Antihypertensive agents: Introduction, Mechanism of Action

SUBJECT- PHARMACEUTICAL CHEMISTRY-VII (4T2)

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Introduction

- Hypertension is a very common disorder, particularly past middle age. It is not a disease in itself, but is an important risk factor for cardiovascular mortality and morbidity.
- It is defined as either..

  “ A sustained systolic blood pressure of greater than 140 mm Hg or a sustained diastolic blood pressure of greater than 90 mm Hg.”

- Epidemiological studies have confirmed that higher the pressure (systolic or diastolic or both) greater is the risk of cardiovascular disease.
- Sympathetic, renin-angiotensin systems and Potential-dependent calcium channels may or may not be overactive, but they do contribute to the tone of blood vessels and cardiac output in hypertensives, as they do in normotensives. Many antihypertensive drugs interfere with these regulatory systems at one level or the other, resulting lowering the blood pressure.
- **Antihypertensives** are the drugs, that are used to treat hypertension (high blood pressure).

There are several glaring evidences available today that may attribute to certain types of hypertension, for instances :

1. **Renin-angiotensin system**
2. **Direct renin inhibitors (DRIs):** block renin action—interfere with generation of Angiotensin-I from angiotensinogen (rate limiting step).
3. **Angiotensin receptor antagonists-** Antagonize the action of Angiotensin-II on target cells.
4. **Aldosterone antagonists**—block mineralocorticoid receptors
5. **Potential-dependent calcium channels**
6. **Sympathetic blockers (β-blockers, adrenergic Neuron blockers, central sympatholytic)**—decrease renin release.

	Systolic Blood Pressure (mm Hg)	Diastolic Blood Pressure (mm Hg)
Normal	120	80
Pre Hypertensive	120-139	80-89
Stage 1 Hypertension	140-159	90-99
Stage 2 Hypertension	≥160	≥100

Renin-angiotensin system

- The renin-angiotensin system is a complex, highly regulated pathway that is integral in the regulation of blood volume, electrolyte balance, and arterial blood pressure.
- It consists of two main enzymes, renin and angiotensin converting enzyme (ACE), the primary purpose of which is to release angiotensin-II from its endogenous precursor, angiotensinogen.
- Angiotensin-II is a potent vasoconstrictor that affects peripheral resistance, renal function, and cardiovascular structure.
- Angiotensinogen is an α2-globulin with a molecular weight of 58,000 to 61,000 Daltons. It contains 452 amino acids, is abundant in the plasma, and is continually synthesized and secreted by the liver.
- A number of hormones, including glucocorticoids, thyroid hormone, and angiotensin-II, stimulate its synthesis.

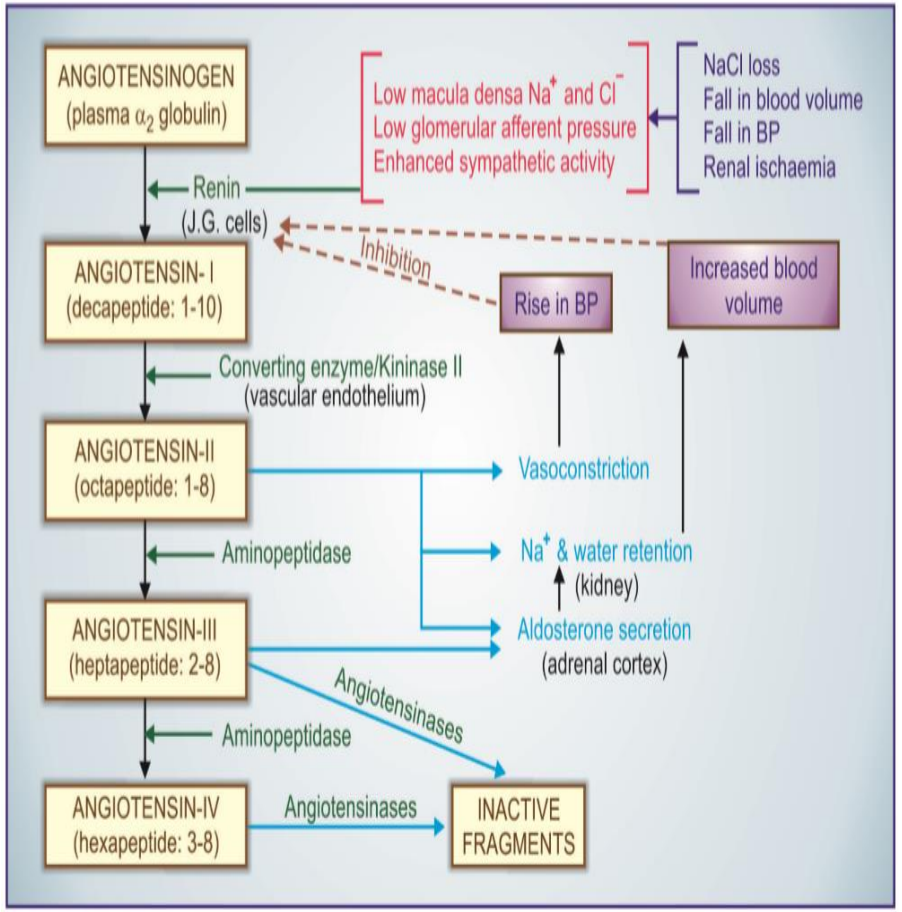


Fig. 36.1: Physiological regulation of electrolyte balance, plasma volume and blood pressure by the renin-angiotensin system

- The most important portion of this compound is the N-terminus, specifically the Leu10-Val11 bond. This bond is cleaved by renin and produces the decapeptide angiotensin-I.
- The Phe8-His9 peptide bond of angiotensin-I is then cleaved by ACE to produce the octapeptide angiotensin-II.
- Aminopeptidase can further convert angiotensin-II to the active heptapeptide angiotensin-III by removing the N-terminal arginine residue. Further actions of carboxypeptidases, aminopeptidases, and endopeptidases result in the formation of inactive peptide fragments.
- An additional compound can be formed by the action of a prolyl-endopeptidase on angiotensin-I. Cleavage of the Pro7-Phe8 bond of angiotensin-I produces a heptapeptide known as angiotensin 1-7.

Actions and Properties of Renin-Angiotensin Pathway Components

- Renin is an aspartyl protease that determines the rate of angiotensin-II production. It is a much more specific enzyme than ACE. Its primary function is to cleave the leucine-valine bond at residues 10 and 11 of angiotensinogen.
- The stimulation of renin release is controlled very closely by hemodynamic, neurogenic, and humoral signals.
- Hemodynamic signals involve the renal juxtaglomerular cells. These cells are sensitive to the hemodynamic stretch of the afferent glomerular arteriole. An increase in the stretch implies a raised blood pressure and results in a reduced release of renin, whereas a decrease in the stretch increases renin secretion.
- Additionally, these cells also are sensitive to NaCl flux across the adjacent macula densa. Increases in NaCl flux across the macula densa inhibit renin release, but decreases in the flux stimulate release. Furthermore, neurogenic enhancement of renin release occurs via activation of β1 receptors. Finally, a variety of hormonal signals influence the release of renin.

- Angiotensin-II is the dominant peptide produced by the renin-angiotensin pathway. It is a potent vasoconstrictor that increases total peripheral resistance through a variety of mechanisms:
  - Direct vasoconstriction
  - Enhancement of both catecholamine release and neurotransmission within the peripheral nervous system
  - Increased sympathetic discharge.
- The result of all these actions is a rapid pressor response. Angiotensin-II directly increases sodium reabsorption in the proximal tubule. It also alters renal hemodynamic and causes the release of aldosterone from the adrenal cortex.
- Finally, angiotensin-II causes the hypertrophy and remodelling of both vascular and cardiac cells through a variety of hemodynamic and nonhemodynamic effects.

Role of the Renin-Angiotensin Pathway in Cardiovascular Disorders

- Because the renin-angiotensin pathway is central to the maintenance of blood volume, arterial blood pressure, and electrolyte balance, abnormalities in this pathway can contribute to a variety of cardiovascular disorders. Specifically, overactivity of this pathway can result in hypertension or heart failure via the mechanisms previously described.
- Angiotensin-II produces the majority of the effects attributed to the renin-angiotensin pathway, compounds that can block either the synthesis of angiotensin-II or the binding of angiotensin-II to its receptor should attenuate the actions of this pathway.
- Indeed, enzyme inhibitors of both renin and ACE, as well as receptor antagonists of angiotensin-II, have all been shown to produce beneficial effects in decreasing the actions of angiotensin-II.

Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors)

The ACE inhibitors are one of the first choice drugs in all grades of essential as well as renovascular hypertension (except those with bilateral renal artery stenosis). Most patients require relatively lower doses (enalapril 2.5–10 mg/day or equivalent) which are well tolerated. They are the most appropriate antihypertensives in patients with diabetes, nephropathy (even nondiabetic), left ventricular hypertrophy, CHF, angina and post MI cases.

Mechanism of Action

- The ACE inhibitors attenuate the effects of the renin angiotensin system by inhibiting the conversion of angiotensin-I to angiotensin-II.
- They also inhibit the conversion of angiotensin-I to angiotensin-III; however, this action has only a minor role in the overall cardiovascular effects of these drugs.

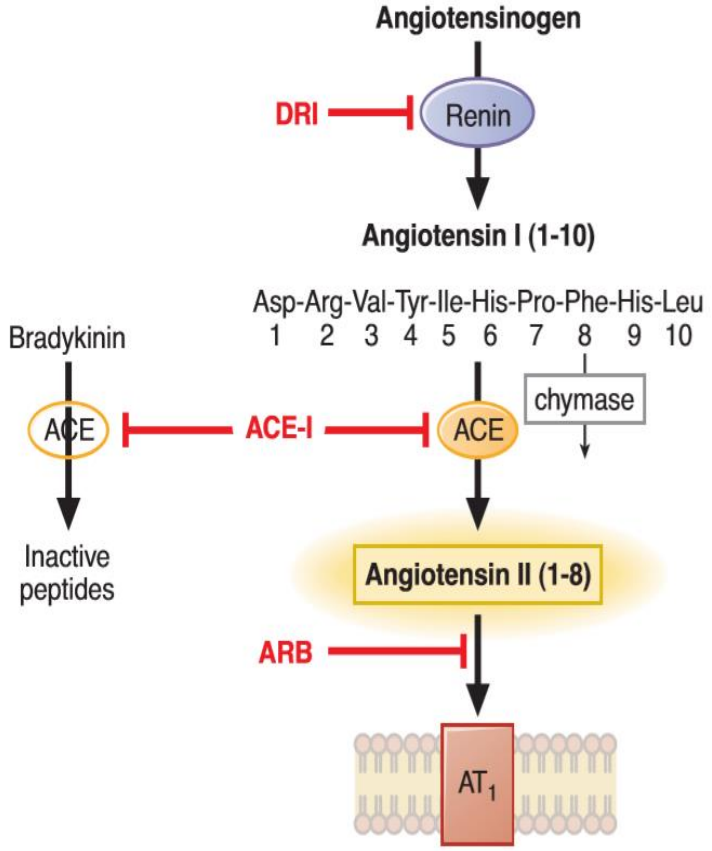


Figure 26-8. *Inhibitors of the RAS.* ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DRI, direct renin inhibitor.

Angiotensin-II Receptor Blockers (ARBs)

- The angiotensin-II receptor exists in at least two subtypes: type 1 (AT1) and type 2 (AT2). The AT1 receptors are located in brain, neuronal, vascular, renal, hepatic, adrenal, and myocardial tissues and mediate the cardiovascular, renal, and central nervous system (CNS) effects of angiotensin-II.
- All currently available ARBs are 10,000 fold more selective for the AT1 receptor subtype and act as competitive antagonists at this site. In terms of relative affinity for the AT1 receptor, telmisartan, valsartan, and losartan have the affinity.
- All ARBs prevent and reverse all of the known effects of angiotensin-II, including rapid and slow pressor responses, stimulatory effects on the **peripheral sympathetic nervous** system, CNS effects, **release of catecholamines**, secretion of aldosterone, direct and indirect renal effects, and all growth-promoting effects.

Direct Renin Inhibitors (DRIs)

Renin is a very specific enzyme that recognizes the Pro7-Phe8-His9- Leu10-Val11Ile12-His13-Asn14 octapeptide sequence of angiotensinogen. Initial attempts to design renin inhibitors focused upon peptide analogs designed to mimic portions or all of this sequence.

- Aliskiren directly inhibits renin, thereby preventing the formation of angiotensin-I and angiotensin-II. As previously mentioned, this is the rate-limiting step in this pathway and is highly regulated by hemodynamic, neurogenic, and humoral signals.

Studies have shown that there are two potential advantages of inhibiting this enzyme as compared to inhibiting ACE or using an ARB. Inhibition of the renin-angiotensin pathway through any of these mechanisms has been shown to cause a compensatory increase in renin concentrations; however, unlike ACE inhibitors and ARBs, the ability of renin inhibitors to directly bind to the enzyme blocks the increases in plasma renin activity seen with ACE inhibitors and ARBs.

Calcium channel blockers

- Calcium is a key component of the excitation-contraction coupling process that occurs within the cardiovascular system.
- It acts as a cellular messenger to link internal or external excitation with cellular response. Increased cytosolic concentrations of Ca^{2+} result in the binding of Ca^{2+} to a regulatory protein, either troponin C in cardiac and skeletal muscle or calmodulin in vascular smooth muscle.
- This initial binding of Ca^{2+} uncovers myosin binding sites on the actin molecule, and subsequent interactions between actin and myosin result in muscle contraction. All of these events are reversed once the cytosolic concentration of Ca^{2+} decreases.

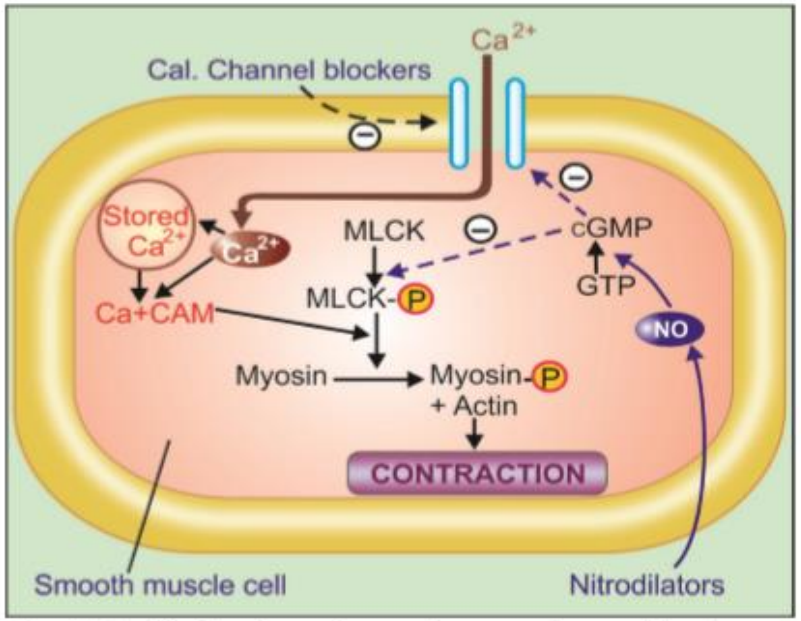


Fig. 39.3: Mechanism of vascular smooth muscle relaxant action of nitrodilators like glyceryl trinitrate and calcium channel blockers; (- - - →) Inhibition
CAM—Calmodulin; NO—Nitric oxide; MLCK—Myosin light chain kinase; MLCK-P—Phosphorylated MLCK; GTP—Guanosine triphosphate; cGMP—Cyclic guanosine monophosphate

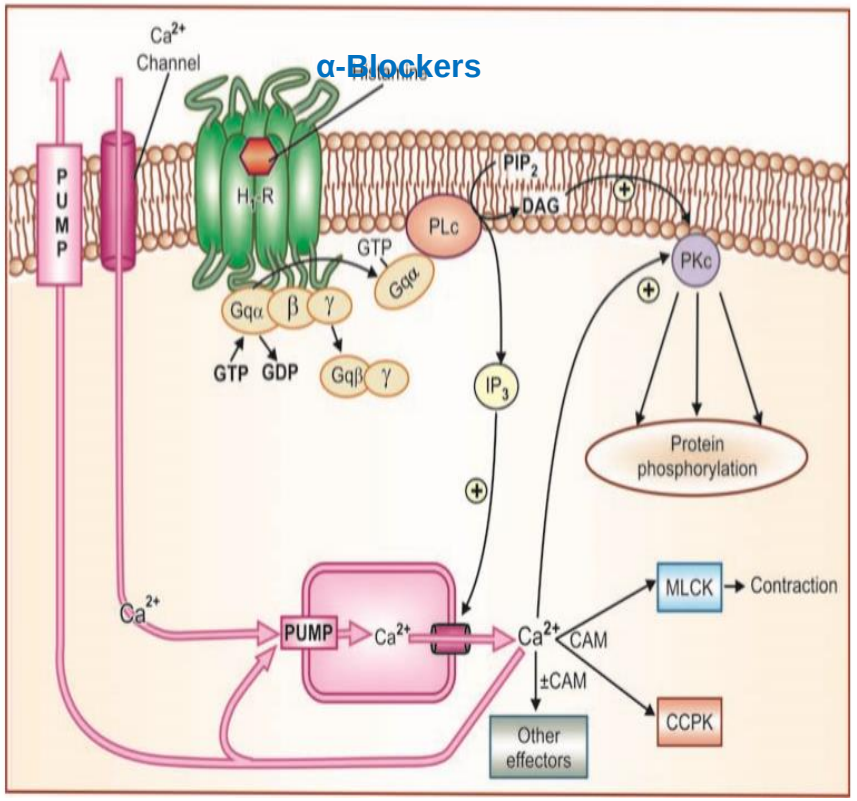
Adrenergic blockers (α and β -Blockers)

β–Blockers-

These drugs inhibit adrenergic responses mediated through the β receptors. All β blockers are competitive antagonists. Propranolol blocks β1 and β2 receptors, but has weak activity on β3 subtype. It is also an inverse agonist: reduces resting heart rate as well. Some β blockers like metoprolol, atenolol, etc. preferentially block β1 receptors, while few others have additional α1 receptor blocking and /or vasodilator properties.

α-Blockers-

These drugs block the effect of sympathetic nerves on blood vessels by selectively binding to α1-adrenoceptors located on the vascular smooth muscle (VSM), which then stimulate the Gq protein, activating smooth muscle contraction through the IP3 signal transduction pathway.



Thank You...