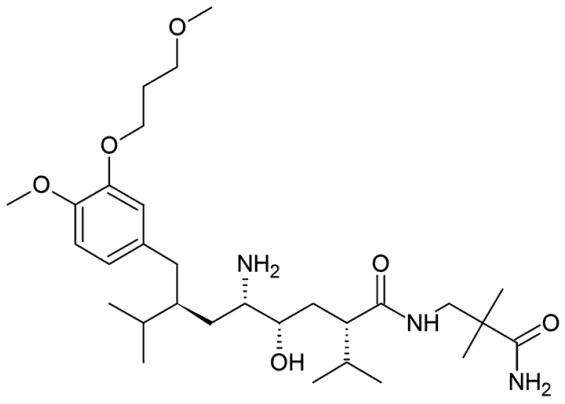

Figure 10. Chemical Structure of Aliskiren.

It is highly specific in binding with the proteolytic active sites of renin. So, it lowers the circulating levels of Ang 1 & 2, decreases blood pressure and aldosterone excretion and also elevates the levels of renin release by preventing the activity of renin. The mechanism of action of aliskiren to inhibit rennin activity is shown in figure 11 (Nussberger, Wuerzner, Jensen, & Brunner, 2002).

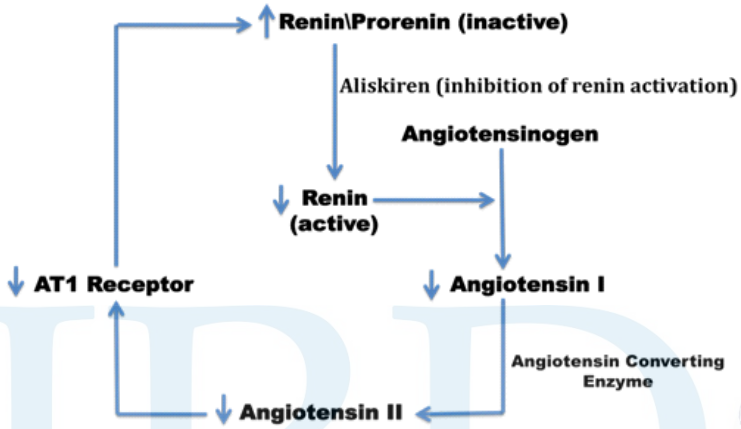

Figure 11. Inhibition of Renin Activity by Aliskiren.

This inhibitor was tested in healthy individuals as well as patients with moderate hypertension. Its administration was done once daily. Within 4 weeks, this dose caused decrease in the activation of plasma renin and systolic blood pressure (Stanton, Jensen, Nussberger, & O'brien, 2003). It is the first oral rennin inhibitor that is available in market and is approved for the treatment of hypertension and heart failure. It is capable to directly inhibit rennin earlier than the other rennin inhibitors like ARBs or ACE in rennin angiotensin aldosterone system. Higher doses may also cause some side effects like diarrhea, cough and edema etc (Siragy, Huang, & Lieb, 2008).

9. Conclusion

Without renin, the maintenance of blood pressure and cardiovascular system is very difficult so renin plays a main role in proper functioning of many organs. It is concluded that cAMP plays vital role in renin secretion along with cGMP but still cAMP is mainly involved. This cAMP activates adenylyl cyclase to stimulate renin release. JG-cells contain gap junctions which enhances calcium waves due to which the calcium level is increased inside the cell, due to which the renin is inhibited. Although this pathway is being studied and understood now, but there are still many question unanswered. Main activation of calcium release and the whole system running is still unknown. Angiotensin II has great role in liberation of kidneys as well as vascular remodeling.

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