CHAPTER

51

Pathophysiology of Renin, RAAS and CCB in Management of Hypertension

Narsingh Verma, Anuj Maheshwari, Mayank Agrawal

ABSTRACT

The renin-angiotensin-aldosterone system (RAAS) is a hormonal cascade that functions in the homeostatic control of arterial pressure, tissue perfusion, and extracellular volume. The classical RAAS cascade begins with the production of renin. Renin converts angiotensinogen to Angiotensin-I (Ang-I). Ang-I requires further activation by angiotensin-converting enzyme (ACE), to form the Angiotensin-II (Ang-II). Ang-II acts by binding to two G-protein coupled receptors, AT1 and AT2; it also acts on the adrenal cortex and causes the release of aldosterone.

The current view of the RAAS also includes a local (tissue) RAAS, alternative pathways for Ang-II synthesis (ACE independent), the formation of other biologically active angiotensin peptides (Ang-III, Ang-IV, Ang[1–7]), and additional angiotensin binding receptors (AT4, Mas) that participate in cell growth differentiation, hypertrophy, inflammation, fibrosis, and apoptosis. Activation of local RAAS and local Ang-II production requires the binding of renin or prorenin to the specific (pro) renin receptor (PRR), located on cell surfaces.

Angiotensin-converting enzyme inhibitors (ACEIs) and Ang-II receptor blockers (ARBs) are used to block the RAAS. Apart from potent antihypertensives, ACEIs and ARBs have significant cardiovascular and renal therapeutic benefits.

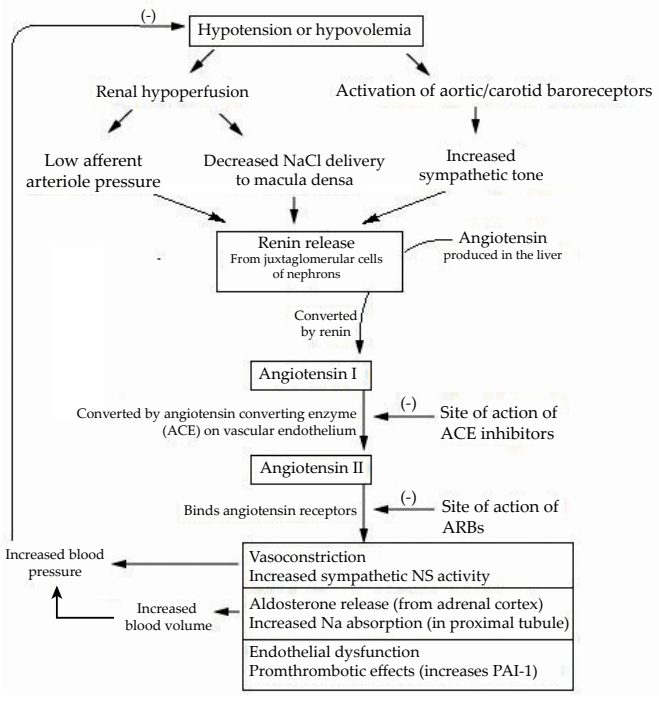


Fig. 1: RAAS

Several types of calcium channels occur (P/Q, N, R, L and T type), with a number of classes of blockers, but almost all of them preferentially or exclusively block the L-type voltage-gated calcium channel. In coronary and peripheral arterial smooth muscle and the heart, inhibition of Ca^{2+} entry blunts the ability of Ca^{2+} to serve as an intracellular messenger. Thus, CCBs are smooth-muscle dilators and have a negative inotropic and negative chronotropic effect on the working myocardial cells of the atria and ventricles.

In 1898, Tiegerstedt and Bergman found a pressor substance from crude saline extracts of the kidney and named it renin. In1940, Braun-Menéndez et al. from Argentina and Page and Helmer from U.S. reported that renin was an enzyme. Renin acted on a plasma protein substrate to catalyse the formation of the actual pressor peptide; that was named hypertension by the old group and angiotonin by the latter. The protein substrate was later renamed as angiotensinogen (Skeggs et al, 1956), and the peptide as angiotensin (Braun-Menendez and Page, 1958). Skeggs et al. demonstrated two distinct forms of angiotensin: angiotensin I (Ang-I, a decapeptide) and angiotensin II (Ang-II, an octapeptide). The relationship between Ang-II and aldosterone was hypothesised by Gross (1958) and subsequently confirmed by Davis (1959). The classical RAAS hormonal cascade begins with the production of renin. Renin, an aspartyl protease produced by the juxtaglomerular cells of the kidney, regulates the initial and rate-limiting step of the RAAS. Renin converts angiotensinogen (an alpha-2-globulin mainly synthesised by the liver) to Ang-I (inactive). Ang-I requires further activation by angiotensin-converting enzyme (ACE, a membrane-bound zinc metalloprotease, synthesised in pulmonary endothelium), a dipeptidyl carboxypeptidase, to form the Ang-II (biologically active). AngII acts by binding to two heptahelical GPCRs, AT1 and AT2. Ang-II acts on the adrenal cortex and causes the release of aldosterone.

Renin secretion from juxtaglomerular cells is controlled predominantly by three pathways:

i. Macula densa pathway

ii. Intra renal baroreceptor pathway

iii. β1 adrenergic receptor pathway

An increased perfusion of the juxtaglomerular apparatus

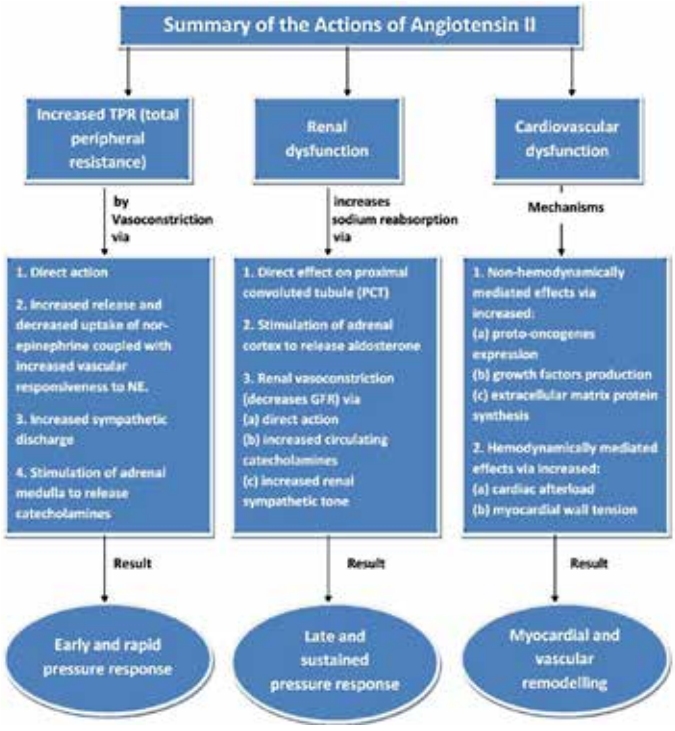


Fig. 2: Effects of Angiotensin II

inhibits the renin release, through a negative feedback mechanism.

ACTIONS OF ANG-II

Under normal conditions, angiotensin II has following effects:

- Vasoconstriction via GCPR AT1 and vascular smooth muscle hypertrophy through protein kinase C. Constriction of the efferent arterioles in kidney leads to increased perfusion pressure in the glomeruli.
- Ang-II has a direct effect on the proximal tubules to increase Na+ reabsorption.
- It stimulates the adrenal cortex to release aldosterone,which acts on kidney tubules, leading tosodium and chloride retention and potassium excretion.
- Stimulation of the posterior pituitary to release vasopressin (antidiuretic hormone, ADH) and secretion of ACTH from the anterior pituitary. It also potentiates the release of norepinephrine by direct action on postganglionic sympathetic fibres.
- Ang-II increases thirst sensation (dipsogen) through the subfornical organ of the brain, decreases the response of the baroreceptor reflex, and enhances the desire for salt.
- Angiotensin II has prothrombotic potential through adhesion and aggregation of platelets and stimulation of PAI-1 and PAI-2.
- It stimulates the proto-oncogenes c-fos, c-jun, c-myc, transforming growth factor beta (TGF- β), which contributes to ventricular remodelling and ventricular hypertrophy of the heart through fibrogenesis and apoptosis (programmed cell death).

The understanding of the RAS has expanded over the past few years. The current view of the RAS also includes a local (tissue) RAS, alternative pathways for Ang-II synthesis (ACE independent), the formation of other biologically active angiotensin peptides (Ang-III, Ang-IV, Ang[1–7]), and additional angiotensin binding receptors (angiotensin subtypes 1, 2, and 4 [AT1, AT2, AT4]; Mas) that participate in cell growth differentiation, hypertrophy, inflammation, fibrosis, and apoptosis.

COMPONENTS OF THE RAAS

The heavy arrows show the classical pathway, and the light arrows indicate alternative pathways. ACE, angiotensin- converting enzyme; Ang, angiotensin; AP, aminopeptidase; E, endopeptidases; IRAP, insulin-regulated aminopeptidases; PCP, prolylcarboxylpeptidase; PRR, (pro)renin receptor. Receptors involved: AT1, AT2, Mas, AT4, and PRR.

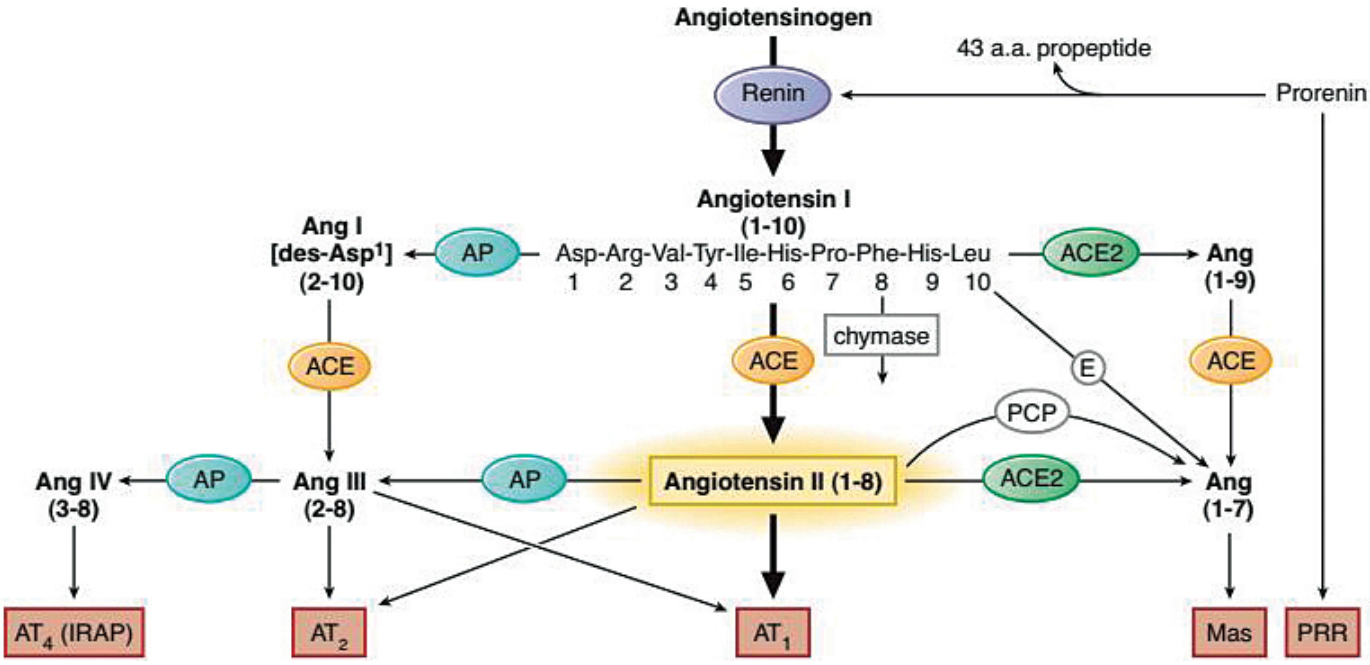
Source: Brunton L, Chabner B, Knollman B. Goodman and Gilman's the pharmacological basis of therapeutics. 12ed. McGraw Hill Medical; 2011.

ACE-related Carboxypeptidase, now termed ACE2 converts Ang-I to Ang(1–9) and Ang-II to Ang(1–7). The physiological significance of ACE2 is still uncertain; it may serve as a counter- regulatory mechanism to oppose the effects of ACE. ACE2 is not inhibited by the standard ACE inhibitors and has no effect on bradykinin. In animals, reduced expression of ACE2 is associated with hypertension, defects in cardiac contractility, and elevated levels of AngII.

Angiotensin III (Ang-III), also called Ang(2–8) is only 25% and 10% as potent as Ang-II in elevating blood pressure and stimulating the adrenal medulla,respectively. Angiotensin IV (Ang-IV), also called Ang(3–8)has potent effects on memory and cognition. Other actions include renal vasodilation, natriuresis, neuronal differentiation, hypertrophy, inflammation, and extracellular matrix remodelling. In animal models, Ang(1–7) induces vasodilation, promotes NO production, potentiates the vasodilatory effects of bradykinin; it has anti- angiogenic, anti- proliferative, and anti- thrombotic effects; and is cardioprotective in cardiac ischemia and heart failure.

The modern view of the RAS also includes the local (tissue) RAS, which is an Ang-II producing system that causes hypertrophy, inflammation, remodelling, and apoptosis. Activation of local RAS and local Ang-II production require the binding of renin or prorenin to the specific (pro)renin receptor (PRR), located on cell surfaces. Prorenin is no longer considered the inactive precursor of renin. Prorenin is capable of activating local (tissue) RAS and Ang-II dependent and independent events that may contribute to organ damage.

Angiotensinogen may be converted to Ang-I or directly to Ang-II by cathepsin G and tonin. Other enzymes that



convert Ang-I to Ang-II include cathepsin G, chymostatin-sensitive Ang-II generating enzyme, and heart chymase. Chymase contributes to the local tissue conversion of Ang-I to Ang-II, particularly in the heart and kidneys.

RAAS IN HYPERTENSION

Inhibition of RAAS lowers systemic vascular resistance and mean, diastolic, and systolic blood pressures in various hypertensive states except when high blood pressure is due to primary aldosteronism. RAAS blockers cause systemic arteriolar dilation and increase the compliance of large arteries, which contributes to a reduction of systolic pressure. The renal vessels are extremely sensitive to the vasoconstrictor actions of Ang-II;RAAS inhibition increases renal blood flow via vasodilation of the afferent and efferent arterioles. Cardiac function in patients with uncomplicated hypertension islittle changed, although stroke volume and cardiac output may increase slightly with sustained treatment. Baroreceptor function and cardiovascular reflexes are not compromised, and responses to postural changes and exercise are little impaired. Aldosterone secretion is reduced, but not seriously impaired, by ACE inhibitors.

RAAS IN LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

Ang-II is an important mediator of cardiac remodelling; it stimulates fibroblasts to produce collagen, causes hypertrophy of cardiac myocytes and promotes cardiac fibrosis.Unless contraindicated, RAAS inhibitors should be given to all patients with impaired left ventricular systolic function whether or not they have symptoms of overt heart failure. Inhibition of RAAS commonly reduces heart rate, afterload, systolic wall stress, cardiac output, cardiac index increase, stroke work and stroke volume. Renovascular resistance falls sharply, and renal blood flow increases. Natriuresis occurs as a result of the improved renal hemodynamics, the reduced stimulus to the secretion of aldosterone by Ang-II, and the diminished direct effects of Ang-II on the kidney. The excess volume of body fluids contracts, which reduces venous return to the right side of the heart. A further reduction results from venodilation and an increased capacity of the venous bed.

RAAS IN ACUTE MYOCARDIAL INFARCTION

After AMI, RAAS activation occurs as a compensatory and adaptive response to maintain blood pressure and systemic perfusion. Ang-II, being positively inotropic, increases myocardial oxygen demand, but causes vasoconstriction of the coronary vasculatures at the same time, thereby exacerbating myocardial ischaemia (after myocardial infarction), and may result in irreversible myocardial damage. Ang-II also has a direct toxic effect on myocytes and stimulates myocyte hypertrophy, the growth of vascular smooth muscle cells and fibroblasts. Moreover, loss of myocytes triggers abnormal deposition of fibrillar collagen in the heart. All these factors lead to progressive ventricular dysfunction after myocardial infarction.Unless contraindicated (e.g., cardiogenic shock or severe hypotension), RAASinhibitors should be started immediately during the acute phase of myocardial infarction and can be administered along with thrombolytics, aspirin, and β adrenergic receptor antagonists. In high- risk patients (e.g., large infarct, ventricular systolic dysfunction), RAAS inhibition should be continued long term.

RAAS IN ATHEROSCLEROSIS

Ang-II promotes the generation of oxidative stress in the vasculatures, which appears to be a key mediator of endothelial dysfunction, endothelial cell apoptosis and lipoprotein peroxidation. Ang-II also induces cellular adhesion molecules, and chemotactic and proinflammatory cytokines, all of which participate in the induction of an inflammatory response in the vessel wall. Ang-II triggers responses in vascular smooth muscle cells that lead to proliferation, migration and a phenotypic modulation, resulting in the production of growth factors and extracellular matrix. While all these effects

contribute to neointima formation and development of atherosclerotic lesions, Ang-II may also be involved in acute complications of atherosclerosis by promoting plaque rupture and a hyper thrombotic state.

RAAS IN DIABETIC NEPHROPATHY

Hyperglycaemia is associated with increased production of Ang-II in glomerular mesangial cells. Ang-II increases the expression of transforming growth factor, which stimulates the mesangial matrix synthesis. It also decreases mesangial matrix degradation through promoting synthesis of type 1 plasminogen activator inhibitor (PAI-1) and inhibiting activity of mesangial cell collagenase. Other mechanisms of renal injury include the production of reactive oxygen species (ROS) and renal fibrosis by up-regulating the expression of Rho A and activating Rho/Rho kinase pathway. These structural changes lead to microalbuminuria, followed by macroalbuminuria and finally chronic renal failure.

CALCIUM CHANNEL BLOCKERS

Several types of calcium channels occur (as shown in the table given below), with a number of classes of blockers, but almost all of them preferentially or exclusively block the L-type voltage-gated calcium channel.

MECHANISMS OF ACTION

Voltage-sensitive Ca2+ channels (L-type or slow channels) mediate the entry of extracellular Ca2+ into smooth muscle and cardiac myocytes and sinoatrial (SA) and atrioventricular (AV) nodal cells in response to electrical depolarization. In both smooth muscle and cardiac myocytes, Ca2+ is a trigger for contraction, albeit by different mechanisms.The entry of extracellular Ca2+ is necessaryfor initiating the contraction of cardiac myocytes (Ca2+-induced Ca2+ release). The release of Ca2+ from intracellular storage sites also contributes to contraction of the vascular smooth muscle, particularly in some vascular beds. Ca2+ channel antagonists, also called Ca2+ entry blockers, inhibit Ca2+ channel function. In vascular smooth muscle, this leads to relaxation, especially in arterial beds. These drugs alsoproduce negative inotropic and chronotropic effects in the heart. They directly reduce aldosterone production by blocking the calcium signal on adrenal cortex cells, which corroborates to lower blood pressure.

The vascular and cardiac effects of some CCBs are summarised in the next Table.

CCB IN HYPERTENSION

Except for nimodipine (whichwas originally developed for treating hypertension but isapproved for subarachnoid haemorrhage) and the short-actingnifedipine (i.e., the immediate-release formulation), all CCBsare approved by the US FDA for lowering blood pressureeither alone or in combination with other antihypertensiveagents.

There are certain newer CCB which has been developed in Japan like Cilnidipine and Benidipine which are not yet approved by US FDA but we have data that clinidipine has lower incidence of Pedal oedema in comparison to Amlodipine. Cilnidipine has been extensively studied by researchers in its preclinical and clinical development phases. Renoprotective, neuroprotective and cardioprotective effects of cilnidipine have been demonstrated in clinical practice or animal examinations. It is noticed that cilnidipine may have pleiotropic effects besides N-type Ca^{2+} channel-blocking action. Therefore, the inhibition of N-type Ca^{2+} channels may provide a new strategy for the treatment of cardiovascular diseases. Benidipine is long acting CCB which blocks L, T and N channels and said to be have cardioprotective and renoprotective effects.

CCB IN STABLE ANGINA

The antianginal effects of CCBs result from either dilation of the coronary artery and the subsequent increase of oxygen supply or decreased oxygen demand (secondary to a decrease in arterial blood pressure, myocardial contractility, or heart rate), or both. Owing to their coronary dilating effects, CCBs are also useful for treating variant angina (also known as Prinzmetal angina, which is caused by transient localised coronary artery spasm.

CCB IN ACUTE CORONARY SYNDROMES

Available evidence suggests that CCBs have a limited role in the management of patients with acute coronary syndromes (ACS), which include unstable angina, non-ST-segment elevation myocardial infarction (STEMI), and STEMI. No CCB has been shown to reduce mortality, and in certain patients with ACS, the short-acting CCBs, may even be harmful.

CCB IN HEART FAILURE

Available evidence points to the lack of benefit of CCBs in patients with systolic heart failure. These agents do not improve exercise tolerance, quality of life, or survival. The negative inotropic effects of CCBs, especially verapamil, may worsen the symptoms in patients with severe left ventricular dysfunction. Based on these observations, the use of CCBs in patients with systolic heart failure was not recommended in the current guidelines.

CCB IN CARDIAC ARRHYTHMIAS

Diltiazem and verapamil are useful antiarrhythmic agents in the management of certain arrhythmias, especially supraventricular tachyarrhythmias. These drugs preferentially affect slow-response myocardial tissues (i.e., sinoatrial and atrioventricular nodes, which depend on calcium currents to generate slowlypropagating action potentials), in contrast to fast-response myocardial tissues (i.e., the atria, specialised intranodal conducting system, the ventricles, and accessory pathways), which rely on sodium channels.

REFERENCES

1. Ma TK, Kam KK, Yan BP, Lam YY.Renin-angiotensin-aldosterone system blockade for cardiovascular diseases: current status. *Br J Pharmacol* 2010; 160:1273-92.
2. Garg M, Angus PW, Burrell LM, Herath C, Gibson PR, Lubel JS. Review article: the pathophysiological roles of

the renin-angiotensin system in the gastrointestinal tract. *Aliment Pharmacol Ther* 2012; 35:414-28.

3. Brunton L, Chabner B, Knollman B. Goodman and Gilman's the pharmacological basis of therapeutics. 12ed. McGraw-Hill Medical; 2011.
4. Te Riet L, van Esch JH, Roks AJ, van den Meiracker AH, Danser AH.Hypertension: renin-angiotensin-aldosterone system alterations. *Circ Res* 2015; 116:960-75.
5. Snutch TP, Peloquin J, Mathews E, McRory JE. Molecular Properties of Voltage-Gated Calcium Channels. Madame Curie Bioscience Database [Internet]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK6181/
6. Elliott WJ, Ram CV. Calcium channel blockers. *J Clin Hypertens (Greenwich)* 2011; 13:687-9.
7. Li YR. Cardiovascular diseases. From Molecular Pharmacology toevidence-Based Therapeutics.John Wiley & Sons, Inc., Hoboken, New Jersey;2015.