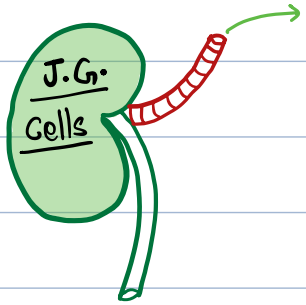
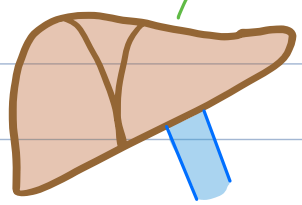
Renin Angiotensin Aldosterone System (RAAS):

regulator of blood volume, electrolyte & blood pressure homeostasis.



↓ blood flow through renal artery

stimulates JG cells to secrete renin

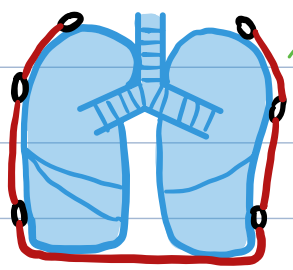


synthesized by

Angiotensinogen

renin

Angiotensin I (A.T-I)



present in alveoli

angiotensin converting enzyme (ACE)

AT-II

(very potent vasoconstrictor)

AT-II Receptors are found on the vascular smooth muscles

Smooth muscle contraction

Vasoconstriction

increase in total peripheral resistance

increase BP

AT-II stimulates the Posterior pituitary

Posterior pituitary releases ADH

ADH acts on the Kidney (Collecting duct) to increase water reabsorption

increased blood volume

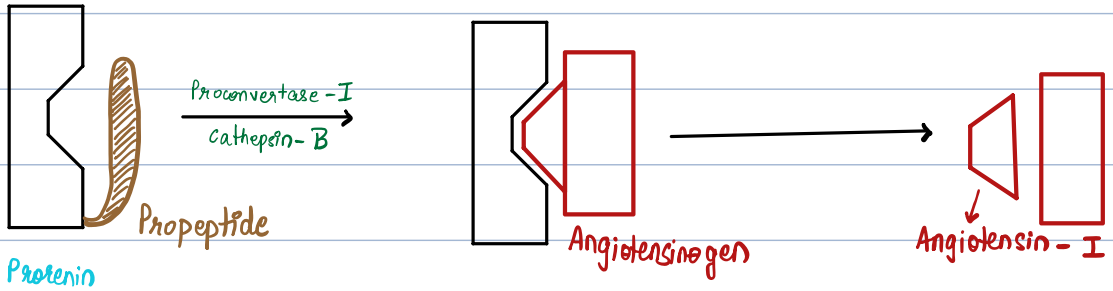
AT-II stimulates the zona glomerulosa cells on adrenal cortex

release of aldosterone

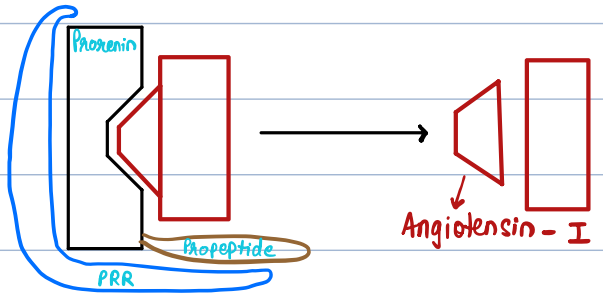
aldosterone acts at the DCT of Kidneys

increases water reabsorption by increasing Na^+ reabsorption

increased blood volume



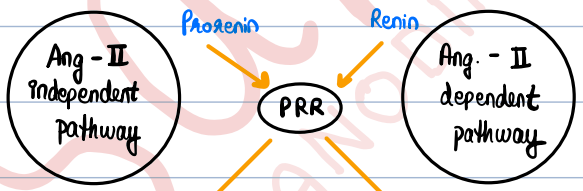
Enzymatic activation of prorenin



Non-enzymatic activation of prorenin

⟹ plays a major role in local RAS where prorenin exerts effects via

- Ang II dependent
- Ang II independent pathways



Intracellular signalling

Nonenzymatic activation / augmentation

Angiotensinogen → Angiotensin I —ACE→ Angiotensin II

Activation of MAP kinase, PAI-1, JAK-STAT, Trans F, protooncogenes

Cell growth, fibrosis, apoptosis, remodelling of myocardium / vascular muscle, nephropathy, retinopathy

AT1 receptors	AT2 receptors
→ present in most of the tissues	→ expressed in fetal tissues; in adults – vascular endothelium, adrenal medulla, kidney, some brain areas

ACE - Inhibitors (ACE-I): inhibit ACE enzyme

∴ conversion of AT-I to AT-II is blocked ⇒ decrease in AT-II

- no vasoconstriction → vasodilation → decreased total peripheral resistance → ↓ BP
- non-stimulation of posterior pituitary → ↓ ADH release → ↓ water reabsorption → ↓ blood volume → ↓ BP
- non-stimulation of zona glomerulosa of the adrenal cortex → ↓ aldosterone
  - → decreased K^+ excretion → hyperkalemia (adverse effect of ACE-I)
  - → ↓ Na^+ reabsorption → ↓ water reabsorption → ↓ blood volume → ↓ BP

AT-II Receptor Blockers (ARBs):

→ work at all sites of action of AT-II ⇒ Vascular smooth muscles
⇒ posterior pituitary
⇒ zona glomerulosa of adrenal cortex

↓ BP

ACE-I / ARBs ⊖ AT-II ↓

- vasoconstriction ↓ → ↑ total peripheral resistance ↓ → ↑ afterload ↓ → ↑ stress on myocardium ↓
- ↓ aldosterone ↑ → ↓↑ Na^+, water reabsorption & ↑ K^+ excretion ↓ → ↑ blood volume ↓ → ↓↑ preload → ↑EDV ↓ → ↑ stress on myocardium ↓
- ADH ↑ ↓ → ↓↑ Na^+, water reabsorption & ↑ K^+ excretion ↓ → ↑ blood volume ↓ → ↓↑ preload → ↑EDV ↓ → ↑ stress on myocardium ↓

ACE-I: "pril"

- Benzapril
- Captopril
- Enalapril
- Lisinopril

ARBs: "sartan"

- Candesartan
- Losartan
- Valsartan
- Irbesartan
- Olmesartan
- Telmisartan
- Eprosartan

ACE - I

Sulfhydryl ACE-I

- Captopril

Carboxyl ACE-I

- Lisinopril
- Enalapril
- Perindopril
- Ramipril

Phosphinyl ACE-I

- Fosinopril

C - Cough
A - Angioedema
P - Prodrug (except captopril & lisinopril)
T - Taste disturbances
O - Orthostatic hypotension
P - Pregnancy C/I
R - b/l renal artery stenosis C/I
I - Increases K^+
L - lower the formation of Ang-II (m.o.A)

ISHITA KANODIA

Indications:

1. Hypertension

(Some African-Americans & older individuals ⇒ low renin hypertension ⇒ Can't use these ACE-I, ARBs)

2. Coronary Artery Disease (h/o MI)
3. Heart failure (CHF)

} ⇒ reducing stress on myocardium

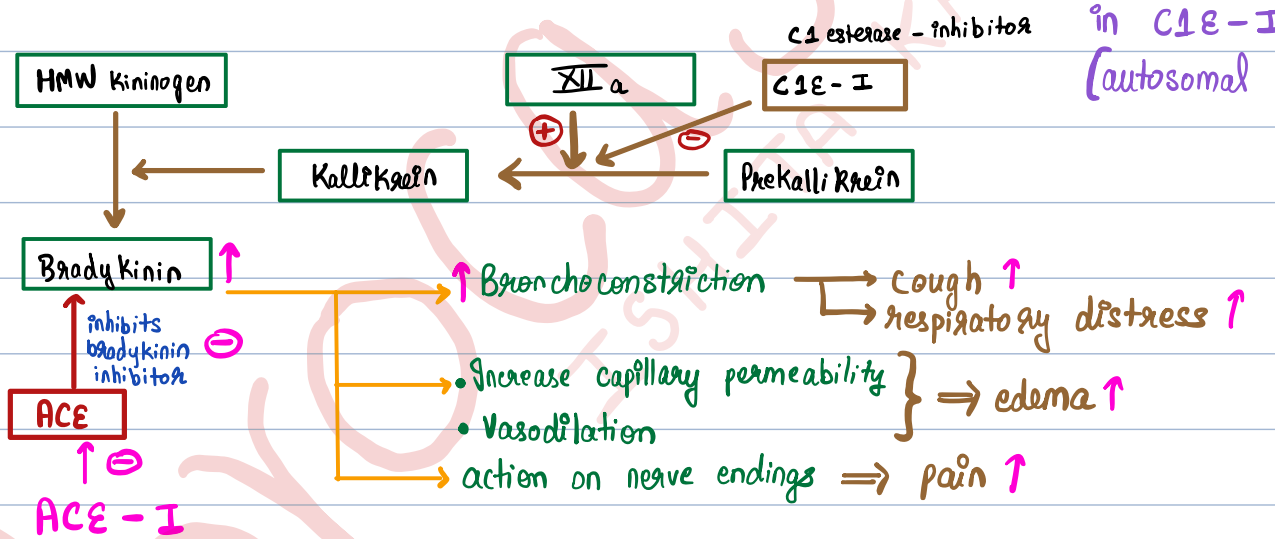
H^2D PCR

4. Proteinuric kidney Disease (eg: diabetic nephropathy) ⇒ to decrease protein in urine
5. Reduce Cardiac Remodelling ⇒ by decreasing stress on myocardium by decreasing preload & afterload. (h/o MI, chronic HTN)
6. Diabetic nephropathy & retinopathy (ratio of circulating prorenin : renin is markedly elevated in diabetes which may be causative in nephropathy & retinopathy)

Adverse Effects:

1. Hyperkalemia
2. Hypotension
3. Angioedema & dry cough (severe reaction to ACE-I)

∴ ACE-I are contraindicated in C1E-I deficiency (autosomal dominant trait)



4. First-dose hypotension
5. Dysguesia (altered taste sensation)
6. Granulocytopenia

H^2AD GF

Contraindications:

CLAP BS²

- C1E-I deficiency
- Angioedema
- Pregnancy (teratogenic)
- Bilateral renal artery stenosis
- Severe CKD
- Serum creatinine > 3.5 mg/dL

- Caution while giving multiple anti-HTN drugs ⇒ hypotension may occur
- K^+ sparing diuretics (aldosterone antagonists) with ACE-I/ARBs ⇒ severe hyperkalemia
- NSAIDs increase Na^+ & H_2O retention & counteract anti-hypertensive action of ACE-I/ARBs
- Lithium (used in bipolar disease) toxicity with ACE-I/ARBs since they decrease Lithium excretion.

Advantages of ARBs:

- safe in diabetics, asthmatics, PVD
- lack of postural hypotension
- prevention of secondary hyperaldosteronism
- renal blood flow well-maintained
- no rebound HTN

Drug Interactions of ACE-I:

→ diuretics synergise with hypotensive action
→ Non-systemic antacids reduce the bioavailability of ACE-I
→ NSAIDs may impair the hypotensive effects
→ K^+ sparing diuretics & K^+ supplements – leads to hyperkalemia
→ Plasma levels of lithium & digoxin elevated

Adverse Effects of ARBs: (well-tolerated)

- Hypotension
- Hyperkalemia
- Fetopathic

– Free from cough & dysgeusia

Combination of ACE-I with ARBs : More complete suppression of RAS

- Ang-II generated by non ACE-effect is blocked by ARBs (which is not blocked by ACE-I)
- ARBs enhance unblocked AT2 receptor mediated effects — prevented by ACE inhibition.

Direct renin Inhibitor - Aliskiren (C/I = pregnancy)

→ binds selectively to catalytic site of renin ⟹ chain of RAS is interrupted.

→ beneficial in CHF, has renoprotective effect

→ side effects - dyspepsia - loose motions - dizziness
- abdominal pain - headache HALD²i

Dose = 150 - 300 mg OD; RASILEZ 150 mg tab; RASILEZ-HC : along with hydrochlorothiazide.

Losartan: Dose - 50 mg OD (rarely BD)

- in liver disease / hypovolemia ⇒ 25 mg OD

LOSACAR, LOSAR, TOZAAR, ALSARTAN 25, 50 mg tabs.

Candesartan: Dose - 8mg OD (max. 8mg BD)

- in liver / kidney impairment - 4mg OD

CANDESAR 4, 8, 10 mg tab. CANDILONG, CANDESTAN 4, 8 mg tabs.

Irbesartan: Dose = 150 - 300 mg OD

IROVEL, IRBEST 150, 300 mg tabs.

Valsartan: Dose = 80 - 160 mg OD (1 hour before meal)

[Initial dose in liver disease = 40 mg]

DIOVAN, STARVAL, VALZAAR 40, 80, 160 mg tabs.

Olmesartan: Dose = 20 - 40 mg OD

OLMAT, OLSAR - 20, 40 mg tabs.

Telmisartan: Dose = 20 - 80 mg OD; TELMA, TELSAR, TELVAS 20, 40, 80 mg tabs.

Eprosartan: Dose = 600 mg OD (400 - 800 mg OD)

TEVETEN, EPROZAR 600 mg tab.