Renin Angiotensin Aldosterone System

Dr Pradnya Rotithor

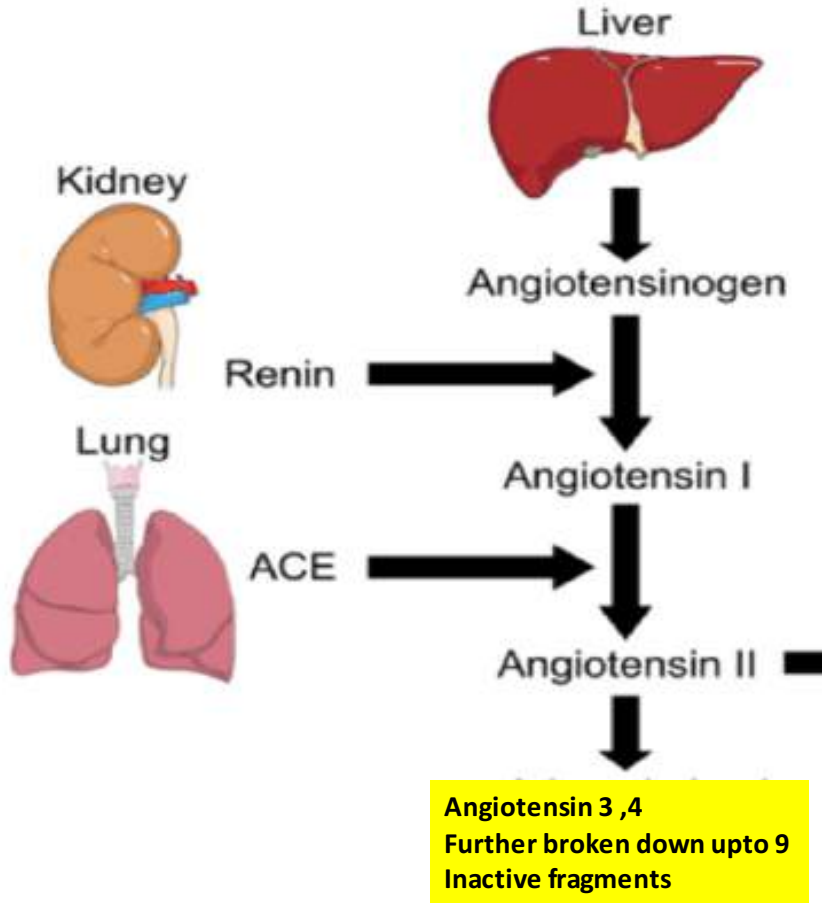
Synthesis of angiotensin II

Cascade of events

Liver –angiotensinogen

Kidney –JG apparatus- renin

Lungs –angiotensin converting enzyme –ACE



Target organs

Adrenal gland –aldosterone

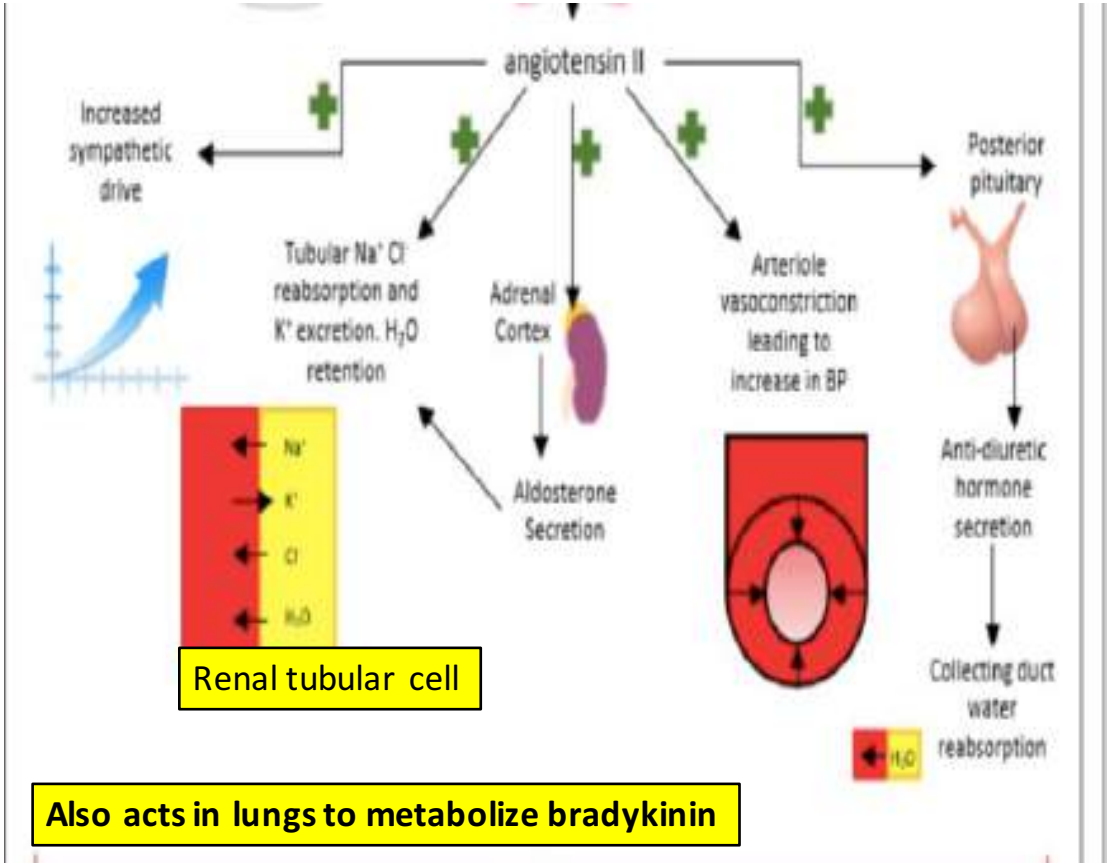
Hypothalamus –post pituitary – thirst ,ADH

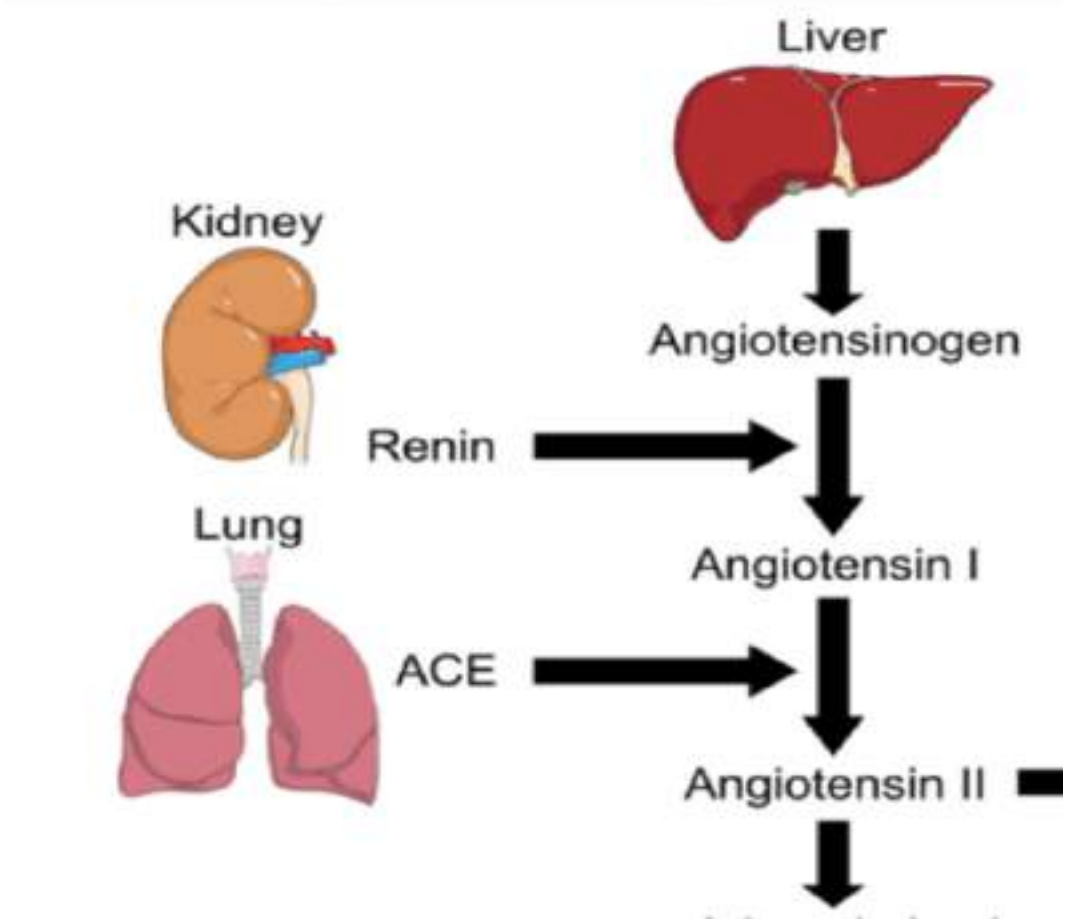
Blood vessels –vasoconstriction

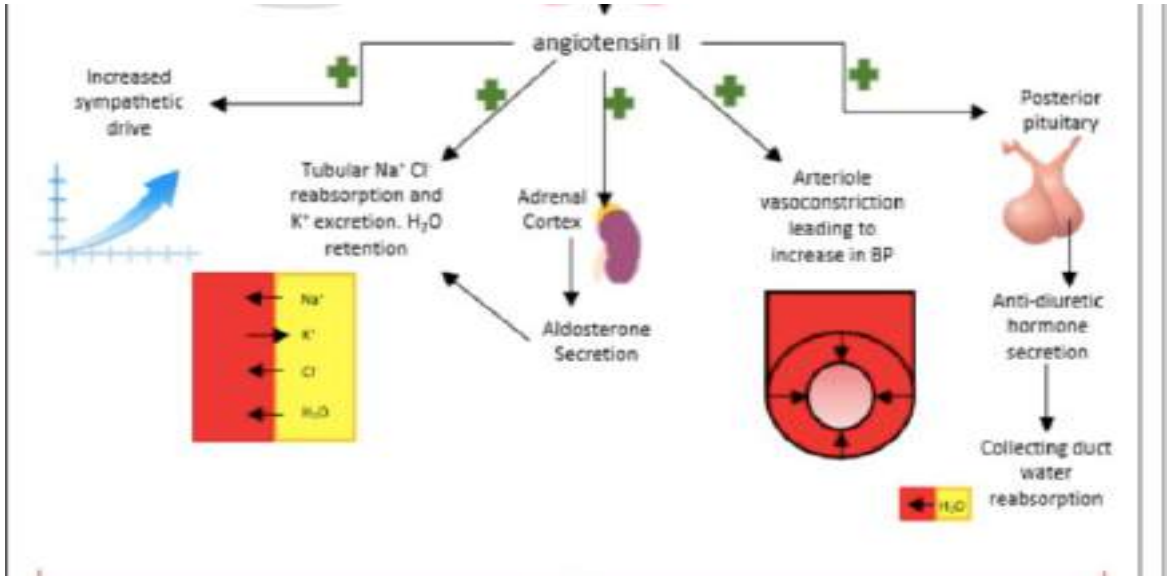
Heart –increased contractility etc

Kidneys –reabsorption of Na and water ,excretion of K

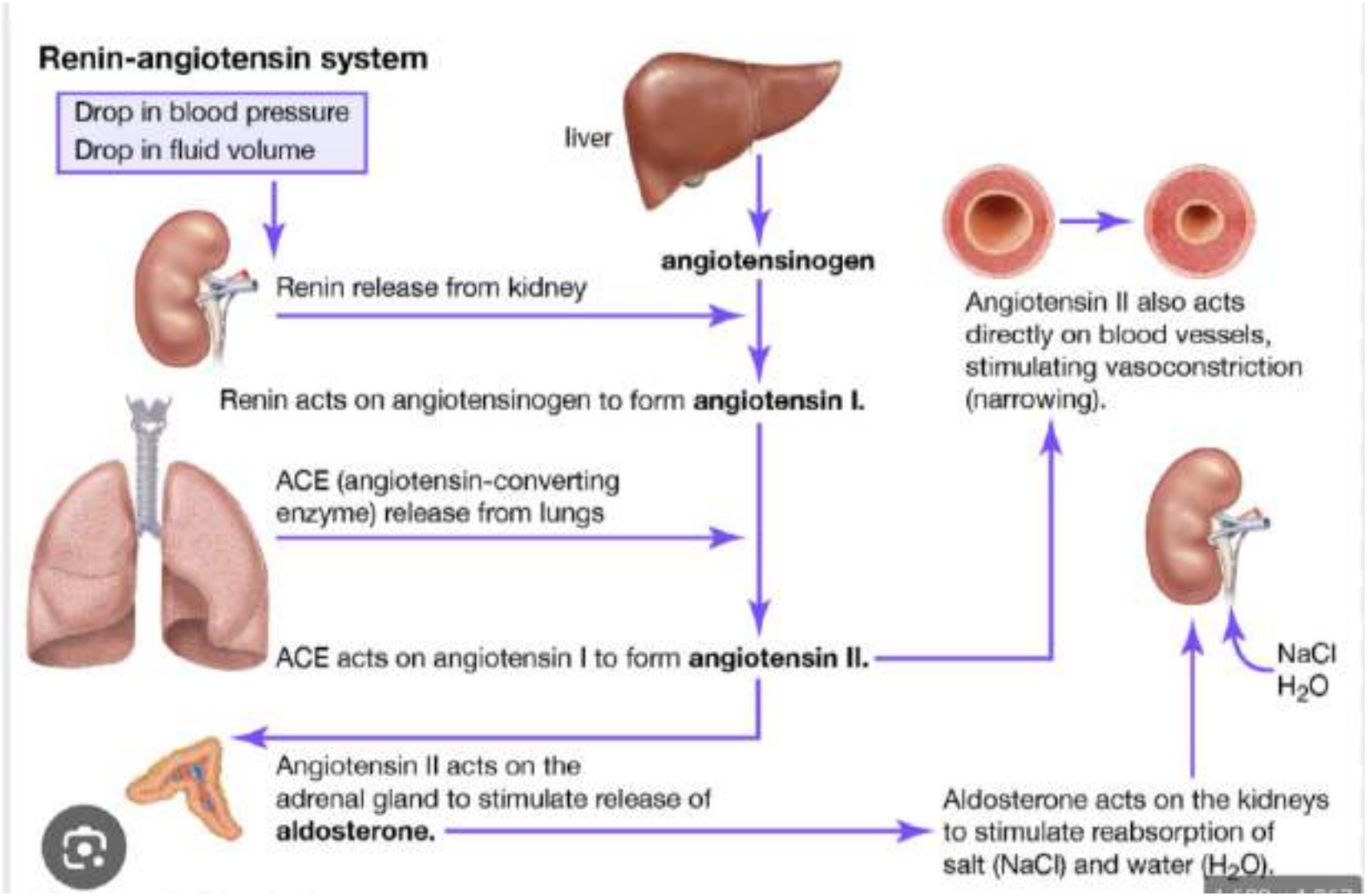
Lungs –metabolizes bradykinin

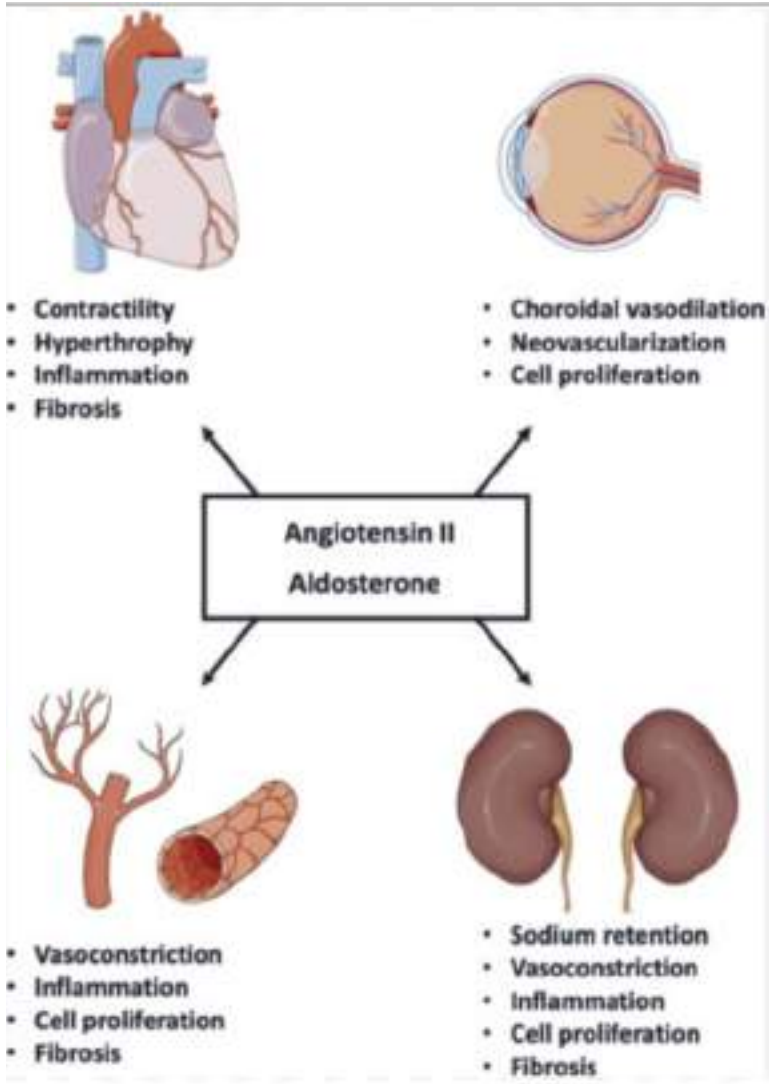



Liver
Kidney
Angiotensinogen
Renin
Lung
Angiotensin I
ACE
Angiotensin II


angiotensin II
Increased sympathetic drive
Tubular Na+ Cl- reabsorption and K+ excretion. H2O retention
Adrenal Cortex
Aldosterone Secretion
Arteriole vasoconstriction leading to increase in BP
Posterior pituitary
Anti-diuretic hormone secretion
Collecting duct water reabsorption
Na+
K+
Cl-
H2O

summary


Renin-angiotensin system
Drop in blood pressure
Drop in fluid volume
liver
angiotensinogen
Renin release from kidney
Renin acts on angiotensinogen to form angiotensin I.
ACE (angiotensin-converting enzyme) release from lungs
ACE acts on angiotensin I to form angiotensin II.
Angiotensin II also acts directly on blood vessels, stimulating vasoconstriction (narrowing).
NaCl
H_2O
Angiotensin II acts on the adrenal gland to stimulate release of aldosterone.
Aldosterone acts on the kidneys to stimulate reabsorption of salt (NaCl) and water (H_2O).


Contractility
Hyperthrophy
Inflammation
Fibrosis
Choroidal vasodilation
Neovascularization
Cell proliferation
Angiotensin II
Aldosterone
Vasoconstriction
Inflammation
Cell proliferation
Fibrosis
Sodium retention
Vasoconstriction
Inflammation
Cell proliferation
Fibrosis

Angiotensin receptors -GPCR type of R

AT1 –angiotensin acts on AT1 R for all its pharmacological actions

Seen in blood vessels, myocardium, brain, kidney, adrenal gland

MOA – different pathways in different tissues

Activation of phospholipase C, IP3/DAG in blood vessels

In myocardium: vasoconstriction, growth and hypertrophy of myocardium

AT2- clinical significance NOT well understood

brain, kidney, vascular endothelium, foetal tissues

Action opposite to AT1R

In myocardium – promote vasodilatation and myocardial fibrosis

inhibit cell growth and hypertrophy

Physiological actions of angiotensin II

Blood vessels –1)arterioles constriction

2)enhances endothelial permeability of large arteries leading to tissue fluid accumulation

Heart : 1)increased force of contraction

by increase in sympathetic outflow and by promoting Ca influx

2) growth and hypertrophy of myocardium

3)enhances vascular intimal thickness

In long standing HTN –leads to re-modelling and myocardial hypertrophy

LVH following MI is due to angiotensin II

Physiological actions of angiotensin II

- Promotes secretion of aldosterone from **adrenal cortex**
- Aldosterone acts on collecting ducts -reabsorption of Na and water ,excretion of K

Renal tubules -reabsorption of Na and water ,excretion of K

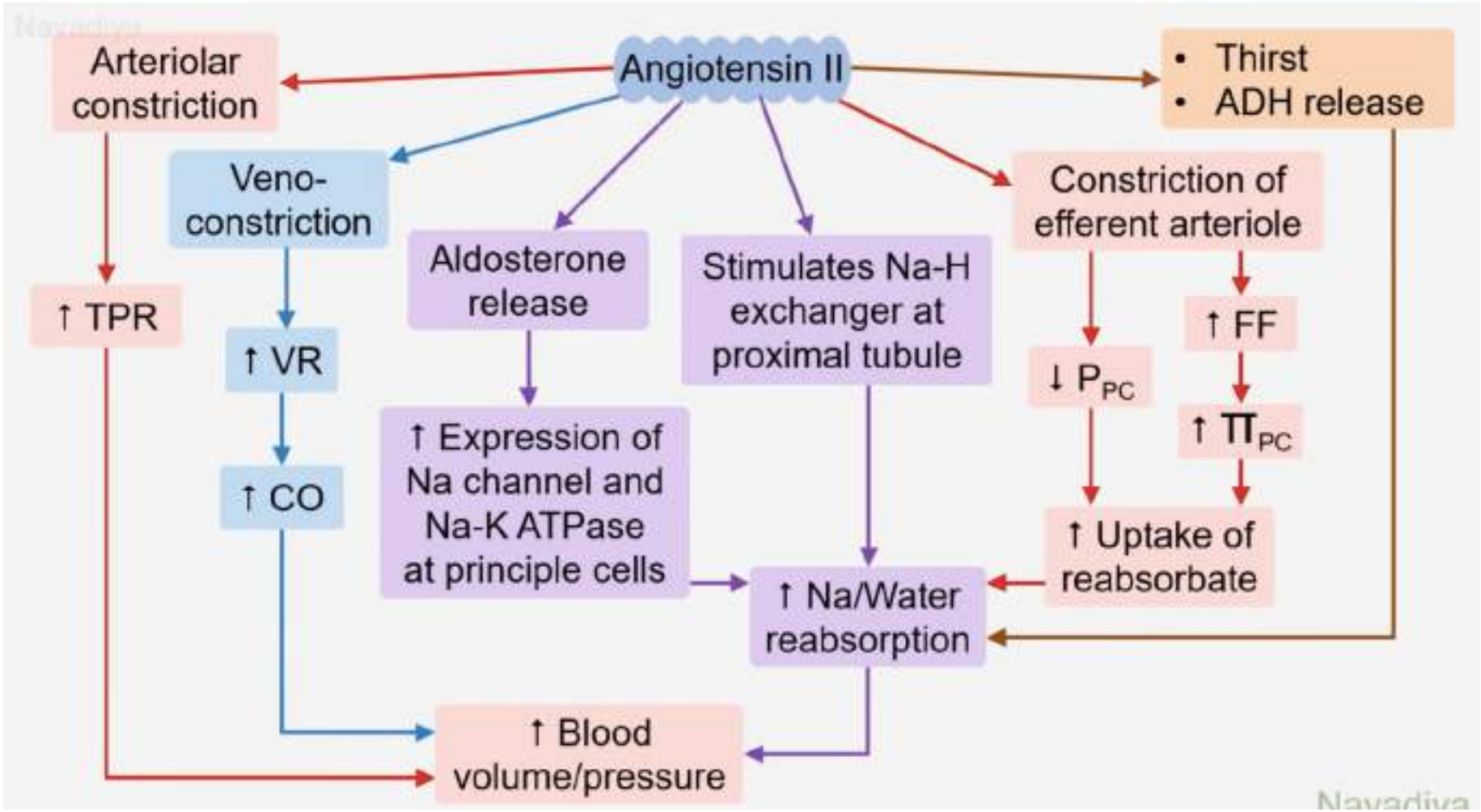
Promotes secretion of **vasopressin/ADH**

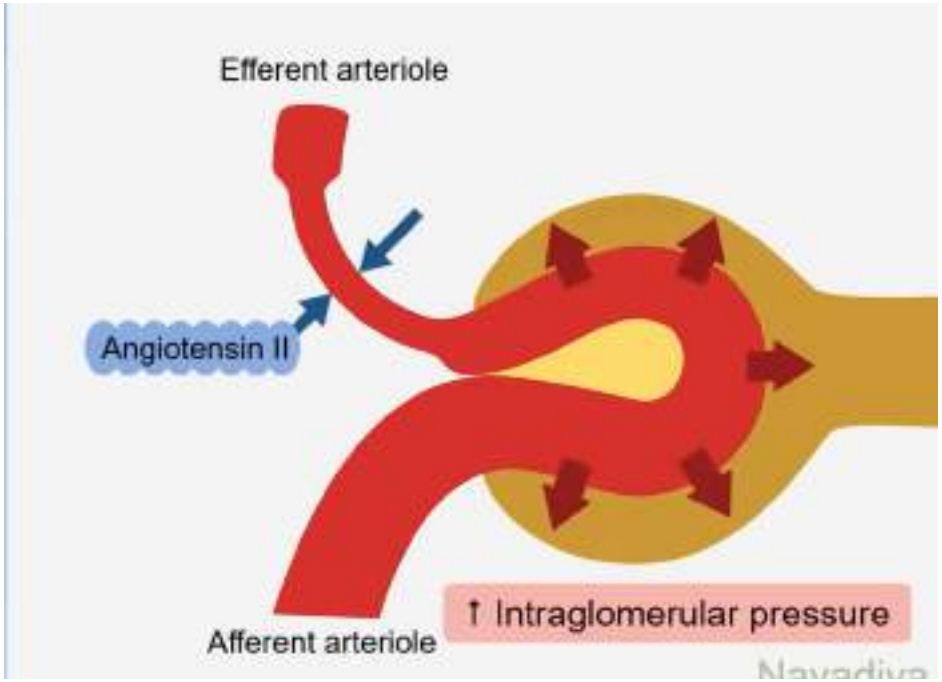
Net result of vasoconstriction -rise in peripheral resistance ,

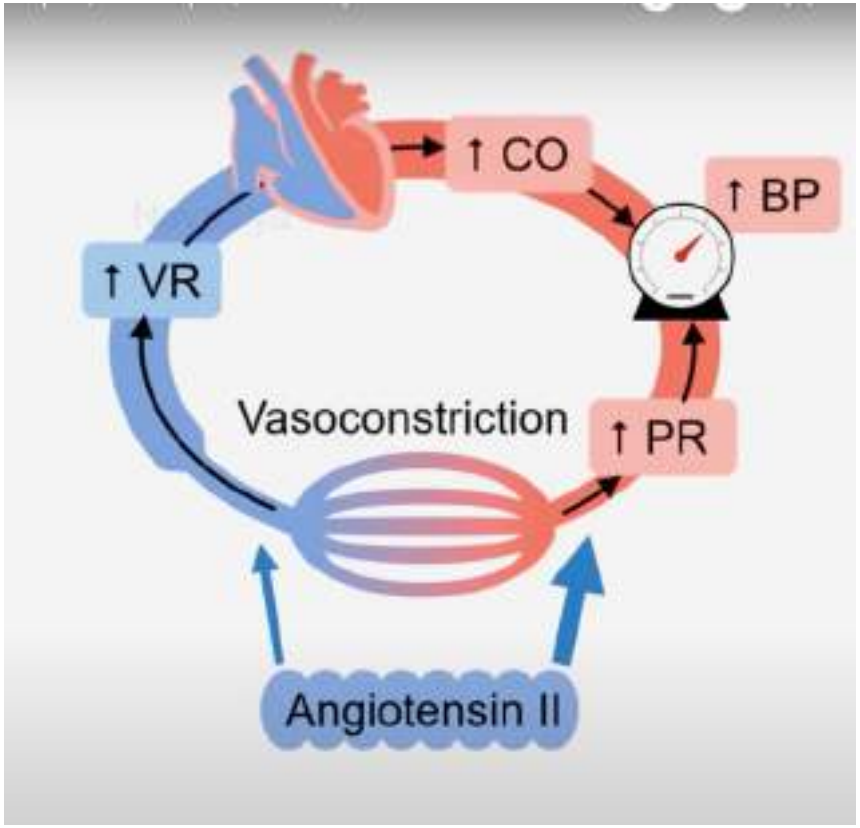
salt and water reabsorption –rise in blood volume

and action on heart leads to rise in blood pressure-

- **Angiotensin converting enzyme (ACE)**
  - Converts angiotensin I into angiotensin II
  - Breaks down bradykinin
- **Angiotensin II**
  - Vasoconstriction → increase blood pressure
  - Aldosterone release
    - Na/water retention
    - K^+ excretion
  - Constriction of efferent arteriole in kidney
- **Bradykinin**
  - Synthesis of NO and prostacyclin → Vasodilatation


Angiotensin II
Arteriolar constriction
Veno-constriction
Aldosterone release
Stimulates Na-H exchanger at proximal tubule
Constriction of efferent arteriole
• Thirst
• ADH release
↑ TPR
↑ VR
↑ CO
↑ Expression of Na channel and Na-K ATPase at principle cells
↓ P_{PC}
↑ FF
↑ Π_{PC}
↑ Uptake of reabsorbate
↑ Na/Water reabsorption
↑ Blood volume/pressure


Efferent arteriole
Angiotensin II
↑ Intraglomerular pressure
Afferent arteriole


↑ CO
↑ BP
↑ VR
Vasoconstriction
↑ PR
Angiotensin II

Drugs that inhibit RAAS

- Renin inhibitors -- Aliskiren ***all kiren***
- ACEI – angiotensin converting enzyme inhibitors captopril ***all prils***
- ARB –angiotensin receptor blockers losartan ***all sartans***

ACE Inhibitors

- Captopril -1977
- Lisinopril
- Enalapril
- Ramipril
- Benazepril
- Fosinopril
- Quinapril
- Except captopril and lisinopril all are PRODRUGS

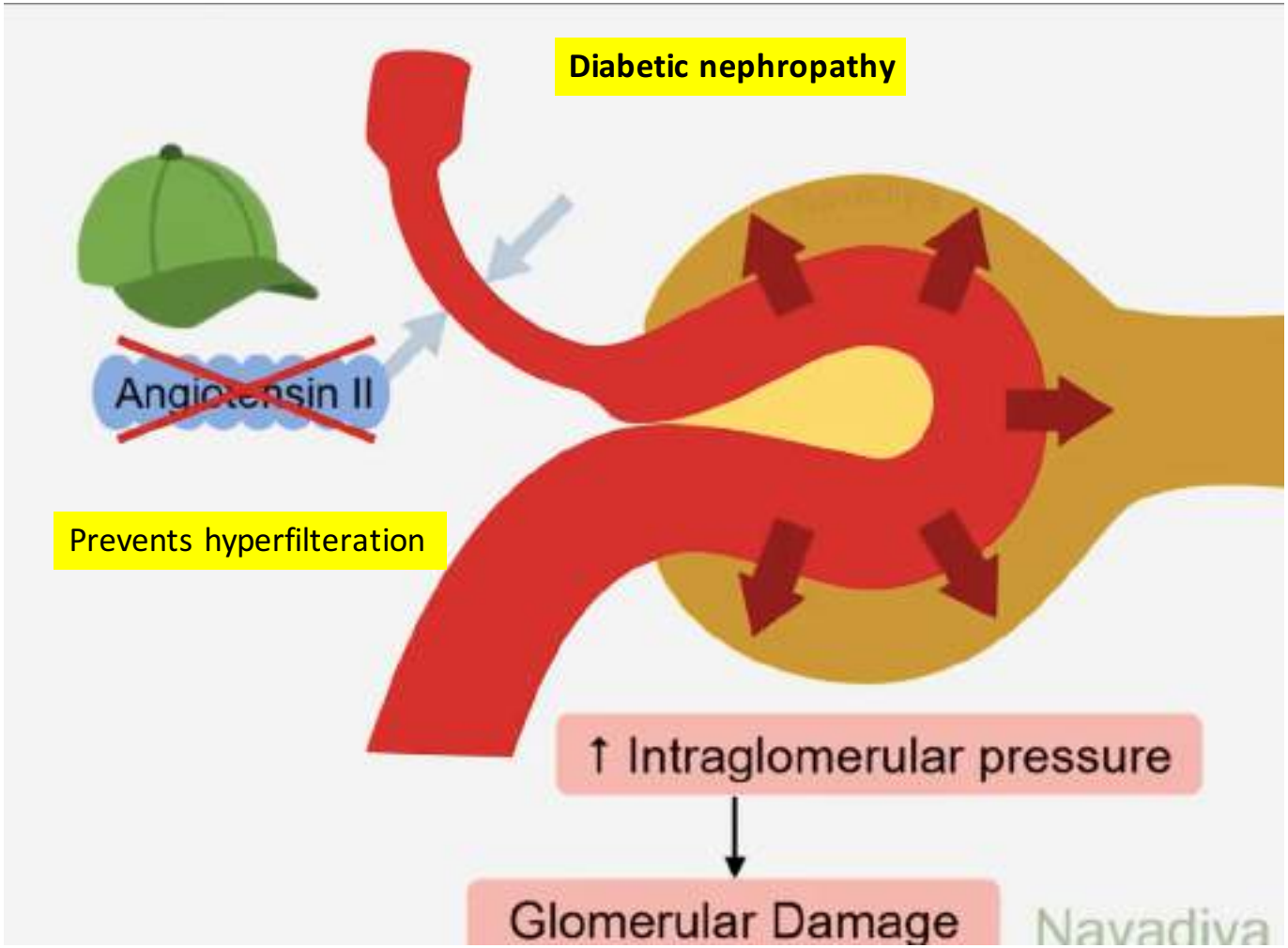
Pharmacological actions

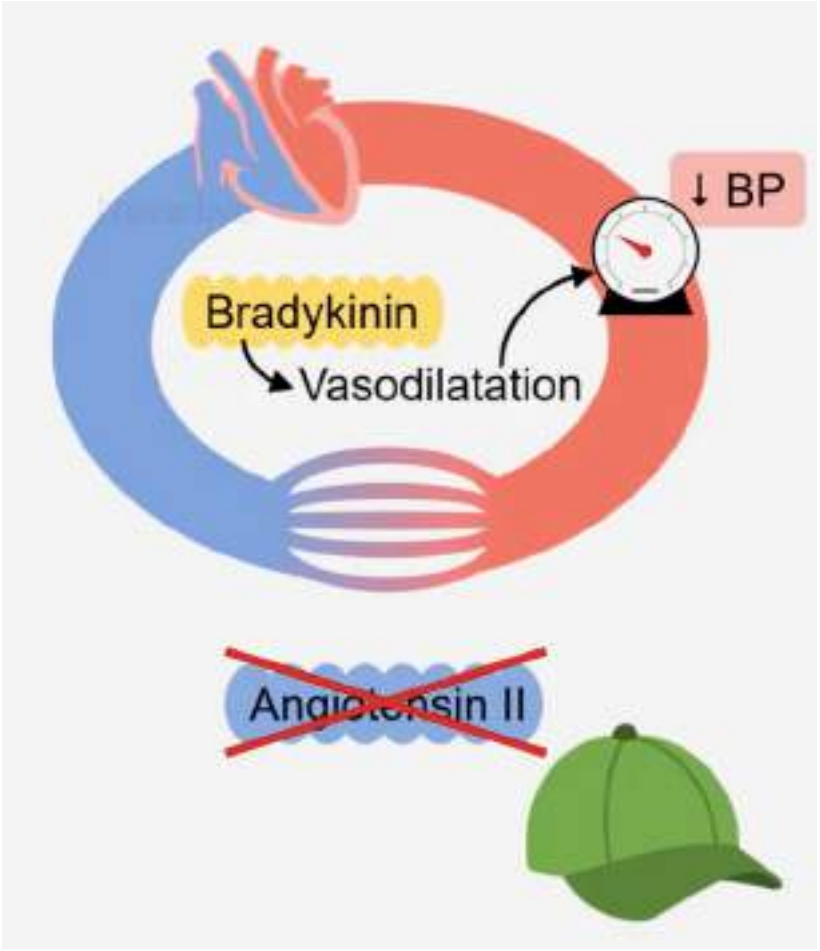
- As formation of Angiotensin II is blocked all the actions of angiotensin II are reversed
- In Addition as Angiotensin II is not available to breakdown bradykinin additional vasodilation action adds to decrease in peripheral resistance
- Fall in serum aldosterone levels and angiotensinII leads to rise in plasma renin levels

- Fall in BP
- LVH is reversed
- In CCF –reduced ventricular afterload improves cardiac output

- **Hypertension**
  - Reduced angiotensin II
  - Vasodilatation by bradykinin
- **Heart failure**
  - ↓ BP → ↓ afterload
  - ↓ VR → ↓ preload
- **Post MI**
- **Prophylactically in patients with high risk of cardiovascular events**
- **Diabetic nephropathy**
  - Reduced resistance of efferent arteriole → reduced intraglomerular pressure → reduced damage
  - Increase the permeability sele[illegible]g membrane
- **Scleroderma renal crisis**

Drug of choice
Slows down renal damage


Diabetic nephropathy
Angiotensin II
Prevents hyperfilteration
↑ Intraglomerular pressure
Glomerular Damage
Navadiva


↓ BP
Bradykinin
Vasodilatation
Angiotensin II

Therapeutic uses

- Hypertension –of all causes of all grades –one of the firstline drug
- Congestive heart failure
- Myocardial infarction
- Prevention of repeat MI
- Coronary artery disorders –prophylaxis
- Diabetic nephropathy
- Chronic renal failure- delays progression of failure
- Scleroderma renal crisis –life saving drug

Adverse effects

- Persistent dry cough –raised bradykinin
- Angioneurotic oedema- rare but serious ADR urgent treatment and withdrawing of ACEI needed
- Skin rash
- Hypotension –first dose effect –start with low dose and raise dose gradually
- Hyperkalaemia-especially with K sparing diuretics digitalis and patient on K supplement
- Dysgeusia –altered taste sensation
- Terratogenicity – malformed lungs growth retardation and even foetal death
- Others –neutropenia ,proteinuria, headache ,fatigue ,vomiting
- Drug interaction –NSAID-antiprostaglandin –blunts advantage of bradykinin

- Contraindicated in renal artery stenosis
- Contraindicated in Pregnancy

pharmacokinetics

- Variable in bioavailability ,duration of action and mode of absorption and excretion
- Except captopril and lisinopril all are PRODRUGS
- For the prodrugs first dose effect is milder and onset of action is slower
- Captopril -Food interferers with absorption, less potent and shorter acting than enalapril
- Enalapril –food doesn't interfere with absorption
- More potent long acting ,taste sensation not much affected
- All are oral drugs except--
- Enalaprilat –only injectable ACEI

ARB –Angiotensin Receptor Blockers

- Conversion of angiotensin I to II is NOT blocked
- But the receptors AT1 through which ACEI bring about its action are blocked
- Thus all actions are similar to ACEI
- Except as bradykinin metabolism is NOT blocked –no dry cough ADR seen

- Drugs: Candesartan, Eprosartan, Losartan, Olmesartan, Telmisartan, Valsartan, Irbesartan, Azilsartan.
- Block AT_1 receptors
- Similar to ACE inhibitors
- Use:
  - Hypertension,
  - Heart failure,
  - Post MI patients
  - Diabetic nephropathy
- Side effects:
  - Hypotension
  - Hyperkalaemia
  - Renal failure in patients with renal artery stenosis
  - Teratogenic

ANTICOAGULANTS

DR PRADNYA ROTITHOR

Clotting factors –proteins synthesized in liver

Coagulation pathways –

Intrinsic pathway -slow

Extrinsic pathway-rapid

Important factors taking part in clotting-

Clotting factors ,prothrombin, thrombin fibrinogen and fibrin

Anticoagulants –

Definition-drugs that reduce the coagulating ability of the blood

Classification of anticoagulants

Oral and Parenteral

Oral –

1)Coumarin derivatives –warfarin

2)Indandione derivatives –phenindione

3)Factor Xa inhibitor –rivaroxaban/apixaban

4)Oral DTI –Dabigatran

TI –thrombin inhibitor

DTI –Direct Thrombin Inhibitor

PARENTERAL

- **Indirect TI**
- **Heparin**
- **LMW Heparin -**
- **Synthetic heparin**
- **Heparinoids**

Direct TI

Hirudin

Argatroban

- **Warfarin, heparin and LMW heparin to be studied in detail**

HEPARIN

first extracted from liver-Hence the name

Found in Lungs liver intestinal mast cells

Strongest acid in the body

Powerful anticoagulant with instant action both in vivo and in vitro

MOA- antithrombin III inhibits activated thrombin and Xa and Ixa. Thus clotting time is prolonged

Heparin makes this physiological process 1000times faster.

FLOW CHART OF MOA

HEPARIN

- **Binds and activates plasma**
- **Antithrombin III**

Other action of heparin –
Activation of lipoprotein lipase →hydrolyses TG →lowers blood lipids

1000 fold faster

Degrades thrombin Xa IXa

Heparin is released

Prevents conversion of fibrinogen to fibrin

- **Anticoagulant**
- **Effect happens**

Pharmacokinetics

- Not effective orally
- IV Or S/C NOT IM
- Iv – onset of action -immediate
- Peak -5 -10 min
- Action wares off 2-4 hrs
- Metabolised by heparinase in liver
- Can be used in pregnancy as it does not cross XXX placental barrier due to high molecular weight.
- Monitored by –aPTT Or clotting time

Dosage

- Therapeutic dose –
- Bolus dose -5000units iv infusion followed by 1000-1500 units /hour by infusion pump

- Prophylactic dose –
- S/C low dose heparin 5000units 12 hrly

A/E of Heparin

1)Bleeding- most common and major A/E

2)Hypersensitivity reaction – more for bovine or porcine source

3)HIT –heparin induced thrombocytopenia

Due to antiplatelet antibodies complex- →damage to vessel wall →thrombosis and DIC

Paradoxical complication of thrombosis results in 1-4% of patients

Less common with LMW

4)Alopecia-reversible

5)Osteoporosis-on long term use

6)Hypoaldosteronism- ↓aldosterone synthesis →hyperkalemia

Contraindications

- bleeding disorders
- HIT
- ITP
- Infective endocarditis
- Threatened abortion
- Haemophilia
- Severe HTN
- Liver cirrhosis

LOW MOLECULAR WEIGHT HEPARIN --

ENOXAPARIN
DALTEPARIN
REVIPARIN
NADREPARIN
Inhibit only factor Xa (MCQ)
aPTT CT not prolonged

Obtained by chemical/enzymatic Rx of un fractioned heparin

Dose calculated on body weight
Given S/C

Uses-venous thrombosis ,pulmonary embolism,unstable angina

Advantages of LMW over Heparin-**SAQ**

- Better bioavailability on S/C inj
- Long acting hence once or twice daily dose
- Predictable PK and plasma levels
- Frequent monitoring not required
- Lower risk of bleeding
- Lower risk of osteoporosis
- Lower incidence of thrombocytopenia

Compare and Contrast SAQ

Unfractioned Heparin

- High molecular weight
- 10000 to 20000unis
- Inhibits thrombin activity at therapeutic dose
- Effects clotting tests significantly
- Strict monitoring essential
- Low bioavailability -20-30%
- Duration of action short -2-4 hrs—dose 4-6 hrly
- High risk of bleeding
- High chances of HIT-Heparin induced thrombocytopenia

LMW Heparin

- Low molecular weight
- 4000 to 7000units
- Thrombin activity is not inhibited
- Not significant
- Not essential
- Better -70 -90%
- Long =18-24 hr hence od dose
- Low risk of bleeding-
- Low risk of HIT

Heparin antidote

- Short acting drug hence just stop the drug in mild overdose
- Use antidote for severe overdose
- **Protamine sulphate (MCQ)**
- **1mg for each 100 units of heparin**
- **Overtreating with protamine sulphate to be avoided –may itself act as weak anticoagulant**

Oral anticoagulants

- Warfarin
- Interferes with production of Vit K dependent clotting factors in liver
- Hence acts only in vivo
- Clinical effect seen after 2-3 days as it does not destroy already circulating factors

MOA OF WARFARIN

Warfarin

↓

Blocks gamma carboxylation of glutamate residue in factors II VII IX X Protein C and S

↓

Incomplete coagulation factor molecules formed

Deficient coagulation factors

↓

Prevention of coagulation

Pharmacokinetics of Warfarin

- Orally absorbed
- 99% bound to plasma proteins
- Metabolized by glucuronide conjugation
- Excretion –renal
- Affected by HME CYP2C9 hence enzyme induction interferes with action

A/E OF WARFARIN

- BLEEDING
- Minor episodes of epistaxis and bleeding gums – common but less risky
- Internal haemorrhage –intracranial or GIT more risky
- Treatment of overdose-
- Stop the drug
- Vit K1 oxide –antidote
- Fresh whole blood –emergency major as antidote effect takes several hours

Heparin	Warfarin
Source –natural, High molecular weight mucopolysaccharide	Synthetic Coumarin derivative
Parenteral route –SC/IV	Oral route
Onset --Rapid-few min	Gradual onset –(1-3) days
Acts on intrinsic pathway	Acts on extrinsic pathway
Does not cross placenta	Crosses placenta-teratogenic
Safe to use during pregnancy	Contraindicated in pregnancy
Duration of action –short -2 to 4hours	long-4-7 days

Acts in vivo and in vitro	Only in vivo
V few drug interactions	Many drug interactions
Eliminated by renal route	Eliminated by liver
Lab monitoring by –aPTT, clotting time	By PT INR
MOA-accelerates action of AT III which inhibits thrombin factors Xa, IXa	Prevents production of vit k dependent clotting factors II VII IX X
Uses-treatment of thromboembolic disorders	-treatment of thromboembolic disorders
Treatment of overdose – Protamine sulfate-antidote	Vit K (antidote),fresh frozen plasma

Therapeutic uses of anticoagulants

For acute action –heparin

Warfarin- long term

1)Venous thrombosis

2)Pulmonary embolism

3)Valvular heart disorders

4)Unstable angina

5)During vascular surgeries

6)haemodialysis

Thrombolytics/Fibrinolytics

Fibrinolytics (thrombolytics)-

Drugs that activate the fibrinolytic system and lyse the thrombus.

Plasminogen **→tPA →plasmin → degrades fibrin →fibrin degradation products bring about clot dissolution.**

Classification of thrombolytics

First generation –older drugs-
Streptokinase urokinase

Second generation – newer drugs
Alteplase tenecteplase

A/E of thrombolytics –
bleeding

Therapeutic uses of thrombolytics

1)Life saving drug in Acute myocardial infarction

Should be given as soon as possible

Newer drugs are better

High cost

2) DVT –deep vein thrombosis

3)Pulmonary embolism

4)Ascending thrombophlebitis

5)Peripheral vascular disorders

Anti fibrinolytics

Opposite of fibrinolytics

Anti fibrinolytics are the drugs that **inhibit**

Dissolution of clot

MOA –BLOCK BINDING OF PLASMINOGEN TO FIBRIN

EACA –epsilon amino caproic acid—oral and injectable

Tranaexamic acid –oral and injectable

Some body tissues are rich in plasminogen activator

Damage to such tissues results in hyper plasminaemic state

Or when there is overdose of fibrinolytic drugs

USES –

1)Overdosage of fibrinolytics

2)PPH- post partum haemorrhage

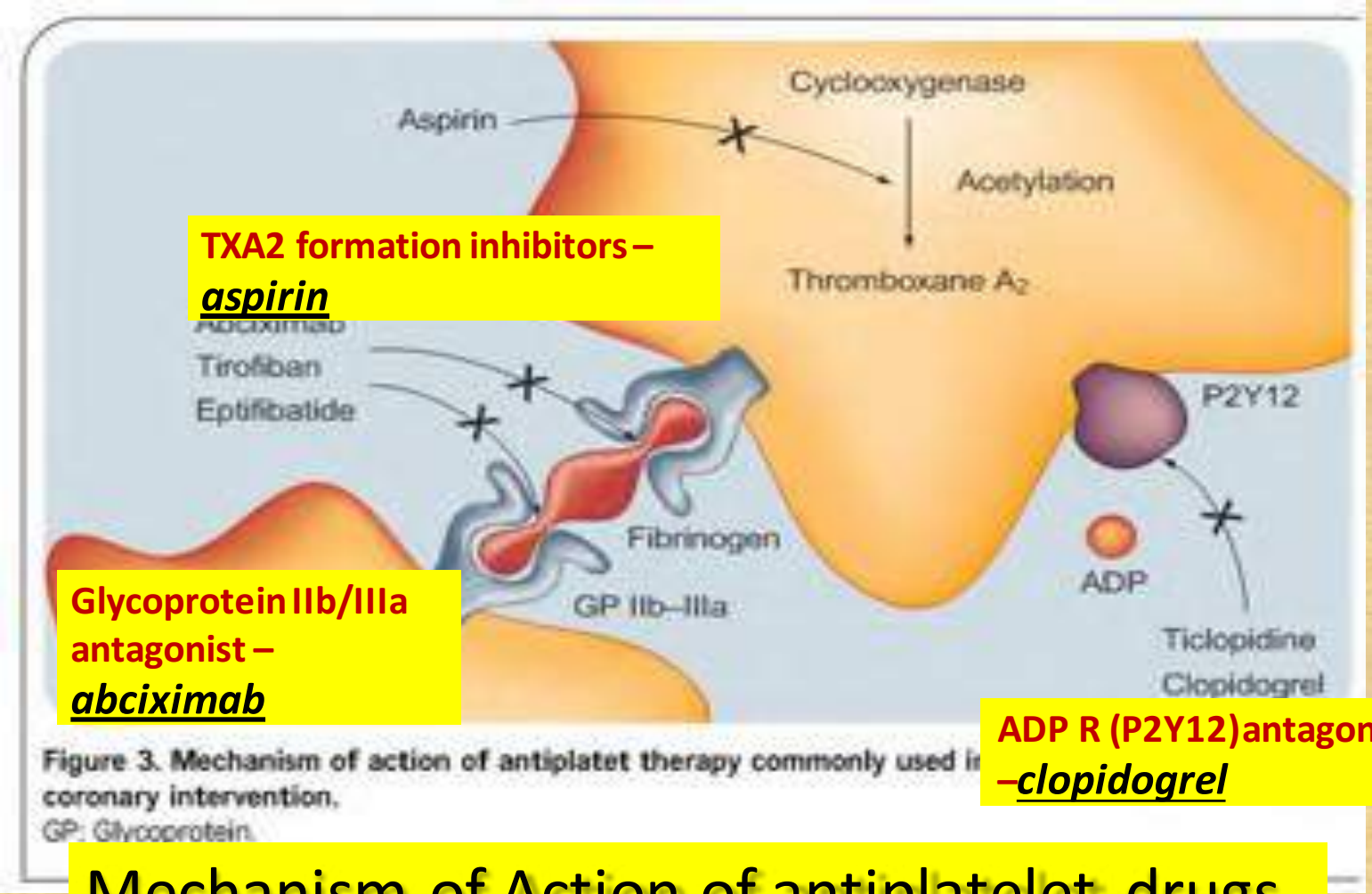
3)Menorrhagia

4)Bleeding peptic disorders, epistaxis,

5)Hereditary angioedema

Antiplatelet drugs

- Platelets are primary haemostatic agent in the body
- Also take part in atherosclerosis of blood vessels



TXA2 formation inhibitors – *aspirin*

Glycoprotein IIb/IIIa antagonist – *abciximab*

ADP R (P2Y12)antagonists –*clopidogrel*

Figure 3. Mechanism of action of antiplatet therapy commonly used i
coronary intervention.
GP: Glycoprotein

Mechanism of Action of antiplatelet drugs

Antiplatelet agents

1) PG synthesis inhibitor –irreversible COX inhibitor –aspirin
2) Phosphodiesterase inhibitor – dipyridamole
3) ADP Antagonists- clopidogrel, ticlopidine
4) Glycoprotein IIb/IIIa receptor antagonist – abciximab, tirofiban
5) Others –PGI2, cilostazol, ridogrel

Antiplatelet MOA of aspirin

TXA2 promotes platelet aggregation

PGI2 inhibits platelet aggregation

COX Enzyme is needed for producing TXA2

Aspirin brings about irreversible acetylation of cox enzyme

Thus inhibits synthesis of TXA2- at low dose only TXA2 is affected and no significant effect on PGI2

Hence low dose aspirin is used for antiplatelet effect

Effect lasts for 7 days –till fresh platelets are formed

Ecosprin -75 mg 150mg 325mg

Uses of antiplatelet drugs

IHD- MI, stable angina pectoris, Unstable angina

Cardiac procedures

Atrial fibrilation

Prosthetic heart valves

CVA

Pulmonary HTN

Haemodialysis

Peripheral vascular disorders

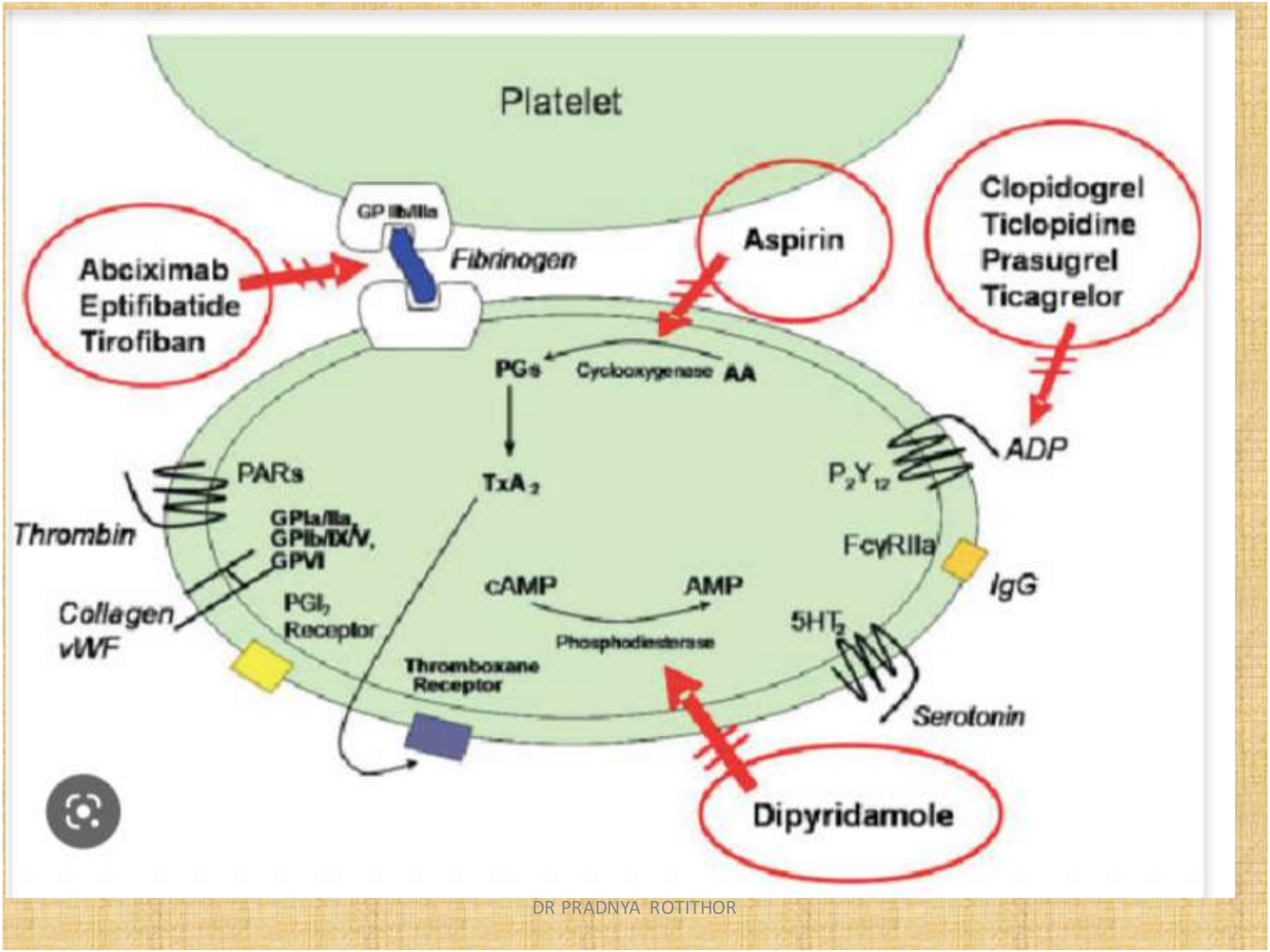
coagulants

- Vitamin K
- Ethamsylate

1-Anticoagulant Drugs

- Heparin and warfarin are the two traditional anticoagulants
- Anticoagulants are used for acute coronary syndromes, deep-vein thrombosis (DVT), pulmonary embolism (PE), and heart surgery
- **Thrombus** - A blood clot that forms abnormally within the blood vessels
- **Embolus** - When a blood clot becomes dislodged from the vessel wall and travels through the bloodstream
- It is also given to certain people at risk for forming blood clots, such as those with artificial heart valves or who have atrial fibrillation (AF)


Heparin
Injection BP
5000 IU/ml
ANTI-COAGULANT
For IV/SC Use
5ml
Heparin
Injection BP
5000 IU/ml
For IV/SC Use
5ml


Platelet
GP IIb/IIIa
Fibrinogen
Abciximab
Eptifibatide
Tirofiban
Aspirin
Clopidogrel
Ticlopidine
Prasugrel
Ticagrelor
PGs
Cyclooxygenase
AA
ADP
PARs
TxA2
P2Y12
Thrombin
GPIa/IIa
GPIb/IX/V,
GPVI
FcγRIIa
IgG
cAMP
AMP
Collagen
vWF
PGI2
Receptor
5HT2
Phosphodiesterase
Thromboxane
Receptor
Serotonin
Dipyridamole

ARB

DR PRADNYA ROTITHOR

ARB-Angiotensin Receptor Blockers

- Alternative to ACEI—does **NOT** inhibit ACE but **blocks the receptors**
- Orally Active
- Antagonist mainly at AT1 R
- Prototype –losartan

Examples of ARB

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

Blocks all overt actions of angiotensin II

- Vasoconstriction
- Sympathetic stimulation-both central and peripheral
- Renal reabsorption of salt and water
- Aldosterone release
- Vasopressin release, no effect on thirst
- Growth promoting action on myocardium and blood vessels

- ***Differs from ACEI on bradykinin –does not block metabolism thus no ADR of dry cough***

Pharmacokinetics

- Orally effective
- But high first pass metabolism hence low bioavailability -33%
- Metabolized in liver –carboxylation-active metabolite
- High PPB –both losartan and metabolite -98%
- T1/2 2 hrs but metabolite -6 -9 hrs
- BBB XXX
- Excreted by kidneys

ADR

- Well tolerated

- Hypotension
- V little first dose effect
- **Hyperkalemia**
- But no cough, angioedema and altered taste like ACEI
- Mild N V
- Headache dizziness

Therapeutic uses

- ✓ First line anti hypertensive drugs
- ✓ Alternative to ACEI
- ✓ CHF
- ✓ MI
- ✓ Diabetic nephropathy

Compare and contrast

ACEI

- **Angiotensin converting enzyme inhibitor**
- **Prevents conversion of angiotensin I to II**
- **Prevents breakdown of bradykinin**
- **Dry cough due to bradykinin accumulation**
- **Angioneurotic oedma**
- **Additional action of vasodilation by bradykinin**
- **Uses –antiHTN, CHF MI etc**
- **Examples –all prils**

ARB

- **Angiotensin receptor blocker**
- **Blocks the action of angiotensin II on AT1 R**
- **No action on bradykinin**
- **Dry cough absent**
- **No angio oedema**
- **No additional vasodilation**
- **Same as ACEI**
- **Examples –all sartans**

Summary of ARB

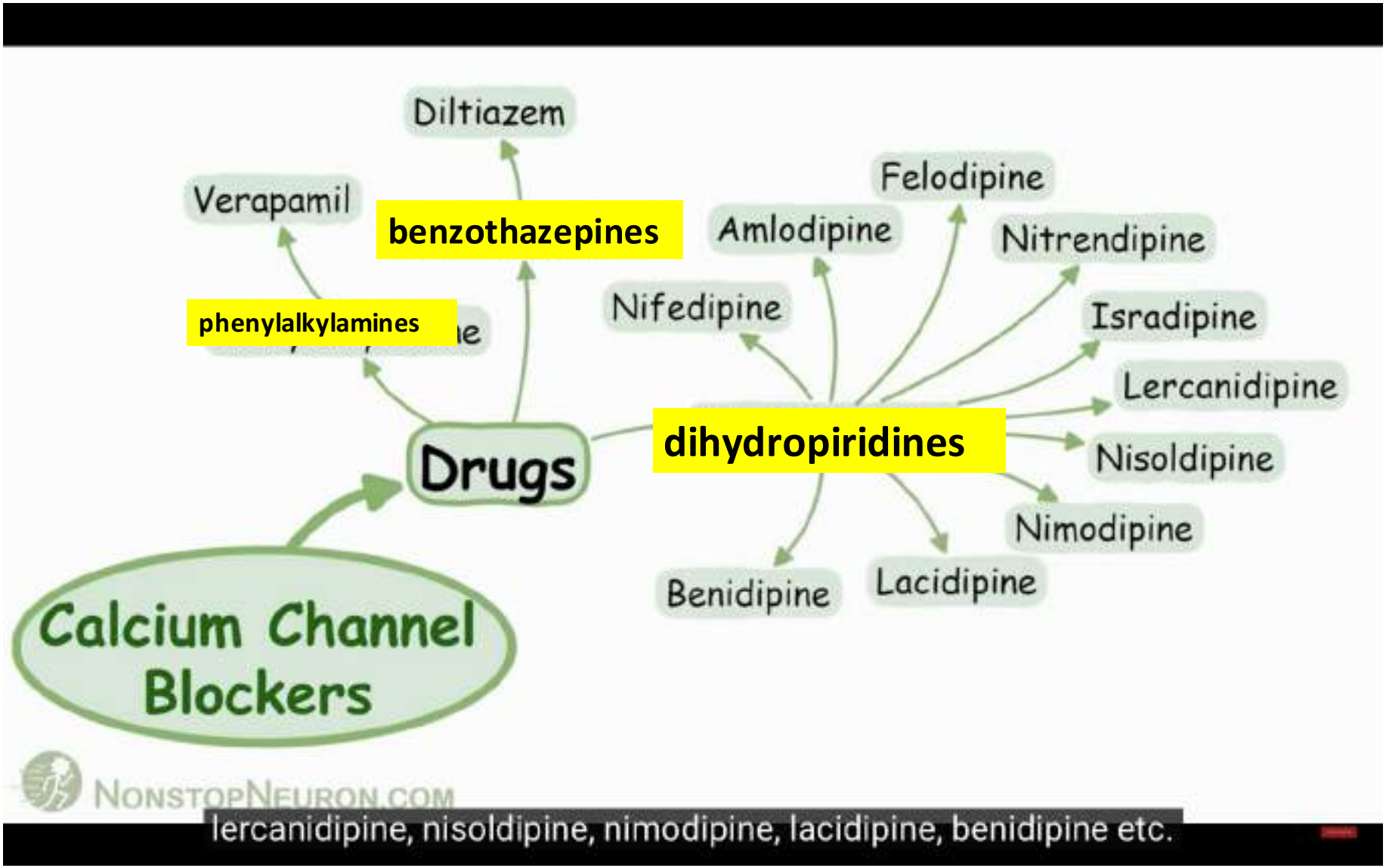
- Drugs: Candesartan, Eprosartan, Losartan, Olmesartan, Telmisartan, Valsartan, Irbesartan, Azilsartan.
- Block AT_1 receptors
- Similar to ACE inhibitors
- Use:
  - Hypertension,
  - Heart failure,
  - Post MI patients
  - Diabetic nephropathy
- Side effects:
  - Hypotension
  - Hyperkalaemia
  - Renal failure in patients with renal artery stenosis
  - Teratogenic

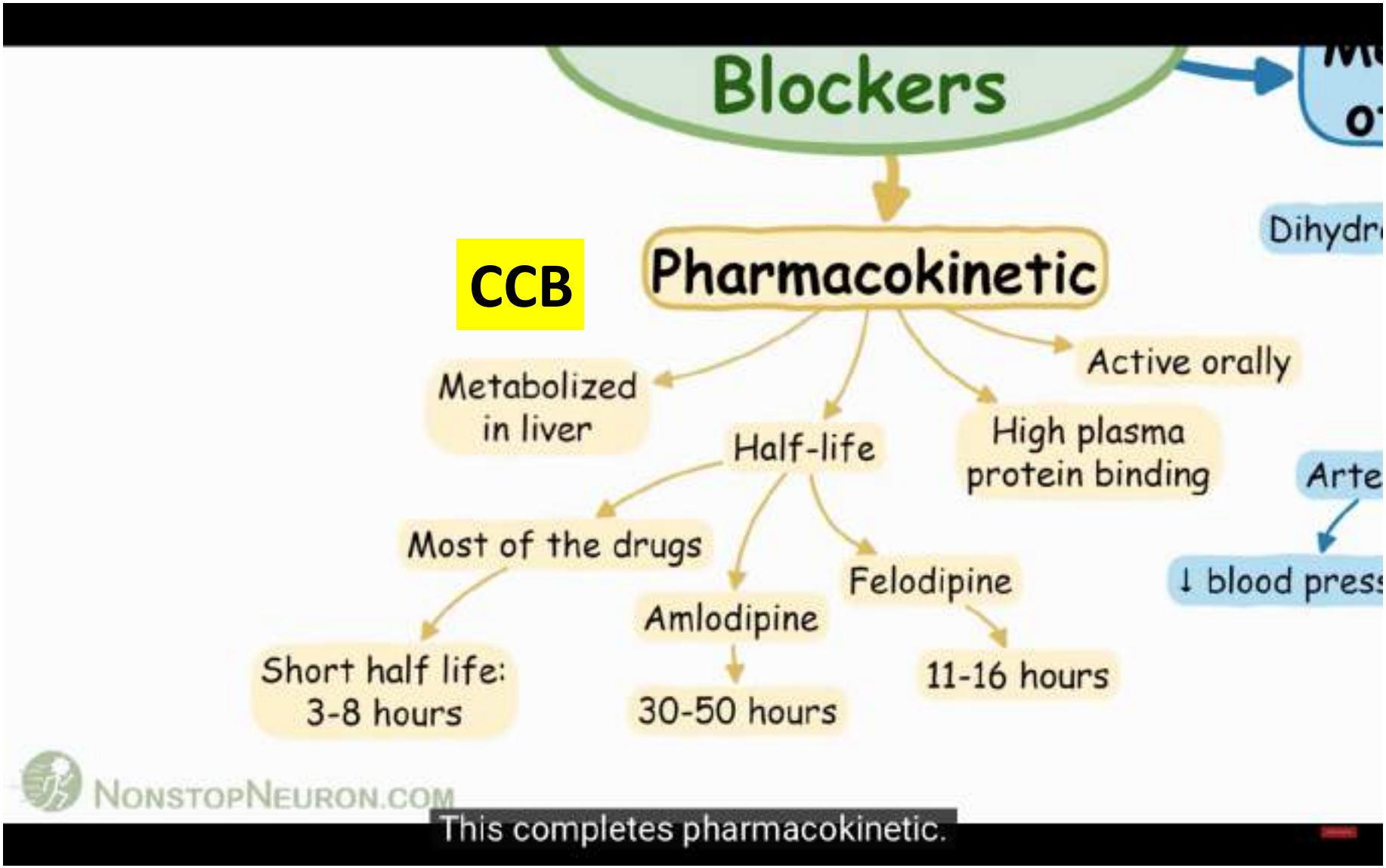
Calcium Channel Blockers

DR PRADNYA ROTITHOR

Inhibit L type of calcium channels in heart and smooth muscles

- **Three groups**
- 1)phenylalkylamines –verapamil
- 2)benzothiazepines-diltiazem
- 3)dihydropyridines- nifedipine amlodepineetc
- **MOA –**
- 1)Smooth muscle relaxation –vascular
- 2)negative chrono,ino and dromotropic action on hreart


Diltiazem
Verapamil
benzothazepines
phenylalkylamines
Felodipine
Amlodipine
Nitrendipine
Nifedipine
Isradipine
Lercanidipine
Drugs
dihydropiridines
Nisoldipine
Nimodipine
Benidipine
Lacidipine
Calcium Channel Blockers
NonstopNeuron.com
lercanidipine, nisoldipine, nimodipine, lacidipine, benidipine etc.


Blockers
CCB
Pharmacokinetic
Metabolized in liver
Half-life
Active orally
High plasma protein binding
Most of the drugs
Amlodipine
Felodipine
Short half life: 3-8 hours
30-50 hours
11-16 hours
NonstopNeuron.com
This completes pharmacokinetic.

Antihypertensive Mechanism of Action

Calcium Channel Blockers

Block Calcium Channels (on vascular and heart muscle cells)

Dihydropyridines

Blood Vessels

Vasodilation

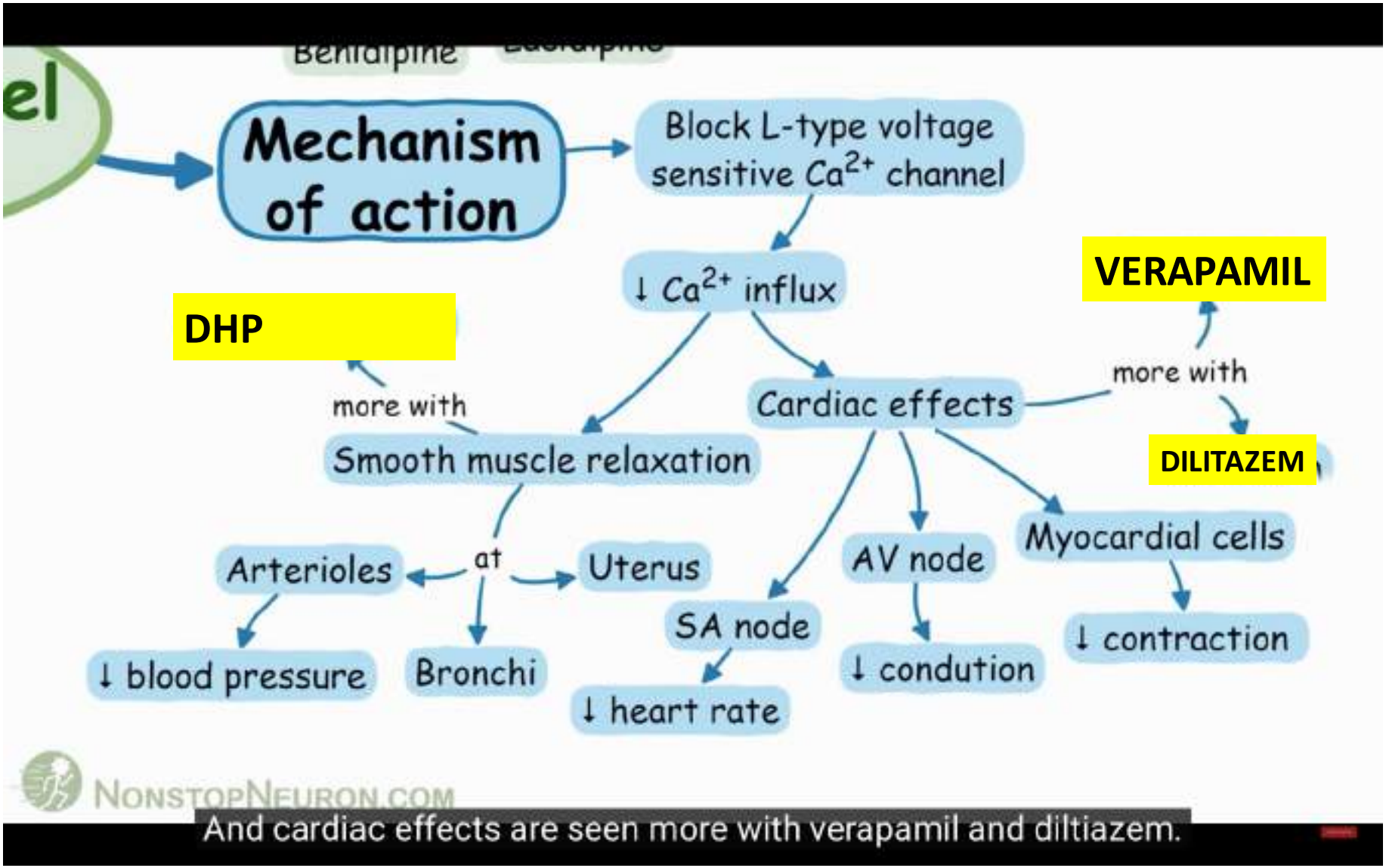
Hypertension

Non-Dihydropyridines

Heart

Decreased HR, Contraction

Tachydysrhythmias


Mechanism of action
Block L-type voltage sensitive Ca^{2+} channel
↓ Ca^{2+} influx
DHP
VERAPAMIL
DILITAZEM
more with
more with
Cardiac effects
Smooth muscle relaxation
at
Arterioles
Uterus
Bronchi
↓ blood pressure
SA node
↓ heart rate
AV node
↓ condution
Myocardial cells
↓ contraction
NonstopNeuron.com
And cardiac effects are seen more with verapamil and diltiazem.

MOA

Action on vascular smooth muscles –

Blocks voltage sensitive Ca channels

Thus prevents inward movement of Ca

Prevents excitation contraction coupling

Markedly relax arterioles ,mild action on veins

Action on other smooth muscles- relaxation of

bronchial biliary intestine bladder smooth muscles

Antihypertensive Mechanism of Action

Calcium Channel Blockers

Block Calcium Channels (on vascular and heart muscle cells)

Smooth Muscle Contraction

Dihydropyridines

Blood Vessels

Vasodilation

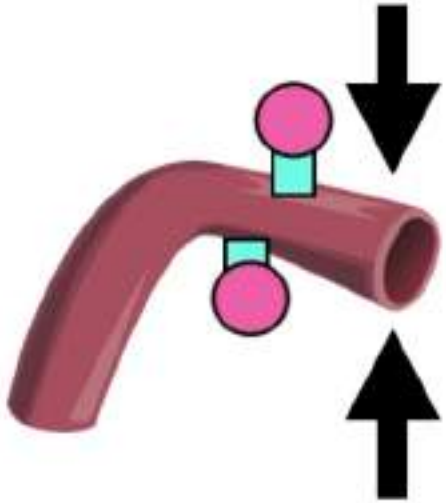
Hypertension

Non-Dihydropyridines

Heart

Decreased HR, Contraction

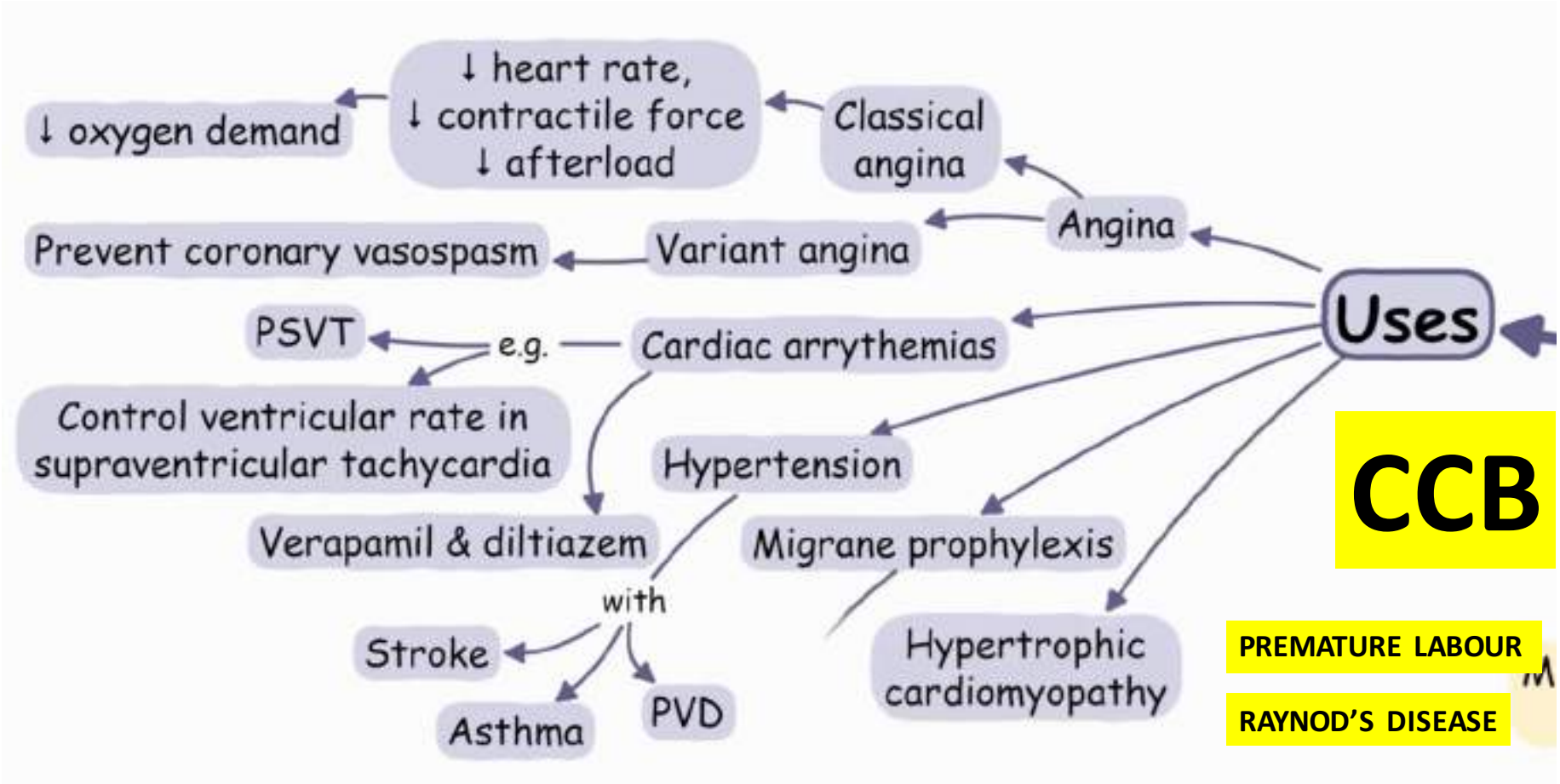
Tachydysrhythmias



Increase BP

Calcium Channel

Calcium


↓ heart rate,
↓ contractile force
↓ afterload
↓ oxygen demand
Classical angina
Angina
Variant angina
Prevent coronary vasospasm
Uses
PSVT
e.g.
Cardiac arrythemias
Control ventricular rate in supraventricular tachycardia
Hypertension
Verapamil & diltiazem
Migrane prophylexis
with
Stroke
Asthma
PVD
Hypertrophic cardiomyopathy
CCB
PREMATURE LABOUR
RAYNOD'S DISEASE

Therapeutic uses -SUMMARY

- ✓ **Antihypertensive**
- ✓ **Angina pectoris**
- ✓ **Arrhythmias**
- ✓ **Hypertrophic cardiomypathy**

Antihypertensive action- DHP

- **One of the first line drugs**
- **All 3 classes useful but DHP IS USED**
- **Long acting DHP like amlodipine is most preferred drug**
- **Reduction in PR without compromising cardiac output**
- **Advantages :-**
- **No Haemodynamic changes**
- **Can be prescribed in asthma, angina, peripheral vascular diseases**
- **No impairment of Male sexual function**
- **Do not interfere with serum levels of lipids uric acid or electrolytes**
- **Renal perfusion not affected**
- **No teratogenicity –may be used during pregnancy**

Angina

- Reduce frequency and severity of **classic** and **variant angina**
- **Classic angina** :-reduced afterload leads to reduces cardiac work
- No significant rise in coronary flow in obstruction but in normal individual coronary flow increases
- **Short acting DHPs NOT prescribed**
- **Variant angina – CCBs help by preventing arterial spasm. -MCQ**

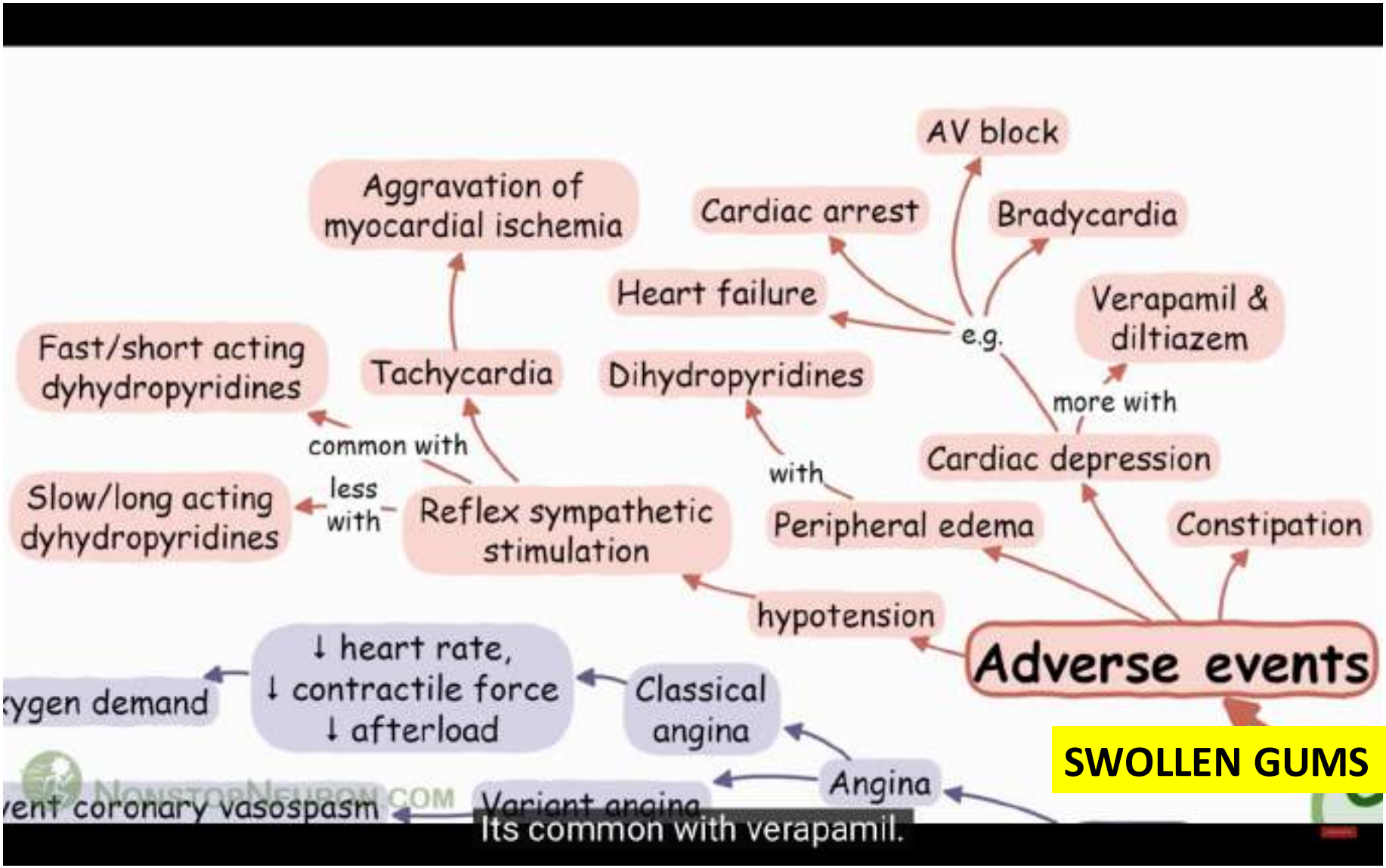
Arrhythmias

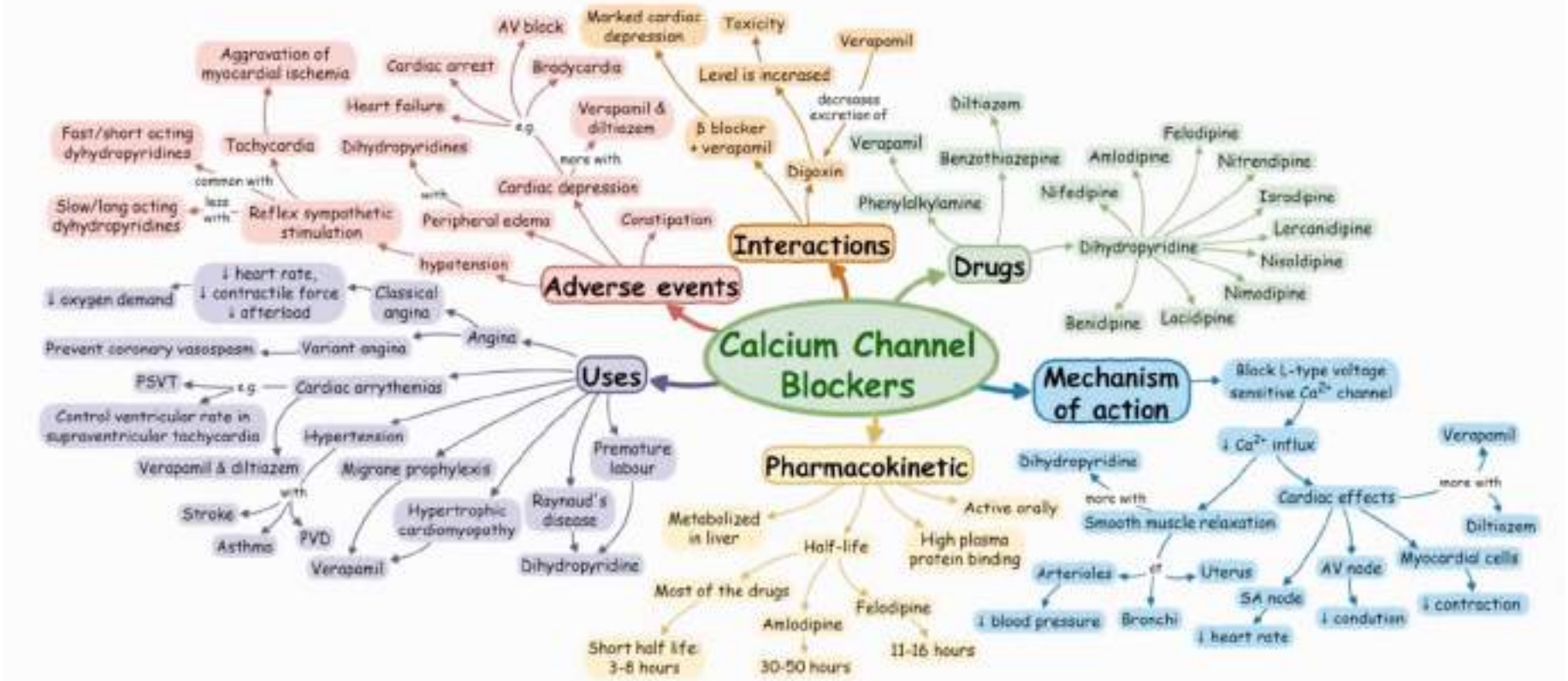
- **Verapamil and ditiazem –**
- **PSVT**

control of ventricular rate in Supraventricular arrhythmias

Hypertrophic Cardiomyopathy

- Verapamil –by negative inotropic action


AV block
Aggravation of myocardial ischemia
Cardiac arrest
Bradycardia
Heart failure
Verapamil & diltiazem
e.g.
Fast/short acting dyhydropyridines
Tachycardia
Dihydropyridines
more with
common with
with
Cardiac depression
less with
Slow/long acting dyhydropyridines
Reflex sympathetic stimulation
Peripheral edema
Constipation
hypotension
Adverse events
↓ heart rate, ↓ contractile force ↓ afterload
Classical angina
Angina
Variant angina
Its common with verapamil.
SWOLLEN GUMS



This completes our mind map of calcium channel blockers.

Central Sympatholytics

- **Clonidine** –imidazoline derivative, orally active
- complex action
- **1)alpha2 R in brainstem**
- Stimulation of alpha2 R in vasomotor centre –→↓sympathetic outflow→fall in BP and bradycardia

- 2)action on specific imidazoline R in brain also reduces sympathetic outflow

ADR of Clonidine

- **Common and disturbing side effects**

- Impotence
- Disturbed sleep
- Dryness of mouth.eyes.nose
- Sedation
- Salt and water retention
- Rebound hypertension on sudden withdrawal MCQ

Alpha Methyl Dopa

- Selective alpha 2 agonist

- Action on central alpha2 R to reduce sympathetic outflow
- **Probably acts on different set of neurons than clonidine**

✓Safe in pregnancy

Vasodilators

- **Hydralazine-**directly acting arteriolar vasodilators
- Little or no action on venous capacitance vessels
- Tpr reduced
- **Greater fall in diastolic BP than systolic BP**
- Compensatory tachycardia –marked

✓**Safe during pregnancy**

Sodium Nitroprusside

- Rapidly acting powerful vasodilator
- ***Relaxes both resistance and capacitance vessels--MCQ***
- Reduces tpr
- Reduces CO
- Reduces cardiac work
- Previously used for hypertensive emergencies but now labetalol is preferred

PHARMACOTHERAPY OF HEART FAILURE

DR PRADNYA ROTITHOR

Terminology

- Myocardium has two types of cells
- **1)Conducting tissue** : SA Node ,AV node ,His Purkinje system
- Automaticity : ability of a cell to generate electrical impulse spontaneously
- SA Node –pacemaker
- Excitability : ability of cell to undergo depolarization in response to stimulus
- **2)Contracting tissue** atria and ventricles
- Contractility :ability of myocrdium to contract adequately to pump blood out of heart

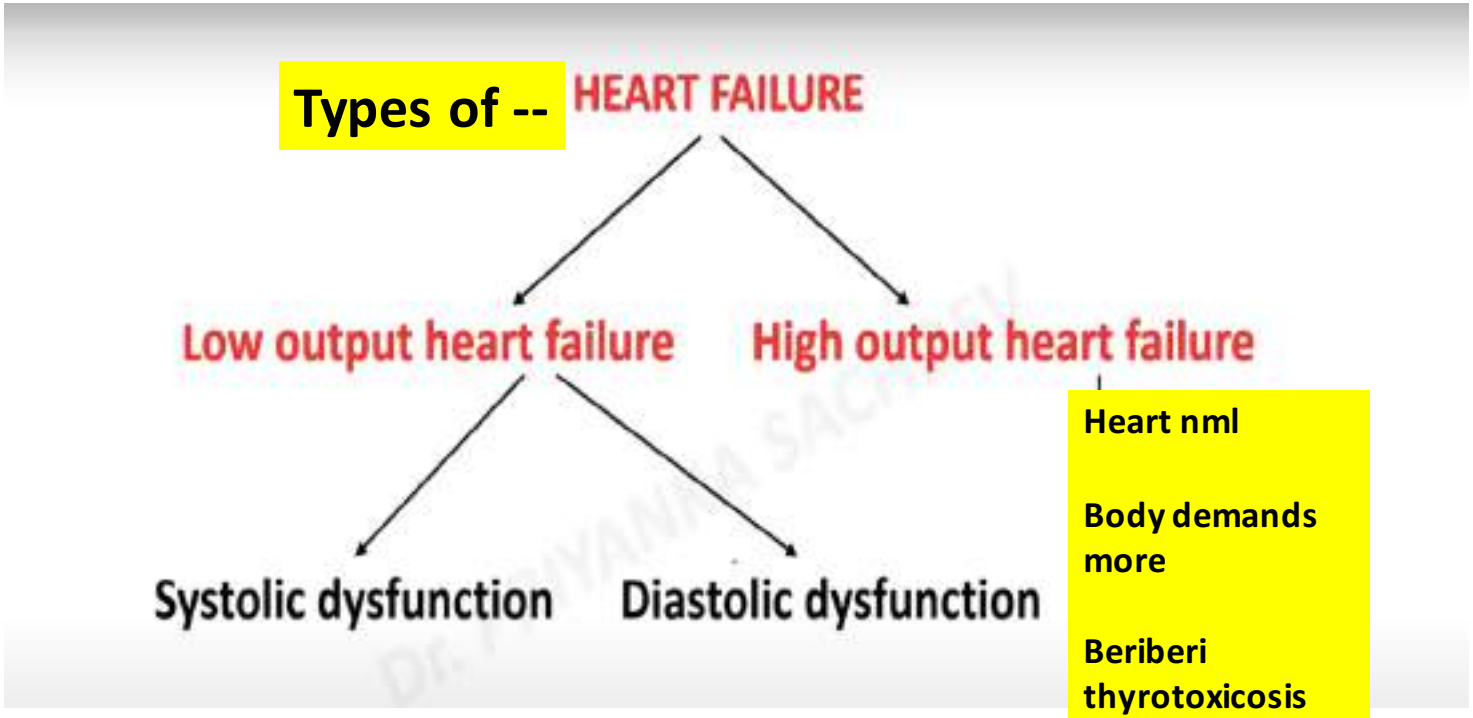
CO Preload Afterload

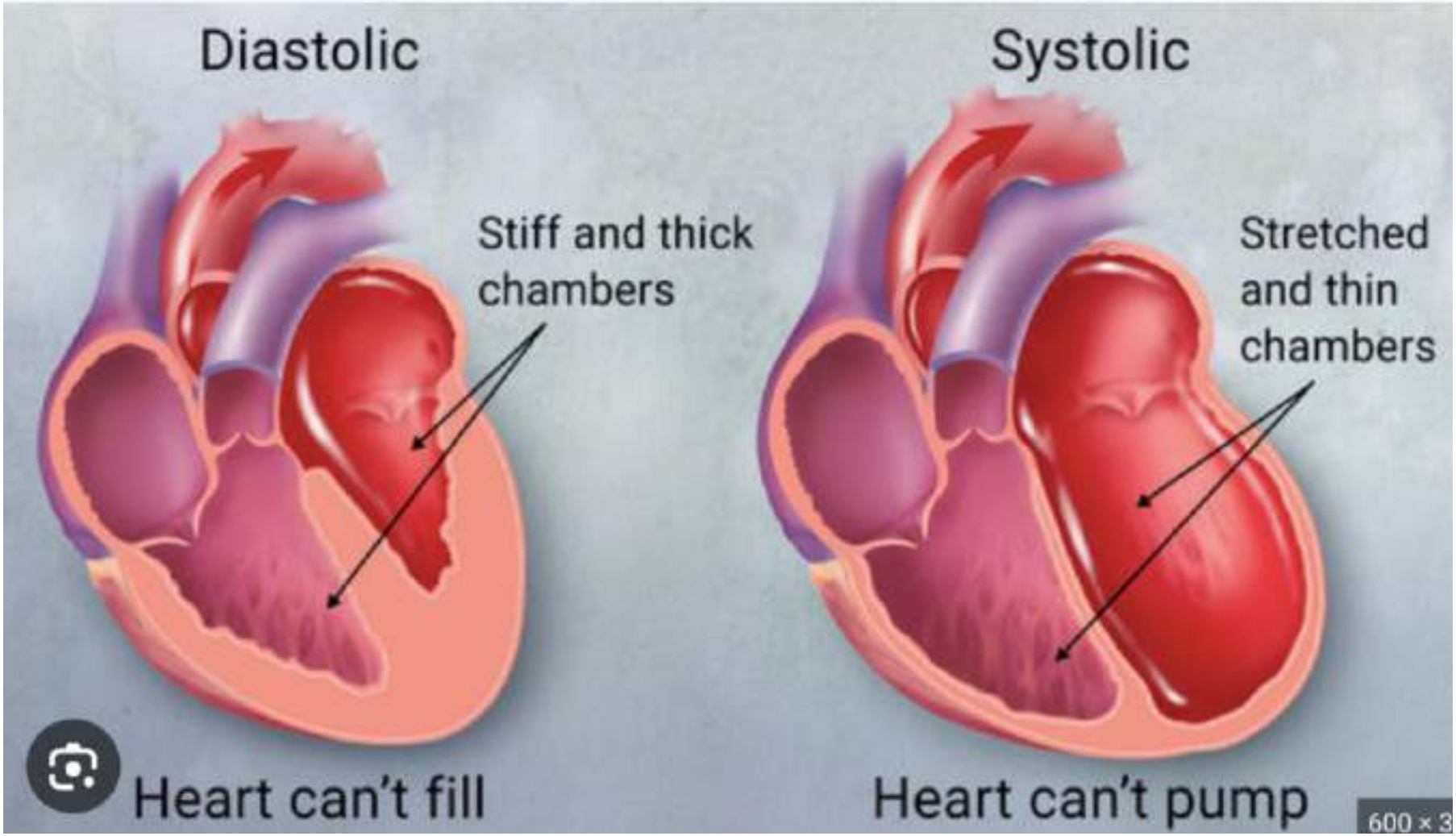
- CO =HR X SV
- Stroke volume depends upon preload afterload and contractility
- **Preload** : is the end diastolic pressure when the ventricle is filled
- load on heart due to VOLUME of blood reaching heart
- Thus on venous return- **more the venous return more the preload**
- **Afterload** : resistance to left ventricular ejection into aorta
- **Arterial constriction leads to more efforts from left ventricle to pump blood**
- Thus on total peripheral vascular resistance-more the tpr more the afterload

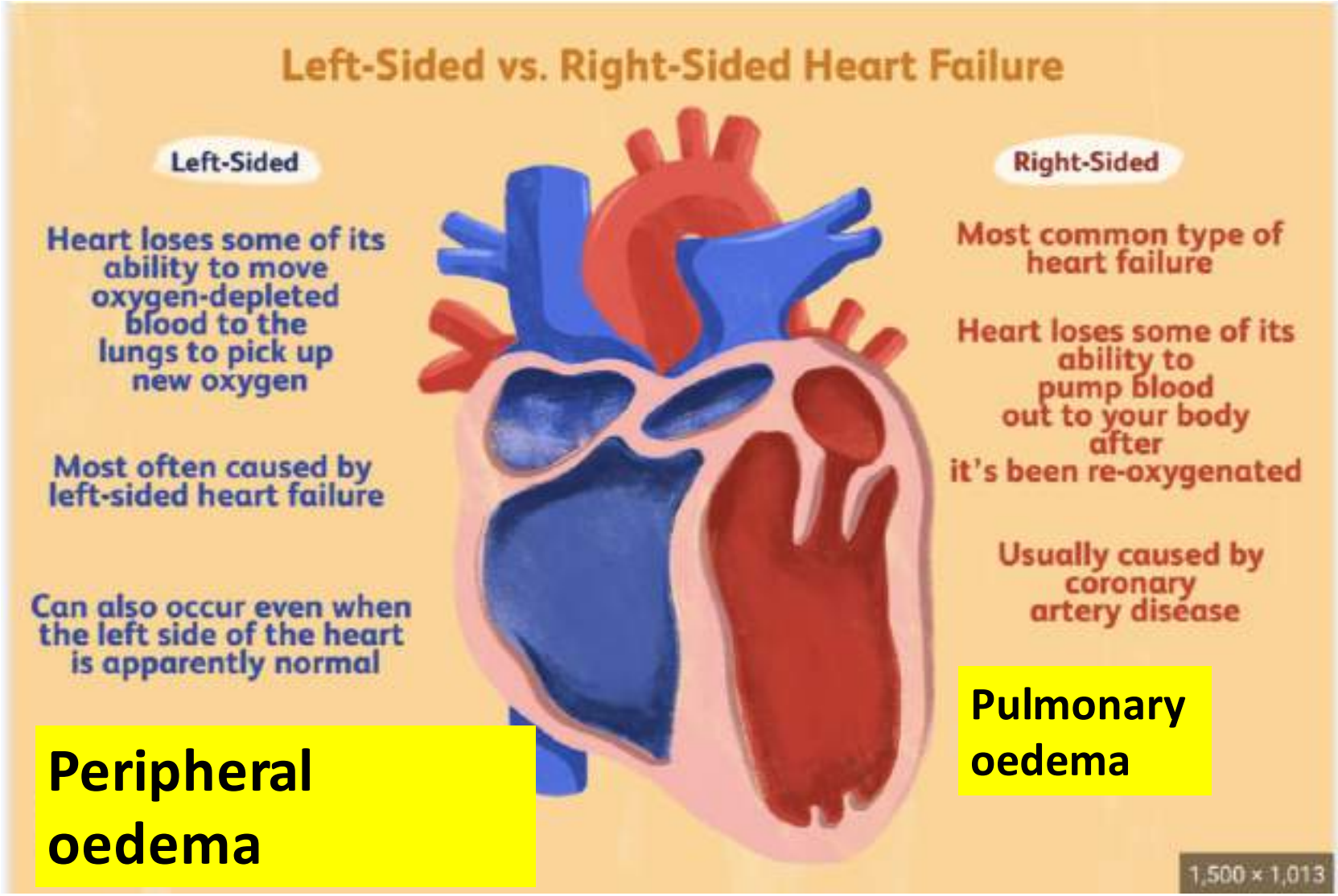
Congestive Heart Failure -CHF

- Heart is unable to pump adequate blood to meet the oxygen demand of the body
- ↓ CO ↓ Ejection fraction from normal 55 -65 % to < 40%

- **Symptoms** : tachycardia peripheral oedema pulmonary oedema
- Dyspnoea reduced exercise tolerance
- CHF is classified on degree of dyspneoa
- Enlarged liver
- Enlarged heart


Types of --
HEART FAILURE
Low output heart failure
High output heart failure
Systolic dysfunction
Diastolic dysfunction
Heart nml
Body demands more
Beriberi
thyrotoxicosis


Diastolic
Stiff and thick chambers
Heart can't fill
Systolic
Stretched and thin chambers
Heart can't pump
600 × 3


Left-Sided vs. Right-Sided Heart Failure
Left-Sided
Heart loses some of its ability to move oxygen-depleted blood to the lungs to pick up new oxygen
Most often caused by left-sided heart failure
Can also occur even when the left side of the heart is apparently normal
Peripheral oedema
Right-Sided
Most common type of heart failure
Heart loses some of its ability to pump blood out to your body after it's been re-oxygenated
Usually caused by coronary artery disease
Pulmonary oedema
1,500 × 1,013

Natural Compensatory mechanism

To increase CO

Stimulation of --

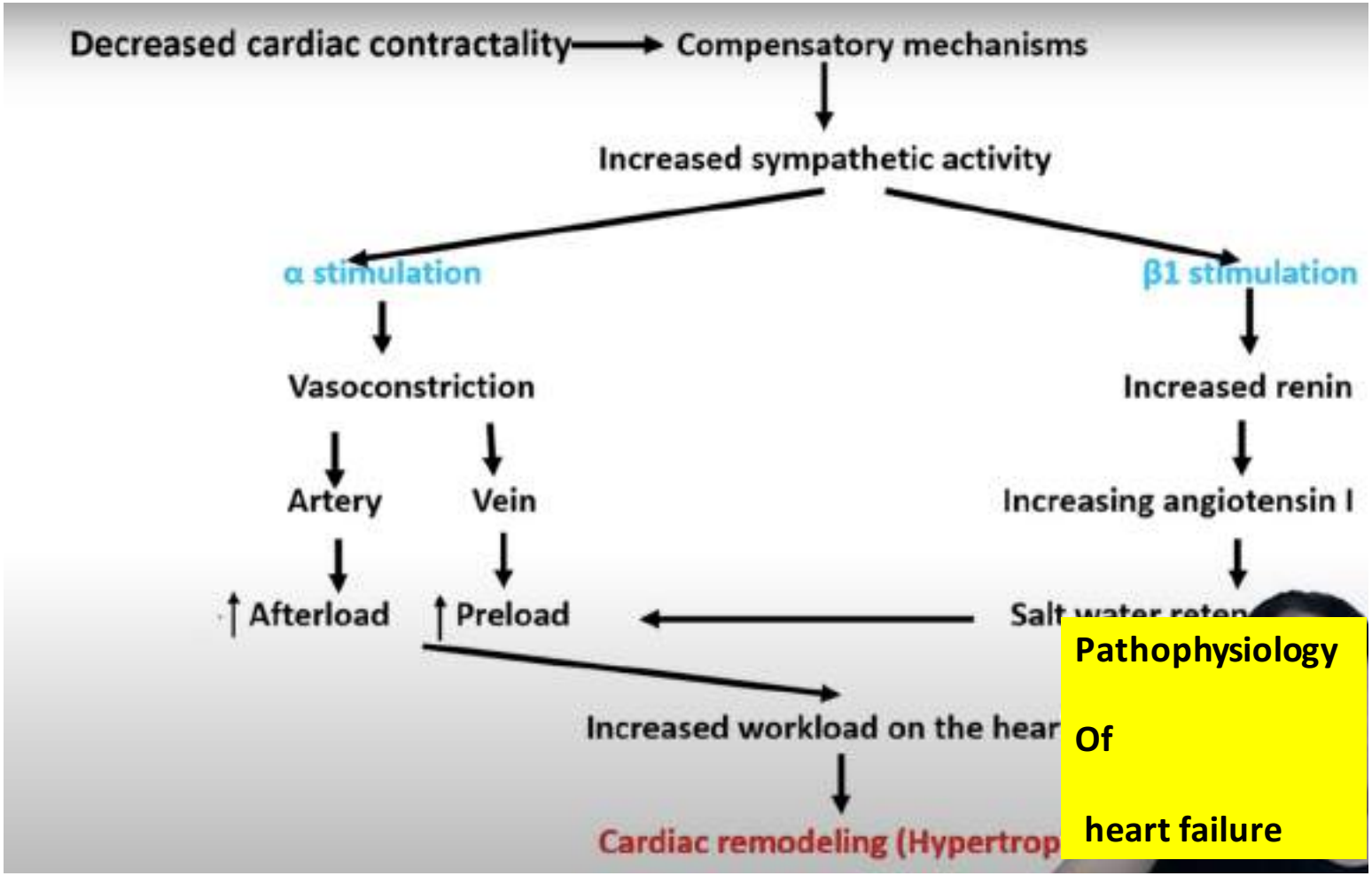
Sympathetic system

RAAS

Atrial natriuretic peptide

B1 R on heart promotes contraction

But rest of the compensatory mechanism leads to complications-RAAS –Angiotensin II effects

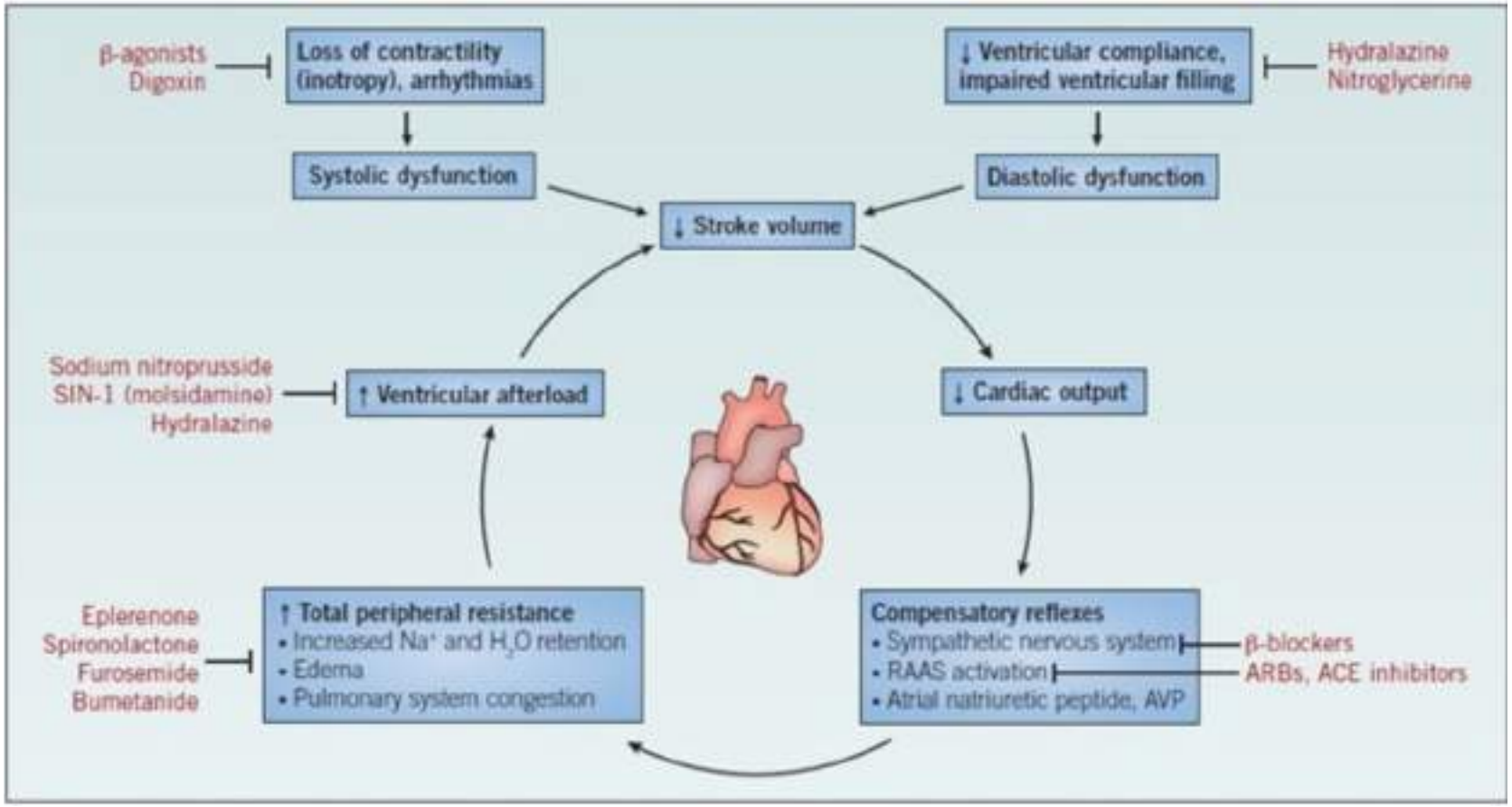

Decreased cardiac contractality
Compensatory mechanisms
Increased sympathetic activity
α stimulation
β1 stimulation
Vasoconstriction
Increased renin
Artery
Vein
Increasing angiotensin I
↑ Afterload
↑ Preload
Increased workload on the hear
Cardiac remodeling (Hypertrop
Pathophysiology
Of
heart failure

Drug therapy

- **Aim: increase CO and reduce Congestion**
- **To increase contractility :**
- 1)cardiac glycosides: digoxin digitalis
- 2) beta adrenergic agonist: dopamine dobutamine dopexamine
- 3) PDE inhibitors: amrinone milrinone sildenafil
- 4) newer ionotropic drugs:levosimendan istaroxime

To overcome compensatory mechanism

- Diuretics:furesimide bumetinide torsemide
- Vasodilators :
- Arteriolar dilators :hydralazine
- Vonodilators : nitrates
- Both arteriolar and venodilators : sodium nitroprusside
- ACEI ARB CCB And alpha blockers like prazosin
- Others –beta blockers
- Newer drugs –serelaxin ivabradine ularitide


β-agonists
Digoxin
Loss of contractility (inotropy), arrhythmias
↓ Ventricular compliance, impaired ventricular filling
Hydralazine
Nitroglycerine
Systolic dysfunction
Diastolic dysfunction
↓ Stroke volume
Sodium nitroprusside
SIN-1 (molsidamine)
Hydralazine
↑ Ventricular afterload
↓ Cardiac output
Eplerenone
Spironolactone
Furosemide
Bumetanide
↑ Total peripheral resistance
• Increased Na+ and H2O retention
• Edema
• Pulmonary system congestion
Compensatory reflexes
• Sympathetic nervous system
• RAAS activation
• Atrial natriuretic peptide, AVP
β-blockers
ARBs, ACE inhibitors

Cardiac glycosides

- Obtained from plant –foxglove family
- leaves of tree-
- Digitoxin -digitalis purpurea
- Digoxin- digitalis lanta
- Pharmacological actions
- Positive ionotropic action
- Cardiotonic effect
- Reduction in heart rate- bradycardia

Comparison between Digoxin & Digitoxin

Name	Digoxin (Lanoxin®)	Digitoxin Most liposoluble cardiac glycoside
Source	*D. lanata.*	*D. purpurea*, & *lanata*
Hydrolysis	→ Digoxigenin + 3 digitoxose	Digitoxigenin+3 Digitoxose
Administration	Usually oral	Oral
Onset of action	After 30 min to 2 hours	After 1-4 hours
Peak	At 2 to 6 hours.	At 8 - 14 hours
Plasma half-life	30 to 40 hours	168 to 192 hours
Complete elimination after discontinuation of therapy	6 to 8 weeks	3 to 5 weeks
Elimination	Eliminated through kidney	Eliminated through liver so recommended for patients with impaired renal function.
Full therapeutic effect	0.5-2ng / ml	14-26 ng / ml
Toxicity symptoms	2.5 ng / ml	35 ng / ml
Indication	When risk of intoxication is great, as it is relatively short-acting&rapidly eliminated	Recommended for patients with impaired renal function.

Positive inotropic action

- Force of contraction increases
- Stroke volume is raised
- Thereby CO improves
- Systole shortened ,diastole prolonged –more rest to heart and better filling of coronaries

- **Dose dependent actions**

Reduced HR

Bradycardia –due to

Increased vagal tone

Direct action on SA AV node

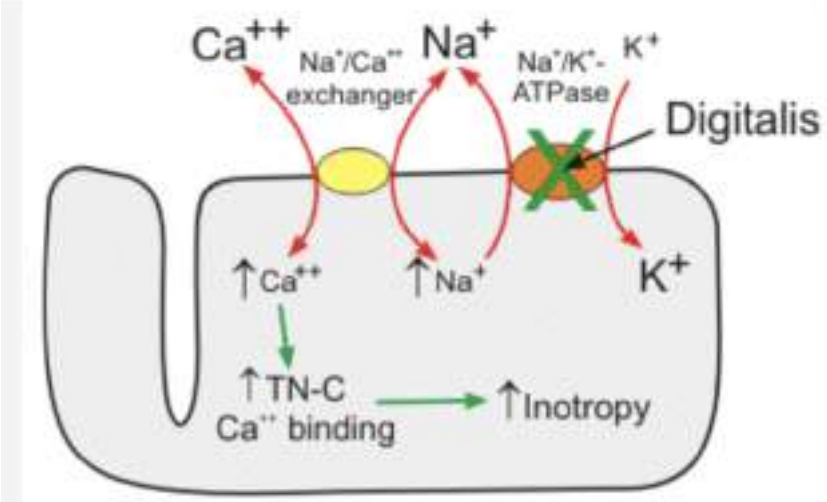
Reduced sympathetic outflow

No significant action on BP

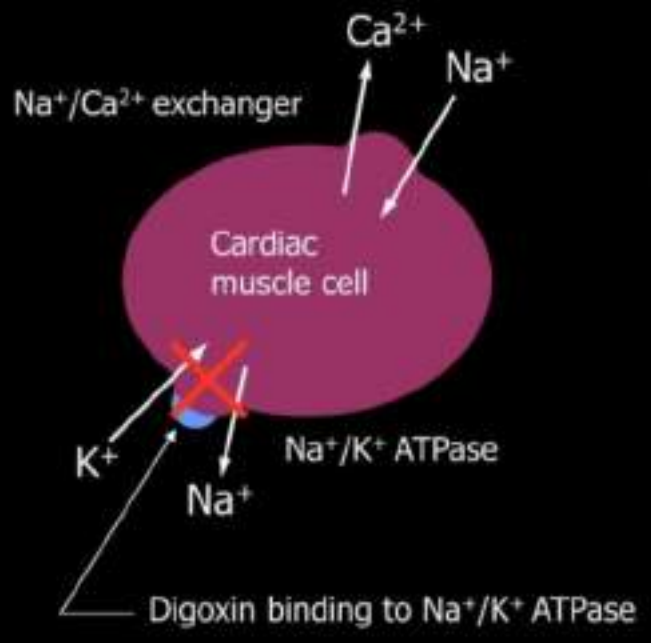
ECG Changes : T inversion PR interval raised shortened QT interval ST depression

MOA

- Inhibit enzyme Na K ATPase—also called as Na pump of heart
- Increased Na and Ca in myocardial cell
- More Ca available for contraction



Mechanism of action of Digoxin



- Digoxin binds to and inhibit Na^+/K^+ ATPase.
- Increases Na^+ in the cell.
- Decreases Ca^{2+} flowing out causing
  - increase force of contraction (+ve ionotropic)
  - decrease heart rate (-ve chronotropic)

Digitalis

↓

Inhibition of Na+ K+ ATPase

↓

↓ Na exit (Na / K exchange)

↓

↑ Intracellular Na

↓

↓ Na / Ca exchange

↓

↑ Ca in the cell

↓

Further ↑ in Ca release from SR (ryanodine receptor)

↓

Ca binds to troponin

↓

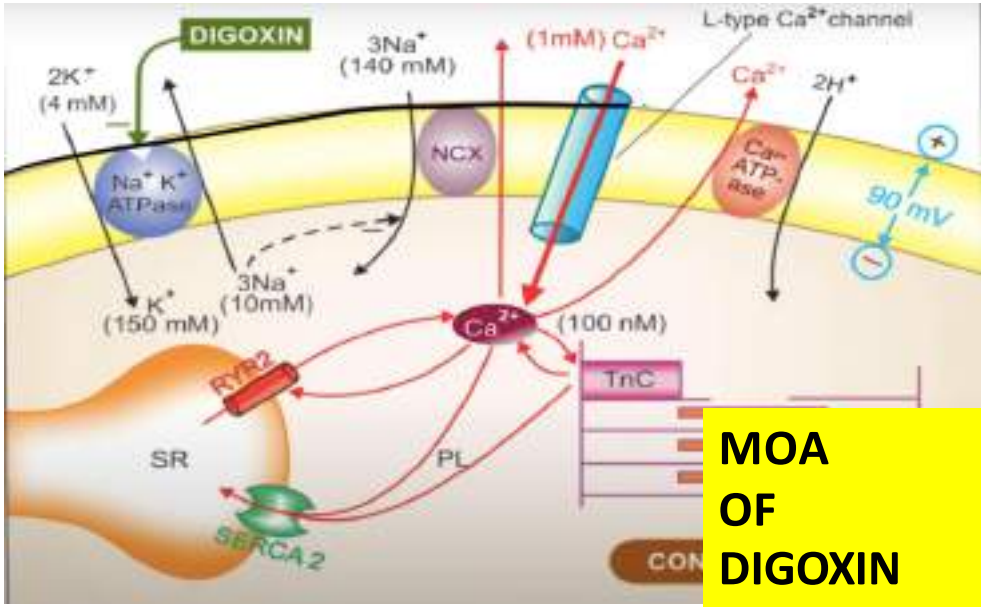
Inhibition of troponin - tropomyosin on actin- myosin binding is released

↓

Actin + myosin combines

↓

↑ Contraction of muscles



MOA OF DIGOXIN

Pharmacokinetics

- Well absorbed orally
- Food delays absorption
- LOW THERAPEUTIC INDEX
- Cumulation seen
- Once suited patient should not change the manufacturing brand
- Preparation: digoxin -0.125mg -0,5mg
- **DIGITILIZATION –**response takes about a week with low dose given to mild to moderate cases
- Rapid digitilization –0.5 to 0.75mg every 8 hours
- needs frequent dosing and constant monitoring

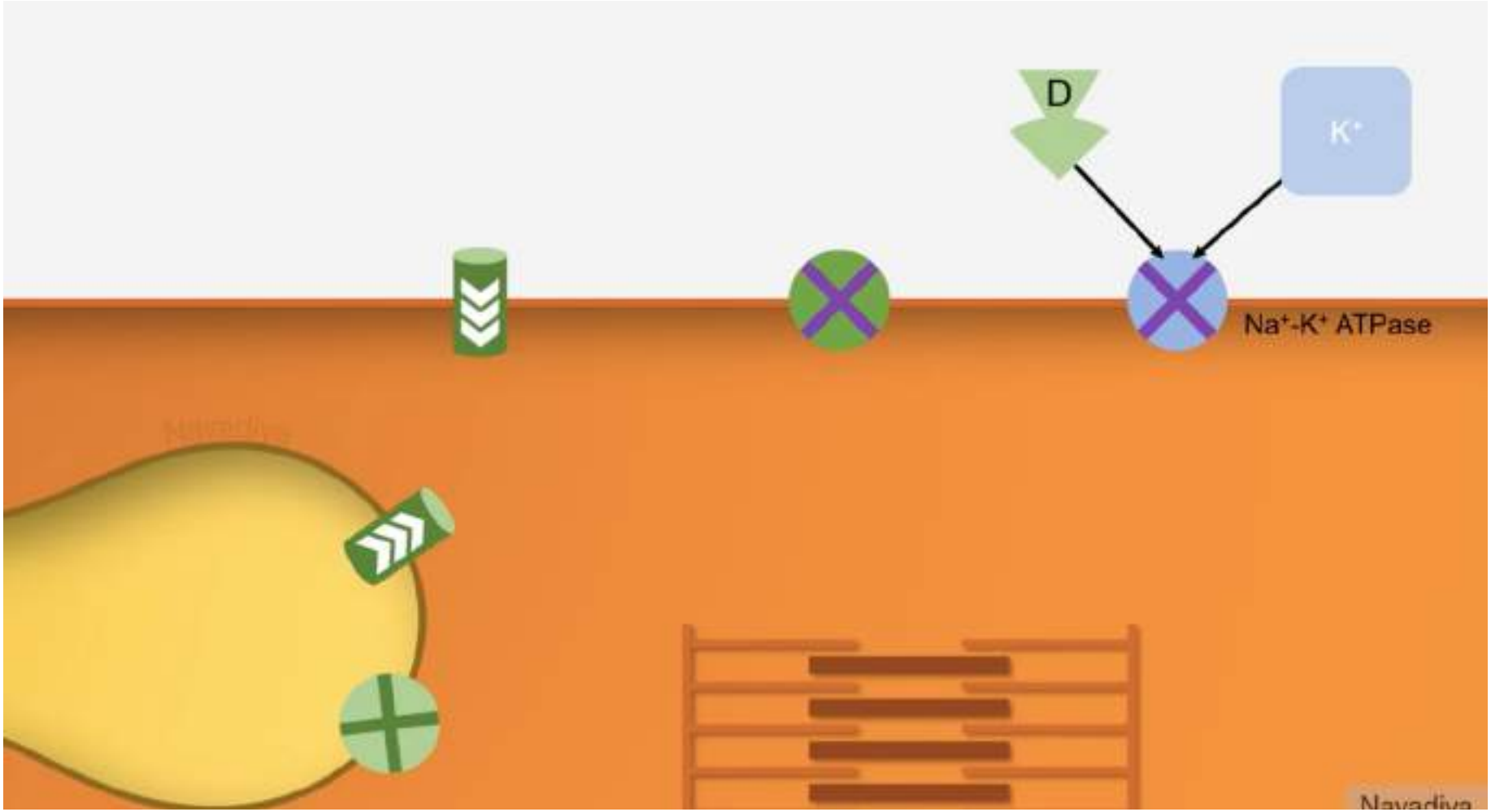
ADR-low TI

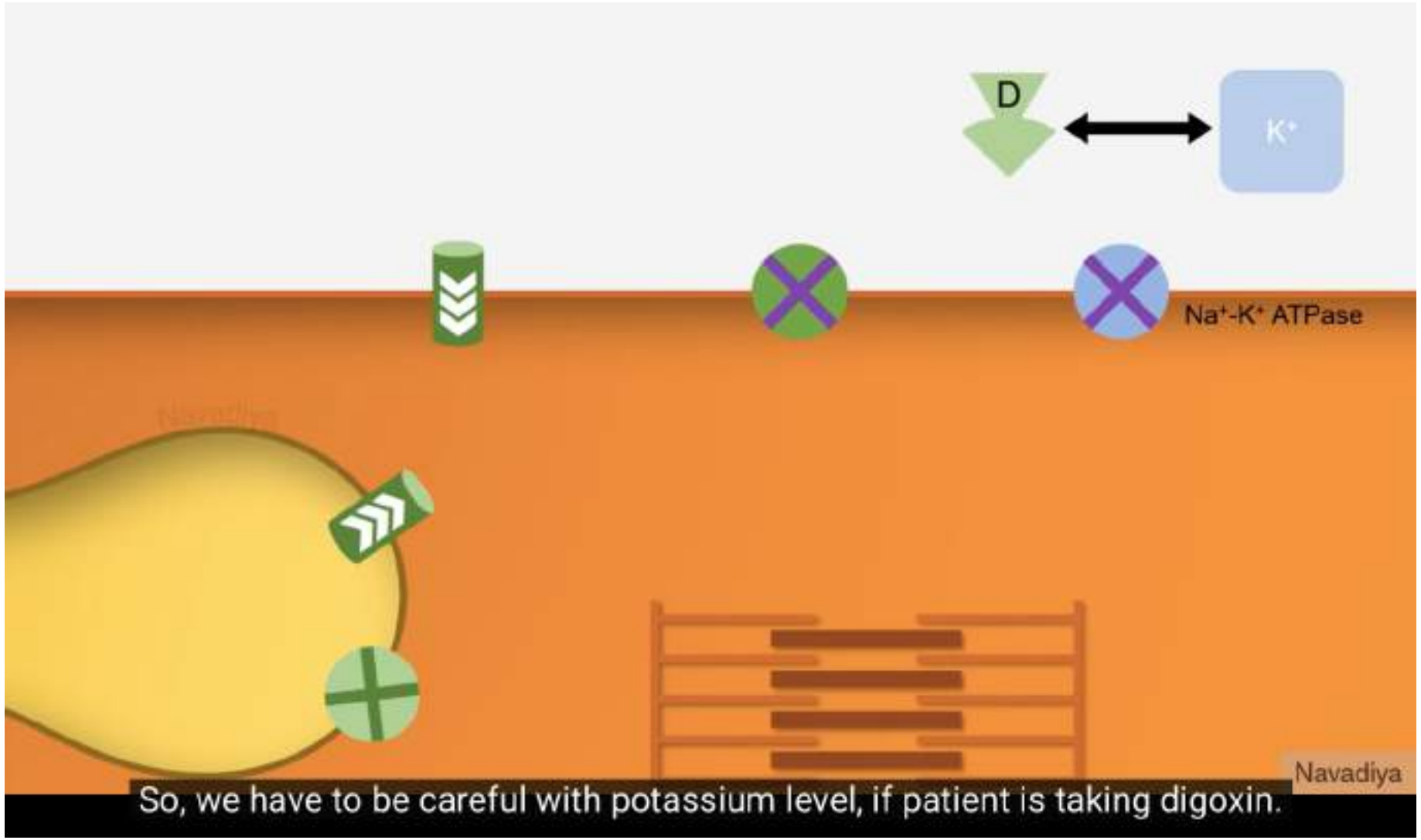
- Cardiac and extra cardiac
- Extracardiac:
- GIT –First to appear ANV –direct stimulation of CTZ
- Neurotoxicity: vertigo blurred vision disturbed colour vision neuralgia
- Hallucination etc
- Others – allergy rash
- Gynaecomastia

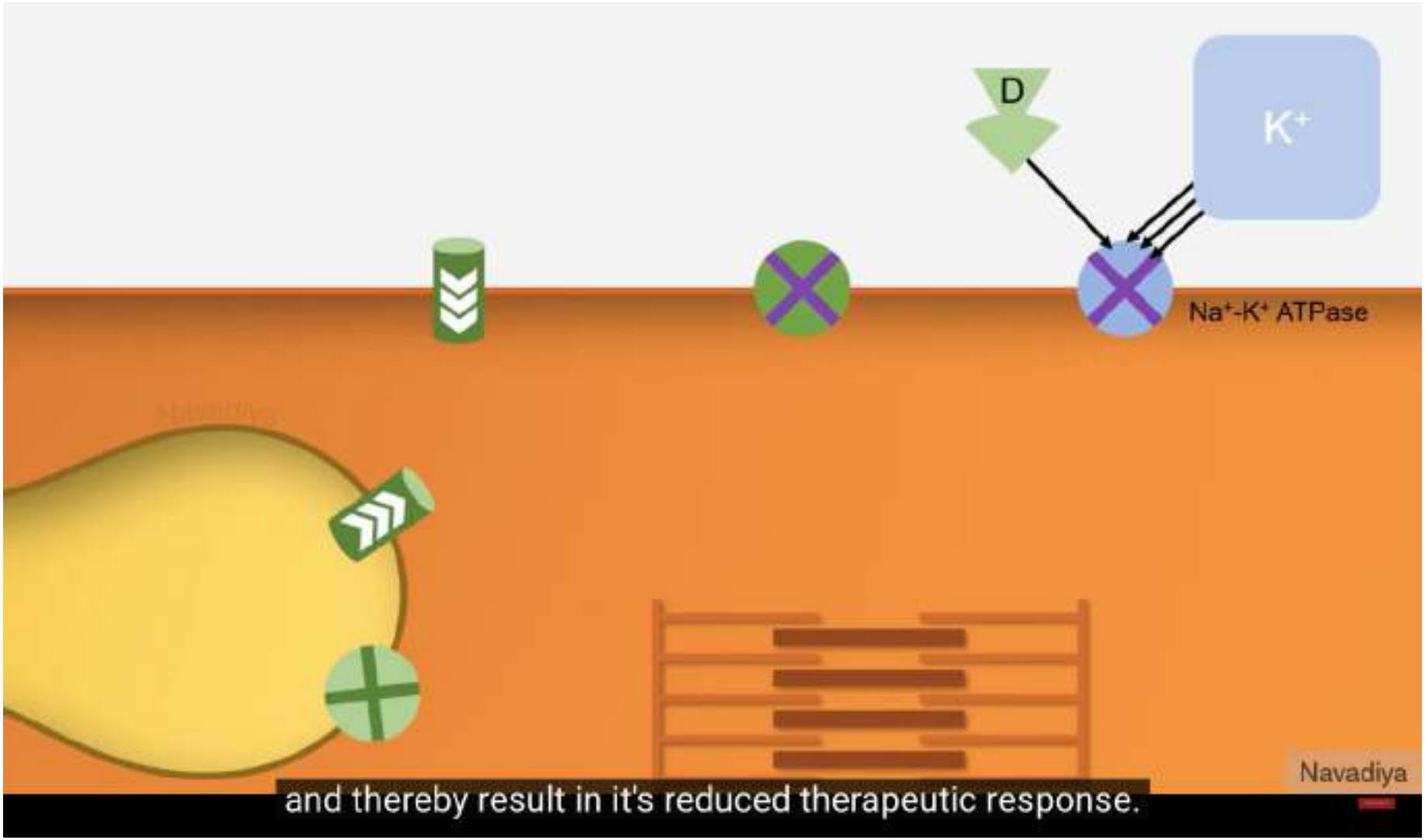
Cardiac toxicity

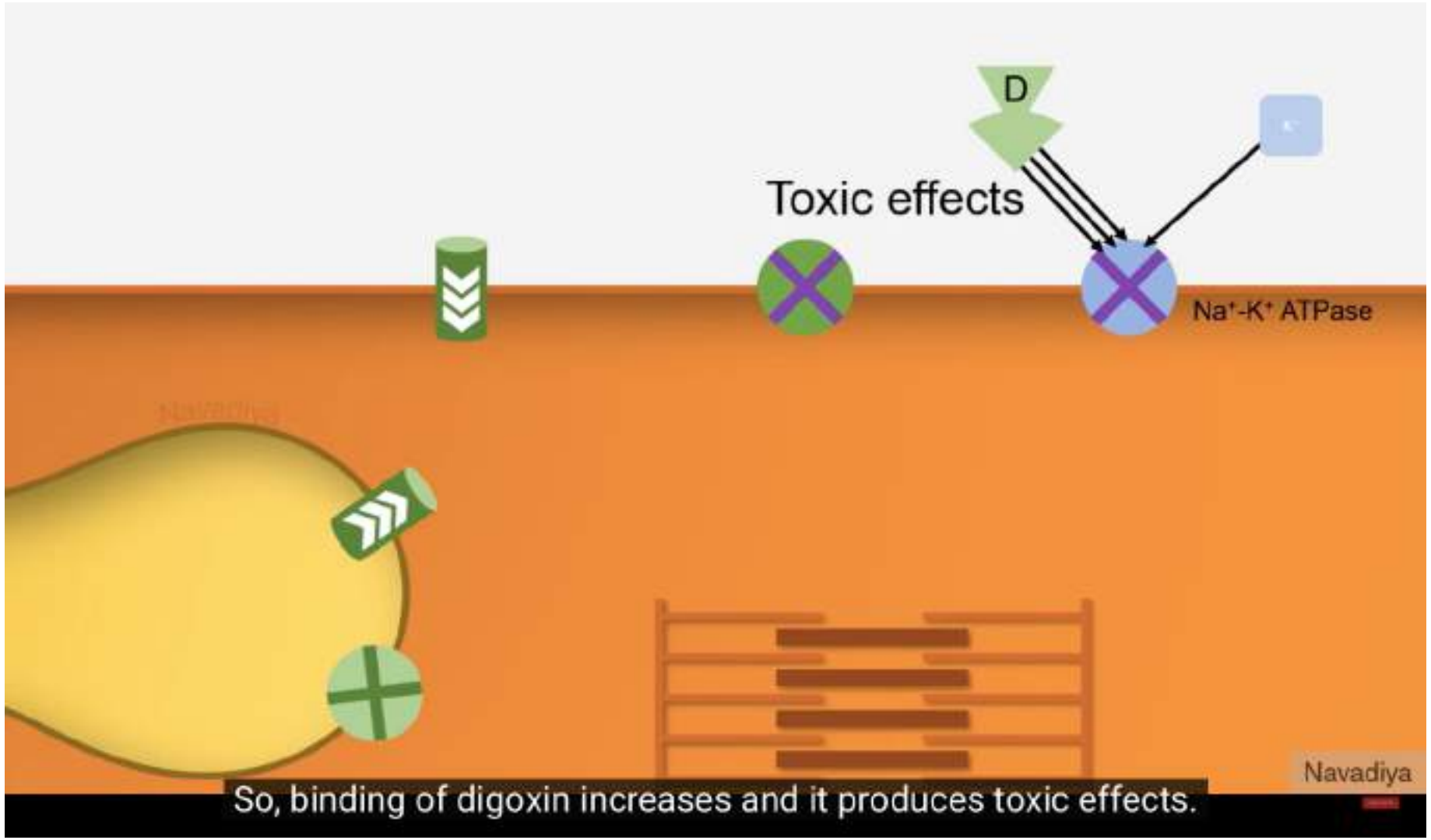
- Arrhythmias- of any type
- Extrasystole
- Bradycadia
- Pulse bigeminy
- AV Block

- Hypokalaemia enhances digoxin toxicity
- Both K and digitalis compete to bind with Na pump
- Hyperkalemia reduces digitalis binding and thus clinical action
- As opposed to that low k levels increase digitalis binding with Na pump and hence more action leading to more toxicity


D
K+
Na+-K+ ATPase


D
K+
Na+-K+ ATPase
Navadiya
So, we have to be careful with potassium level, if patient is taking digoxin.


D
K+
Na+-K+ ATPase
Navadiya
and thereby result in it's reduced therapeutic response.


D
Toxic effects
Na⁺-K⁺ ATPase
Navadiya
So, binding of digoxin increases and it produces toxic effects.

- Serum K levels DO NOT indicate myocardial k level
- Nausea vomiting diarrhoea lead to low K thus high digitalis toxicity

- Hypercalcaemia- increased digitalis toxicity especially arrhythmias
- Rapid digitilization and iv administration –more toxicity

- Elderly patient with poor reserve are more prone

Treatment of toxicity

- Stop the drug
- Oral k
- Iv k
- Ventricular arrhythmia-lignocaine or phenytoin
- Bradycardia –atropine
- SVT-propranolol
- Temporary pacemaker –AV block

Drug interactions

- Drugs that increase digoxin action
- Diuretics –cause hypokalaemia
- Quinidine verapamil methyldopa –increase digoxin levels

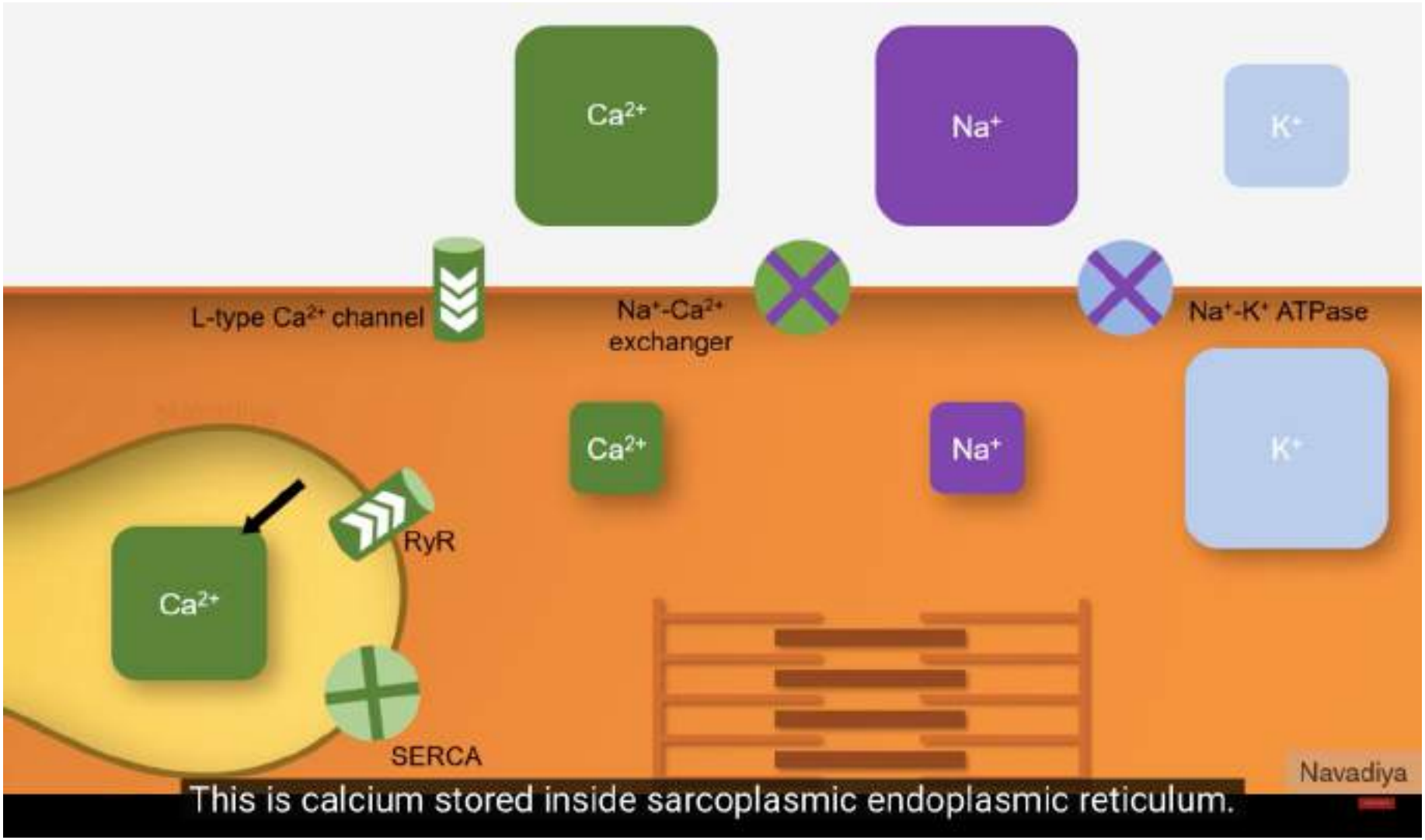
- Drugs that reduce digoxin levels
- By decreasing absorption- antacids neomycin metoclopramide
- By hastening metabolism- rifampicin phenobarbitone

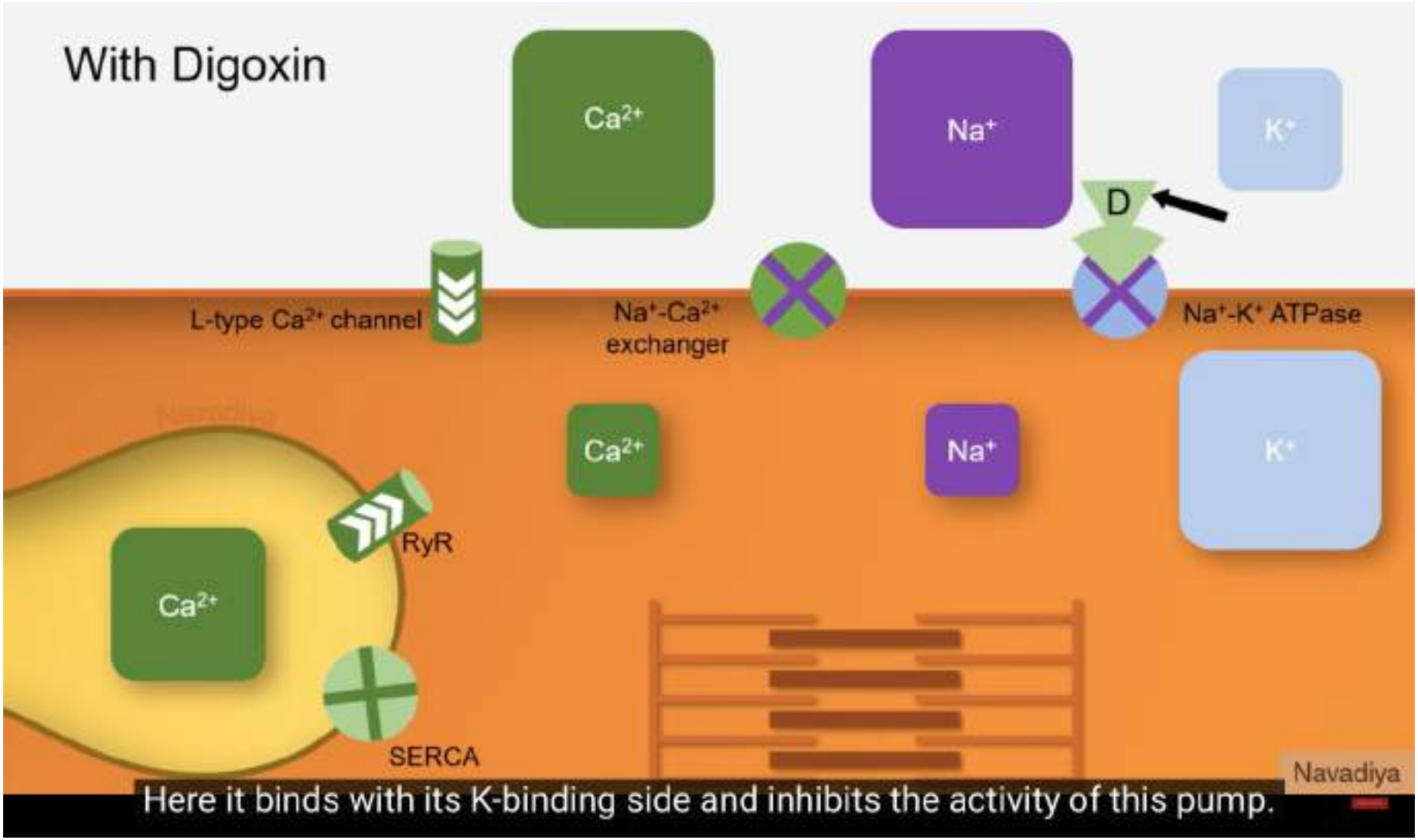
Digibind -*****MCQ

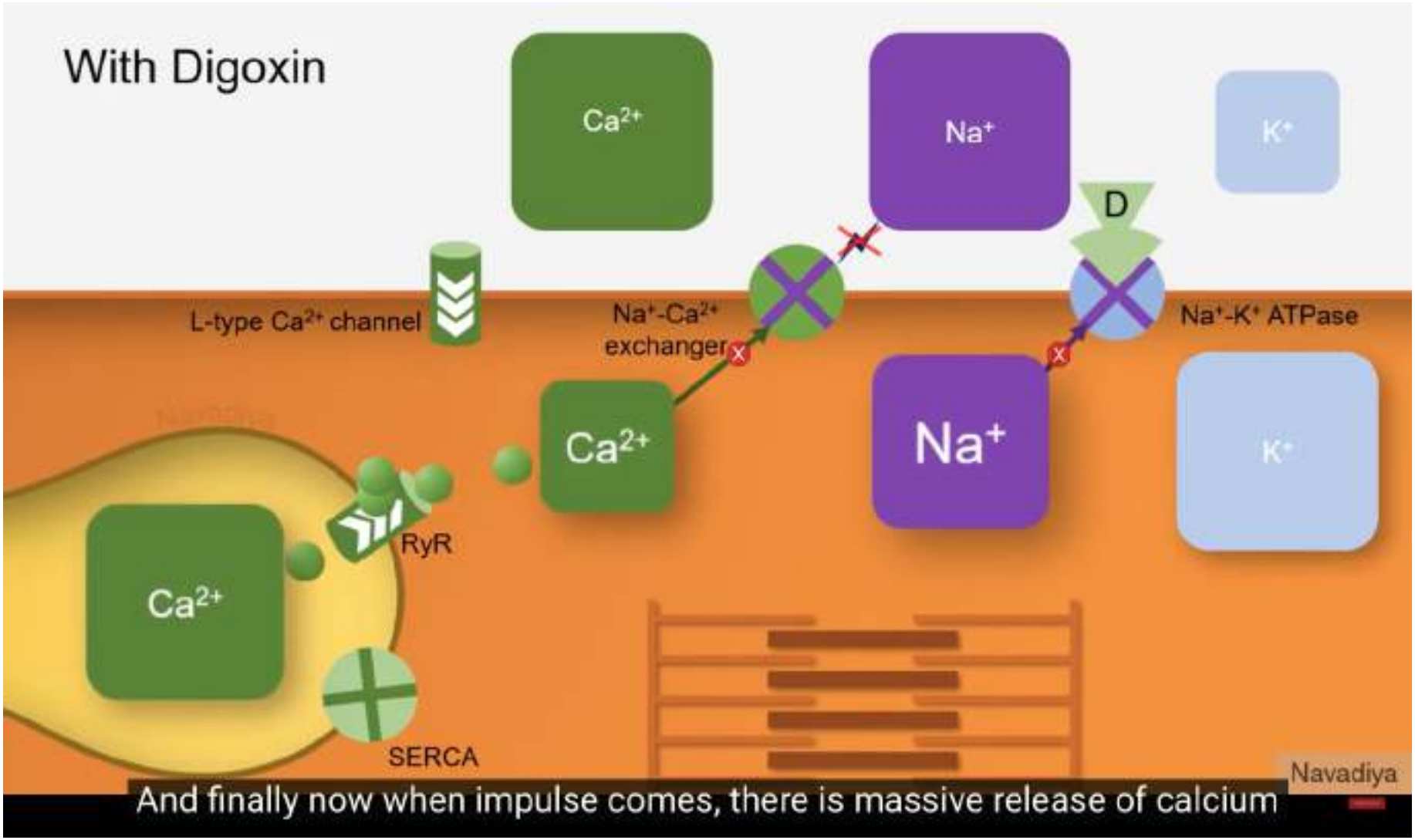
- Anti digoxin immunotherapy
- Obtained from sheep
- Binds to digoxin and reverses toxicity
- Life saving in critical toxicity

Therapeutic uses

- Heart failure
- Cardiac arrhythmias- atrial flutter and fibrillation
- PSVT


Ca2+
Na+
K+
L-type Ca2+ channel
Na+-Ca2+ exchanger
Na+-K+ ATPase
Ca2+
Na+
K+
RyR
Ca2+
SERCA
Navadiya
This is calcium stored inside sarcoplasmic endoplasmic reticulum.


With Digoxin
Ca2+
Na+
K+
D
L-type Ca2+ channel
Na+-Ca2+ exchanger
Na+-K+ ATPase
Ca2+
Na+
K+
RyR
Ca2+
SERCA
Navadiya
Here it binds with its K-binding side and inhibits the activity of this pump.


With Digoxin
Ca2+
Na+
K+
D
L-type Ca2+ channel
Na+-Ca2+ exchanger
Na+-K+ ATPase
Ca2+
Na+
K+
RyR
Ca2+
SERCA
Navadiya
And finally now when impulse comes, there is massive release of calcium

DIURETICS

DR PRADNYA ROTITHOR

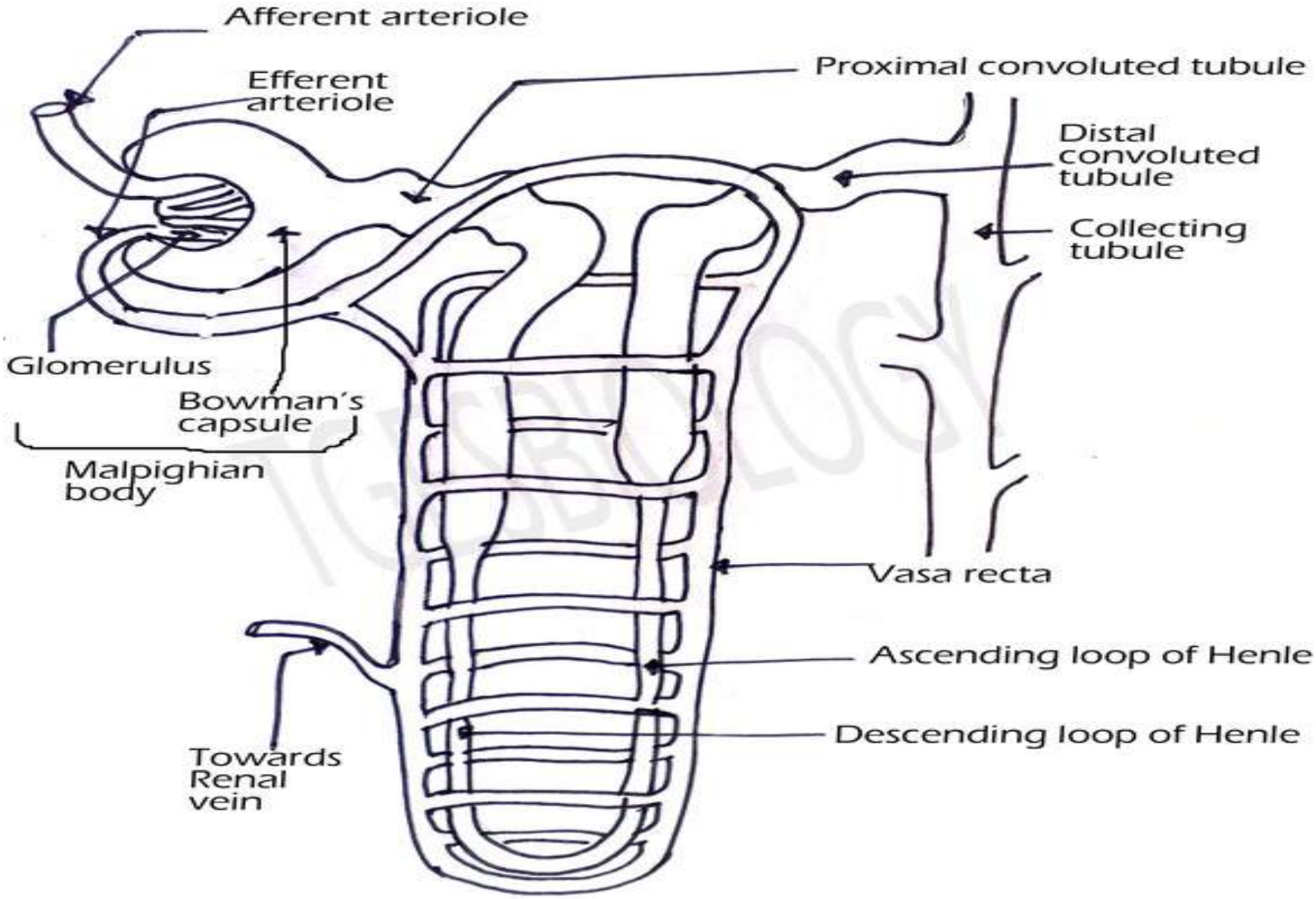
MECHANISM OF URINE FORMATION

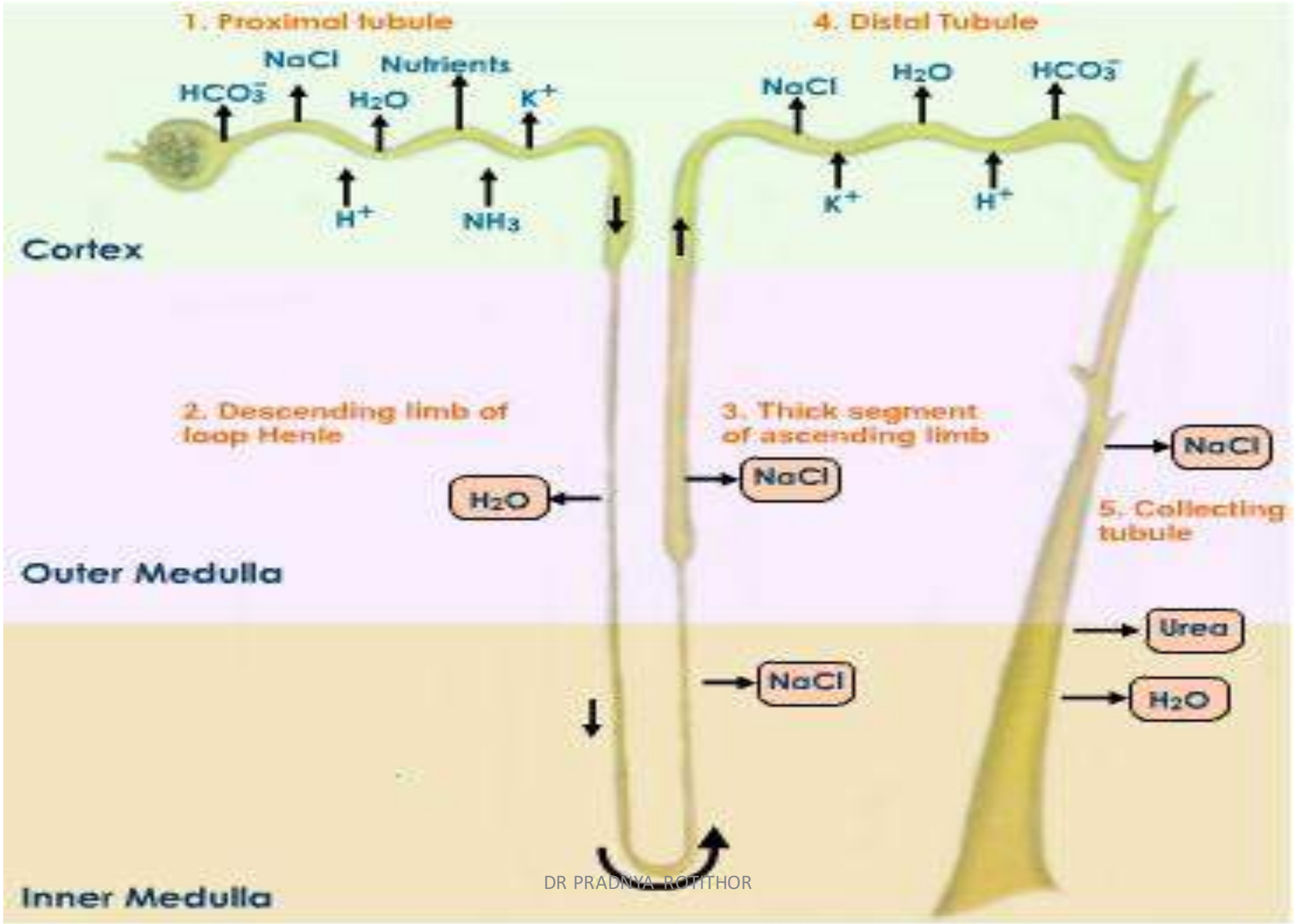
- GF –180L/24 Hrs
- 99 % of GF –reabsorbed
- Urine output -1.5 L/day
- Diuretics prevent re absorption to produce diuresis
- Re absorption happens due to –

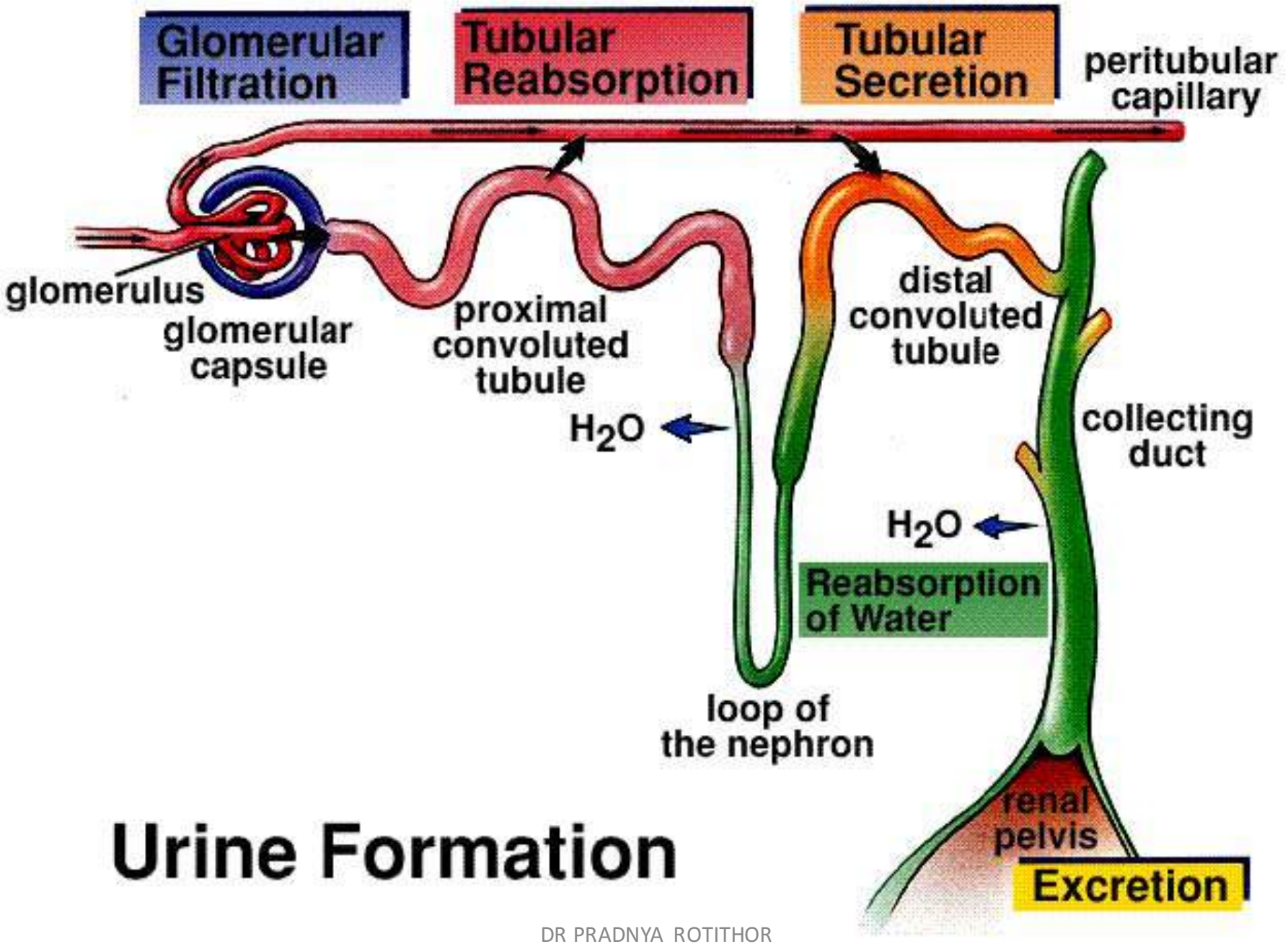
  osmotic gradient between renal interstitium and tubular fluid

  active transport of ions

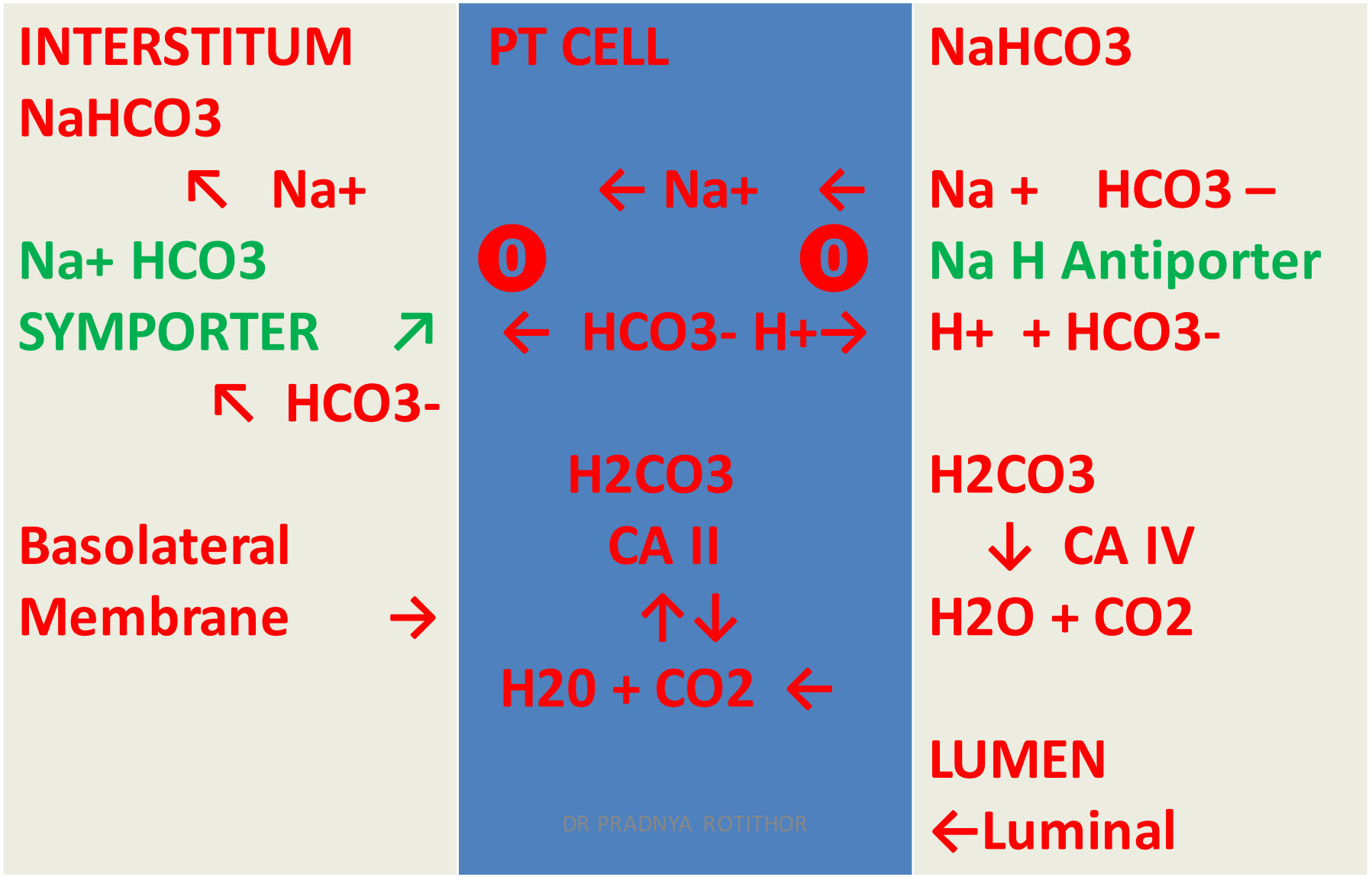
  hormones like aldosterone /ADH


Afferent arteriole
Efferent arteriole
Proximal convoluted tubule
Distal convoluted tubule
Collecting tubule
Glomerulus
Bowman's capsule
Malpighian body
Vasa recta
Ascending loop of Henle
Descending loop of Henle
Towards Renal vein

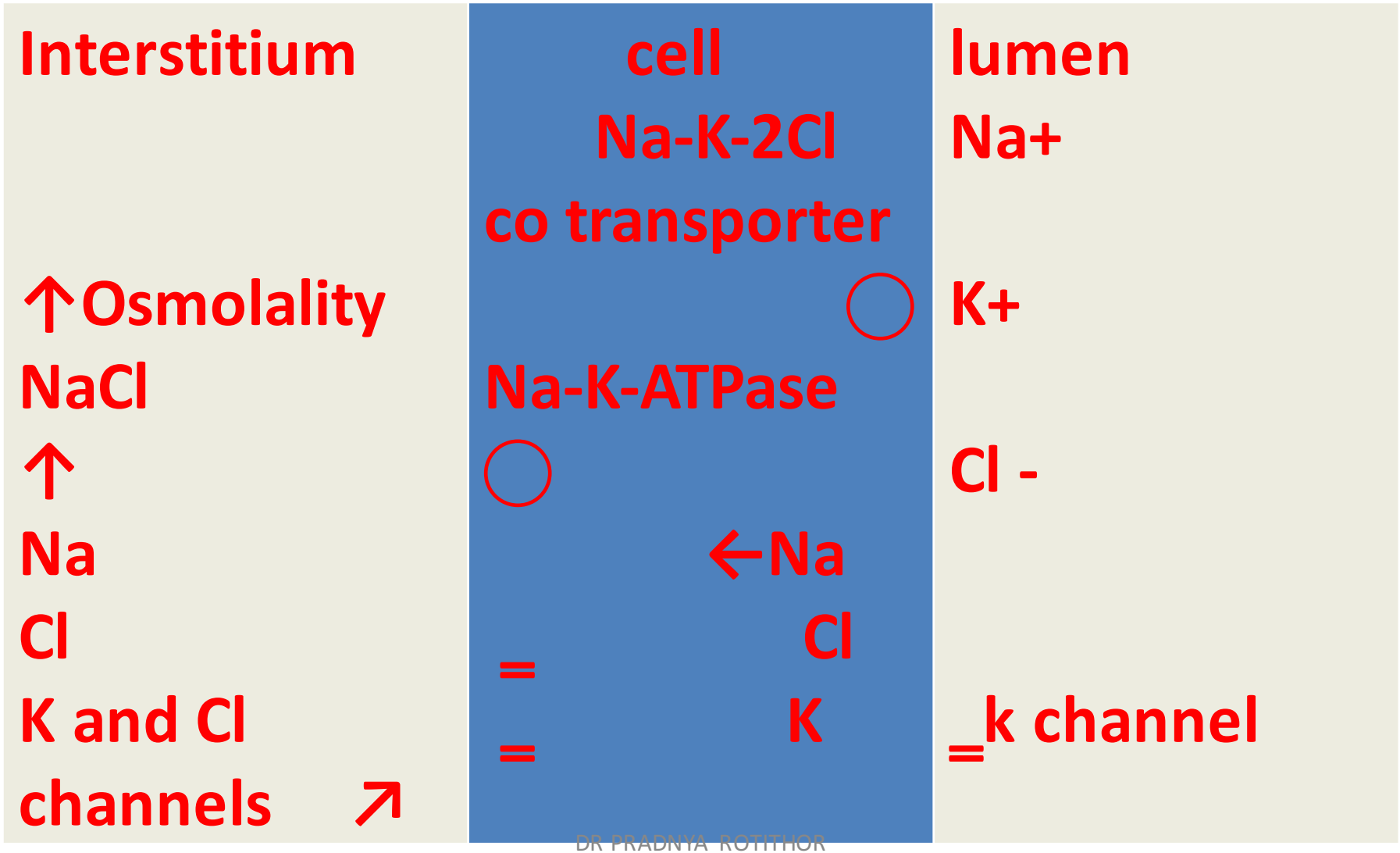



Glomerular Filtration
Tubular Reabsorption
Tubular Secretion
peritubular capillary
glomerulus
glomerular capsule
proximal convoluted tubule
distal convoluted tubule
collecting duct
H_2O
H_2O
Reabsorption of Water
loop of the nephron
renal pelvis
Excretion
Urine Formation

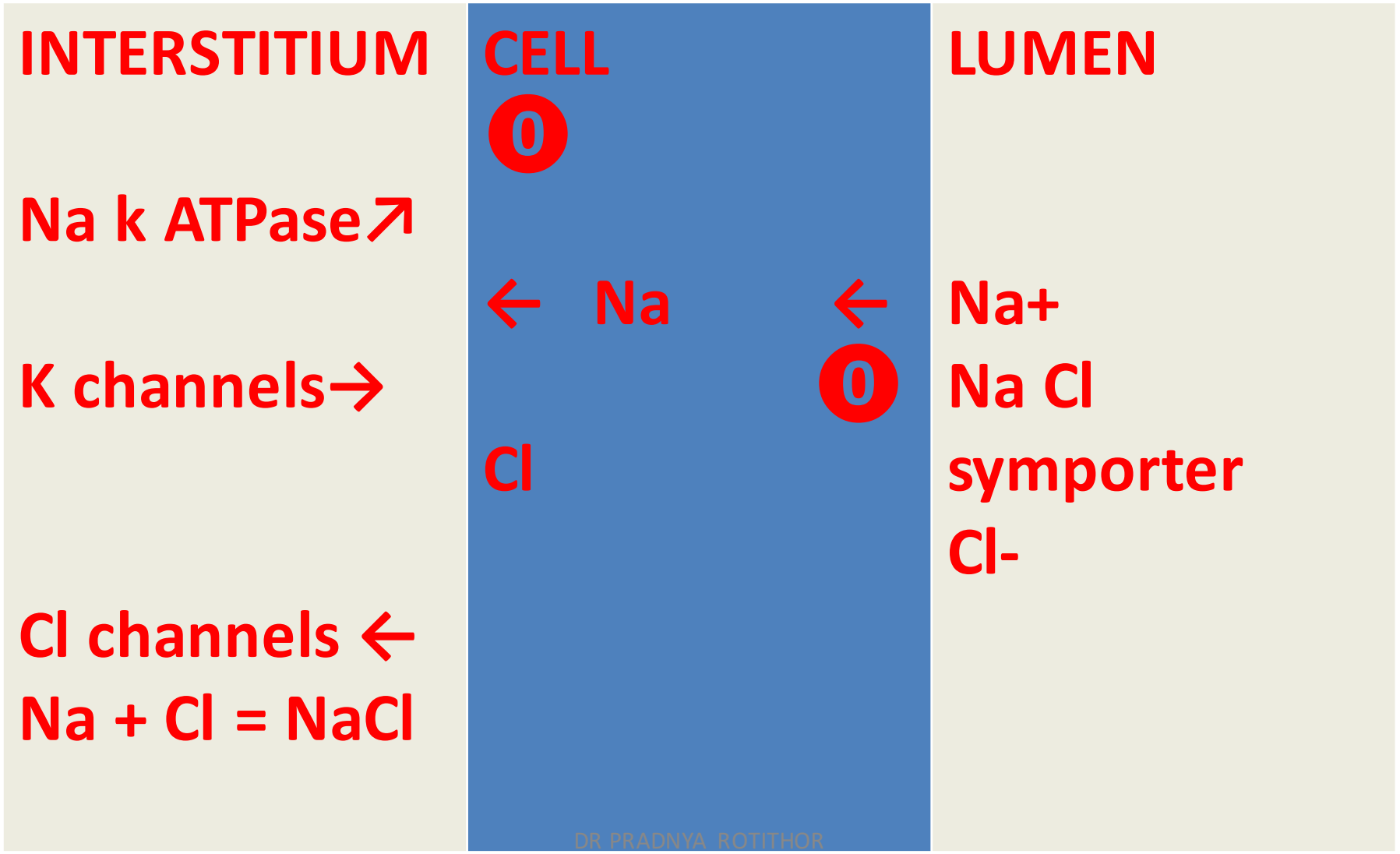
BICARBONATE REABSORPTION
site for CA Inhibitors



THICK ASC LOOP
site for loop diuretics



EARLY DCT
site for thiazides



SITE AND MECHANISM OF ACTION

- Loop thick Asc LH ↓ Na K Cl cotransport
- Thiazides early DT ↓ Na Cl co transport
- Osmotic PT thin dsc LH CD ↓ passive water reabsorption
- CA inhibitor PT ↓ Carbonic anhydrase
- K sparing later DT CD Na ch inhibition -amiloride aldosterone R antagonist – spironolactone

URINARY EXCRETION DUE TO DIURETICS

	Na	Cl	K	Ca	NaHCO3	Water	
Loop	++++	+++	++	+++ & Mg	Nil or +	+++	
thiazides	+++	+++	++	- -	Nil or +	++	
K sparing	+	+	- -	+	_	+	
CA Inhibitors	+	Nil or _	++	++	++	+	
osmotic	+	+	nil	nil	nil	+++	

EFFECT ON PLASMA

- Loop –hypo kalemic metabolic alkalosis
  serum K Ca Mg levels ↓
  hyperurecaemia
  Hyperglycaemia

Thiazides –hypo chloraemic metabolic alkalosis
  serum Cl levels ↓ and Ca ↑
  hyperurecaemia
  hyperglycaemia

K sparing – hyperkalaemia

CA inhibitors –hypo K and hypo Ca

Osmotic diuretics –hypo Na and transient rise in ECF volume

Na + REABSORPTION

- Relative magnitudes of sodium reabsorption at different tubular sites---

- PT 65-70%
- Asc LH 20-25%
- DT 8-9%
- CD 1-2%

K+

reabsorbed in PT and Asc LH

AND

Secreted in DT and CD

FACTORS AFFECTING NET K+ LOSS

- Na load delivered to distal segments
- Availability of H+ ions
- Intracellular K+ stores
- Presence or absence of aldosterone

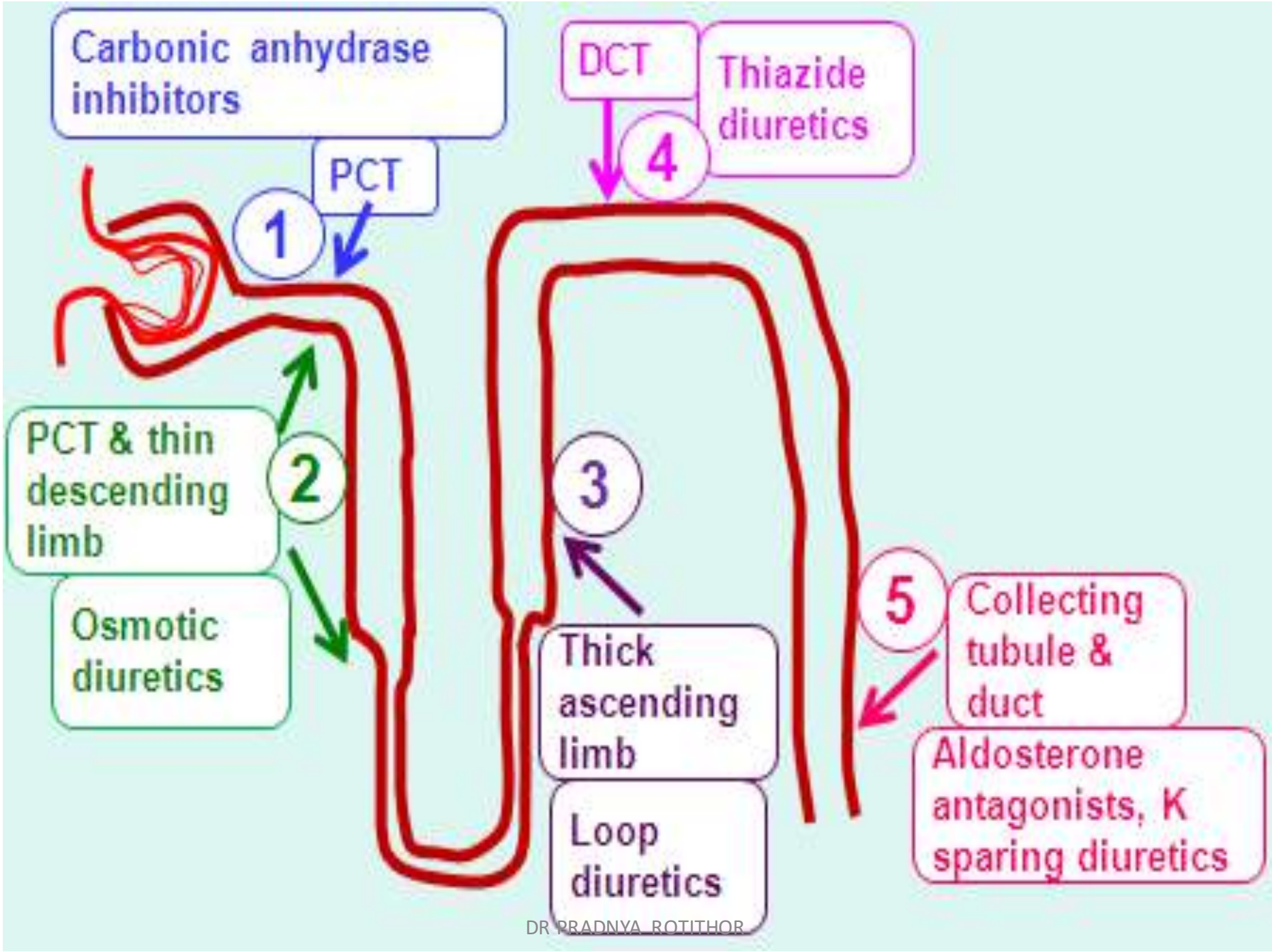
- Loop diuretics lead to high K + loss due to high Na load delivered to DT /CD

ADH

- CD cells respond to ADH
- If ADH is absent –hypotonic fluid in CD is passed as it is ---dilute urine is produced
- If ADH is high – CD cells become fully permeable to water –equilibrate with hyperosmotic medulla ---concentrated urine is passed

Free water clearence

- Zero ---when urine is isotonic
- Positive –when urine is diluted
- Negative –when urine is concentrated



DIURETIC DRUGS

Definition—drugs which cause net loss of sodium and water

Carbonic anhydrase inhibitors –1950

ChLorthiazide –first modern orally active diuretic 1957

Loop diuretics –mid 1960s

Diuretics are among the most widely prescribed drugs

CLASSIFICATION

1) high efficacy diuretics

inhibitors of Na k 2Cl cotransport **Loop -thick**

Ex –**furosemide** bumetanide torasemide

2) medium efficacy diuretics

inhibitors of Na Cl symport **DCT**

a) thiazides –**hydrochorthiazide** benzthiazide

b) thiazide like –chorthalidone , metolazone

Indapamide clopamide

3) carbonic anhydrase inhibitors –**acetazolamide** **PCT**

4) potassium sparing diuretics –**last part of DCT CD**

a)aldosterone antagonists -**spironolactone ,eplerenone**

b) Na channel inhibitors –**triamterene , amiloride**

5) osmotic diuretics –**mannitol ,isosorbide, glycerol** PCT loop-thin

LOOP /HIGH CEILING DIURETICS

Inhibitors of Na+ K+ 2Cl- cotransport

Prototype drug –furosemide (lasix)

Rapidly acting --2-5min for iv 10-20 min –im

20-40 min -oral

Highly effective –DRC steep

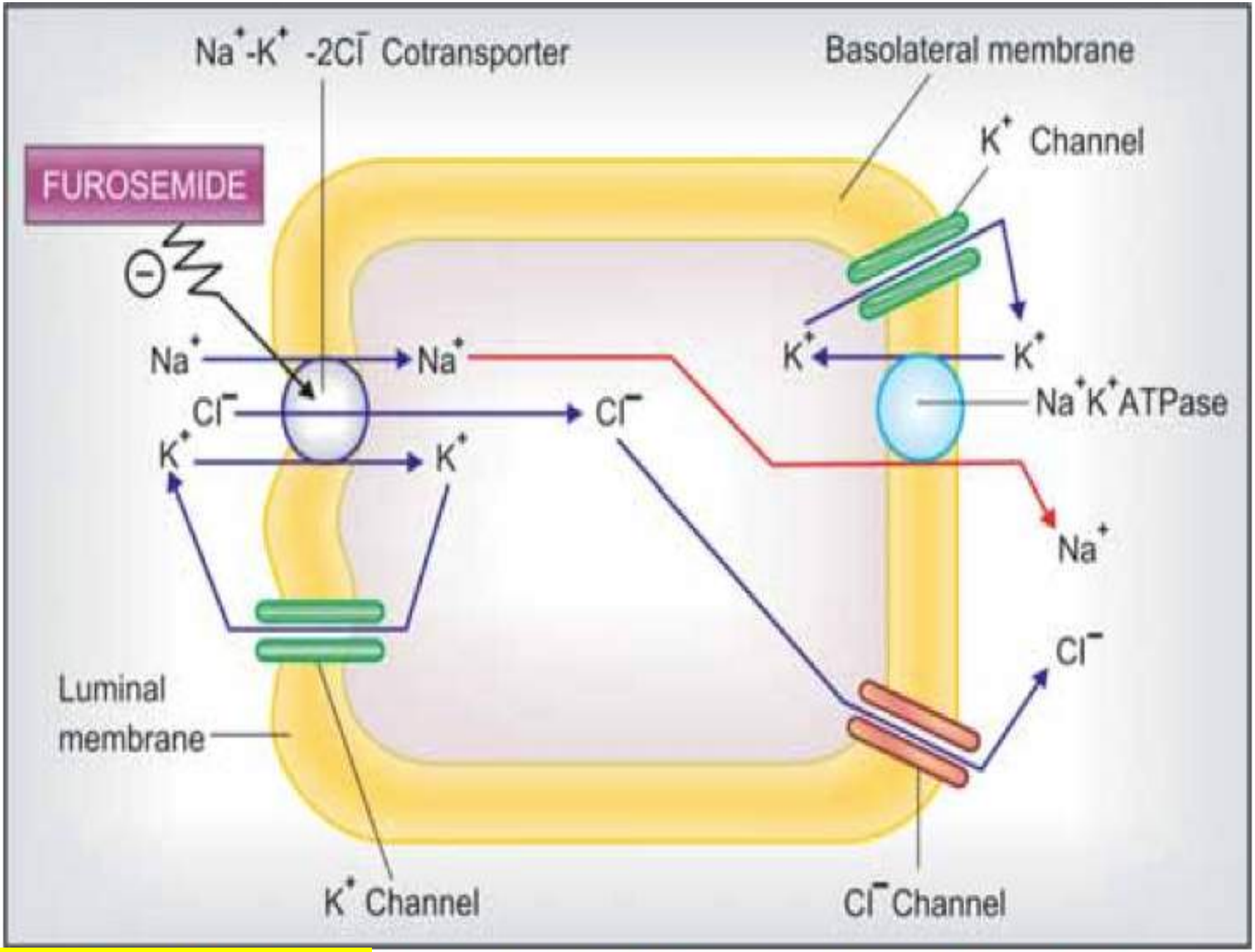
Maximal natriuretic effect

Active even in renal failure

Site of action –luminal membrane of thick Asc LH ,

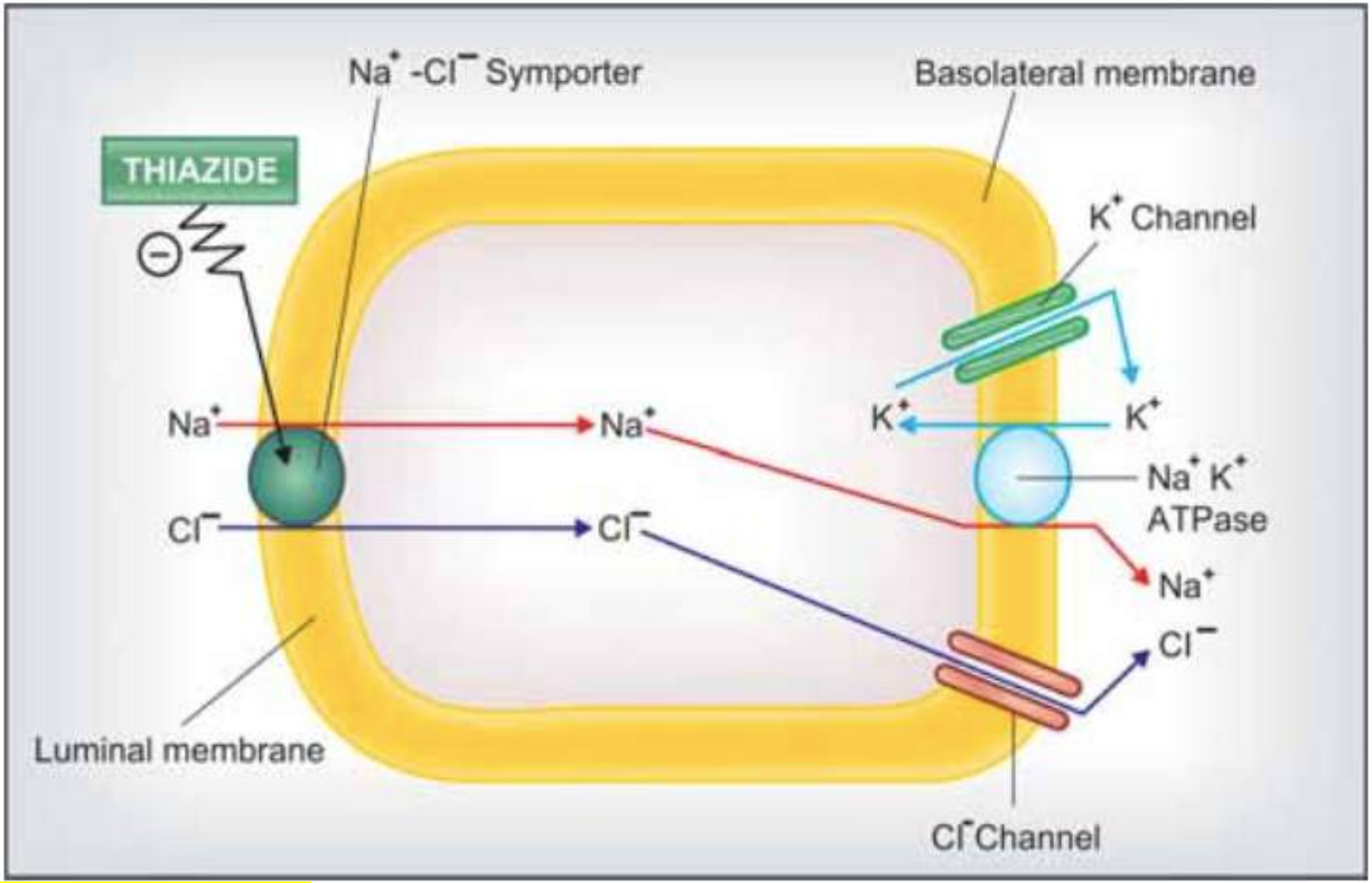
minor action at PT inhibitory action on carbonic anhydrase – excretion of HCO3

Secreted in PT by organic anion transport and reaches site of action



MOAOF LOOP DIURETICS

of salt reabsorption in the thick ascending limb of loop of Henle (AscLH) cell, and site of action of furosemide on the Na^+-K^+-$2Cl^-$ cotransporter



MOA OF THIAZIDES

echanism of salt reabsorption in early distal tubular cell and site of action of thiazide diuretics on Na^+Cl^- symporter

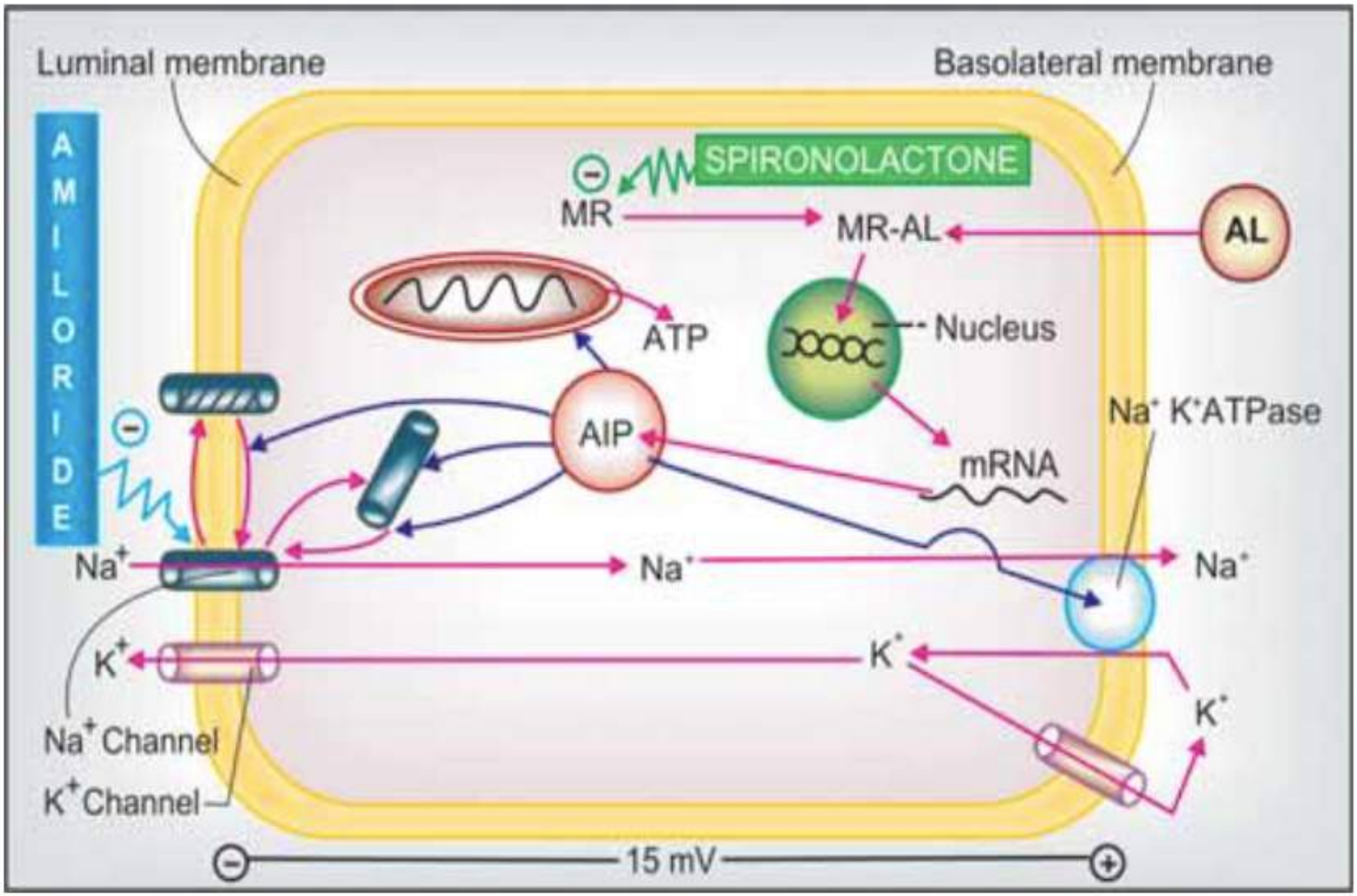


Fig. 13.5: Site and mechanism of action of potassium sparing diuretics on the late distal tubule/collecting duct cell Aldosterone (AL) penetrates the cell from the interstitial side and combines with the mineralocorticoid receptor (MR). The complex translocates to the nucleus—promotes gene mediated mRNA synthesis. The mRNA then directs synthesis of aldosterone-induced proteins (AIPs). The AIPs include Na^+K^+ ATPase and amiloride sensitive Na^+ channels. The AIPs also activate Na^+ channel, translocate Na^+ channels from cytosolic site to luminal membrane and Na^+K^+ATPase to basolateral membrane, increase ATP production by mitochondria. All these changes promote Na^+ reabsorption—more K^+ and H^+ is secreted indirectly. Spironolactone binds to MR, prevents AL action and produces opposite effects.

Amiloride approaches the Na^+ channel from the luminal side and blocks it—reducing the lumen negative transepithelial potential difference which governs K^+ and H^+ secretion.

LOOP DIURETICS ---

Actions –

Abolishes Cortico-medullary osmotic gradient

Both positive and negative free water clearance is blocked

K excretion is high due to high sodium load reaching DT

↑Ca ++ excretion –thiazides ↓

↑ Mg ++ excretion

↓ uric acid excretion

Hyperglycaemia

At equinatriuretic dose K loss < thiazides

Weak CA inhibitory action -↑ HCO_3 excretion

No effect on acid base balance –mild alkalosis at higher doses

Haemodynamic changes

Transient ↑renal blood flow

Redistribution of blood flow from outer to mid cortical zone

Pressure relationship between vascular interstitial and tubular compartments is altered that leads to ↓ PT re absorption

Iv dose -- prompt ↑venous capacitance

↓ LV filling pressure

quick relief in LVF and Pulmonary oedema

PhamacoKinetics

Oral IM IV

Rapid Oral absorption

Bioavailability 60%

Plasma t1/2 ---1-2 hrs

Dose –20-80 mg od

iv –pulmonary oedema LVF

Torasemide -3 times more potent

Bumetinide –40 times more potent

Indications of loop diuretics

Acute pulmonary oedema –iv

Acute LVF following MI –rapid action

Hypertensive crisis –prompt action

Cerebral oedema

Oedema –CHF ,Ascites

to prevent circulatory overload -With blood transfusion in severe anamia

Hypercalcaemia (of malignancy)and hyperkal

HT –not preferred --thiazides are preferred

THIAZIDES

Medium efficacy –as 90% of GF is already reabsorbed

Flat DRC

Site –cortical diluting segment of early DT

Inhibit Na Cl symport from luminal side

Positive free water clearance is ↓

But negative free water clearance is not affected

Reach site by organic acid secretion at PT

Most brands have additional weak CA inhibition action

Contd--

K loss is α Na presented to distal segment

GFR is reduced

↓ Ca excretion but ↑ Mg excretion

Extrarenal actions –slow Fall in BP

PK –well absorbed orally

No injectable preparations

Chlorthalidone –long acting t1/2 -40-50 hrs

Metolazone –mainly used for oedema

Indapamide –HT

1	CA inhibi	Chr. (wide angle) glaucoma (dorzolamide), Narrow angle (acute) (acetazolamide IV), prevention of Acute Mountain Sickness, Epilepsy
2	Osmotic	Cerebral edema (To decrease ICT), Drug overdose, shock, trauma (Maintain urine flow & prevent acute renal failure), Acute narrow angle glaucoma(mannitol, glycerol IV), Severe hemolysis or rhabdomyolysis (Maintain high urine flow in patients with solute overload)
3	Loop (↑RBF, ↓ vascular resistanc e)	Edema (CHF, ascites), acute pulmonary edema, hypertensive crisis (prompt action), treatment of severe hypercalcemia & hyperkalemia

4	Thiazides	Hypertension, mild-moderate HF-Edema, hypercalciuria, urinary calcium-oxalate stones, diabetes insipidus(decrease urine output)
5	Aldo. anta K sparing	HF (prevent remodeling,decrease mortality), Maintain K, prevent hypokalemia by other agents, Secondary hyper -aldosteronism (CHF, cirrhosis – hepatic edema, nephrotic syndrome), Primary hyperaldosteronism (Conn Syndrome) Prevent hypokalemia by other agents, Lithium induced diabetes insipidus

INDICATIONS

HT- mild moderate – first line of drug

Oedema – cardiac origin -CHF

Diabetes insipidus -↓free water clearance -only drugs effective in renal DI

Hypercalciurea --associated with urolithiasis- urinary stones –oxalates and calcium

COMPLICATIONS WITH DIURETIC THERAPY

- Hypokalemia –most significant ADR
- Rx –high dietary intake
- KCl suppliment
- concurrent use of K sparing diuretics
- Acute saline depletion –haemoconcentration ↑ risk of dvt
- Dilutional hyponatraemia
- GIT –N V D
- CNS –headache

CA inhibitor	Metabolic acidosis (urinary alkalosis), hypokalemia, Drowsiness, paresthesia, Renal stones, decreased ammonia excretion (worsen cirrhosis), bone marrow suppression, hypersensitivity
Osmotic	Dehydration, H, N, V
Loop	-↓ Na, *K*, Cl, Mg, ↓ Calcium -↑ glucose, lipids, uric acid-gout Hypokalemic metabolic alkalosis, hypovolemia, hypotension, Ototoxicity (ethacrynic acid)

Thiazide	-↓ Na, *K*, Cl, Mg -↑ glucose, lipids, uric acid-gout, ↑ <u>Calcium</u> --Hypokalemic metabolic alkalosis, Hypotension, -Ototoxicity, Sulfa allergy: chlorthalidone, metolazone, indapamide
Aldosterone Antagonist K sparing Na ch inhibitors	Hyperkalemia, anti-androgenic effects, sexual dysfunction, gynecomastia, impotence, menstrual disturbances, increased Ca excretion, abd pain, aggravation of peptic ulcer Amiloride: ↓ Mg, Ca excretion, ↑urate excretion, hyperkalemia Triamterene: Photosensitivity, impaired glucose tolerance, megaloblastic anemia, hyperkalemia

ALDOSTERONE

DT and CD ---Aldosterone R

AIP ----ATP

Na pumps

Na K ATPase

Site for K sparing diuretics

Spironolactone eplernone–R inhibitor – prevents formation of AIP

Triamterene /amiloride –Na pump inhibitor

Aldosterone

(aldesterone → Na retention, K loss)

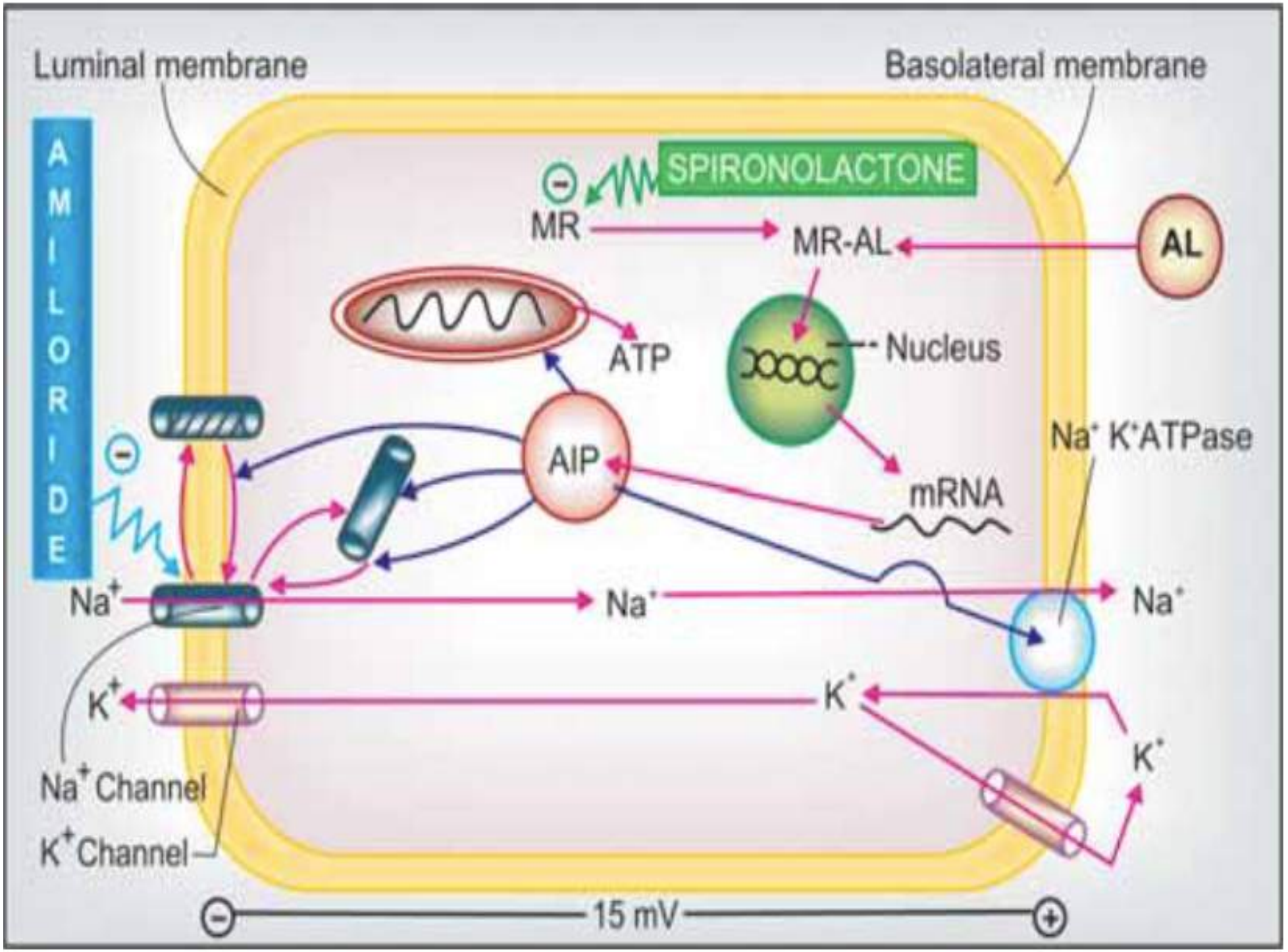
(aldesterone antagonists → Na loss, K retention)

Act from interstitial side of tubular cells (most diuretics act from luminal side) **MCQ**

Spironolactone (25-50 bid-qid), **Eplerenone**

Actions highest when aldosterone levels are high: Hepatic cirrhosis, Heart failure, Nephrotic syndrome

Ineffective in absence of aldosterone: Addison disease


Luminal membrane
Basolateral membrane
AMILORIDE
SPIRONOLACTONE
MR
MR-AL
AL
ATP
Nucleus
AIP
mRNA
Na⁺ K⁺ATPase
Na⁺
Na⁺
Na⁺
K⁺
K⁺
K⁺
Na⁺ Channel
K⁺ Channel
15 mV

Therapeutic uses

Aldosterone antagonist

Heart failure- (prevent remodeling, decrease mortality), Maintain K,

prevent hypokalemia by other agents –mainly loop diuretics

Adjuvant to other diuretics in antihypertensive rx

Secondary hyper -aldosteronism (CHF, cirrhosis – hepatic edema, nephrotic syndrome),

Primary hyperaldosteronism (Conn Syndrome)

Na ch inhibitors- Amiloride ,triamterene

Prevent hypokalemia by other agents, Lithium induced diabetes insipidus

Adverse effects

Aldosterone antagonist

Hyperkalemia,

anti-androgenic effects, sexual dysfunction, gynecomastia, impotence, menstrual disturbances,

increased Ca excretion,

Abdominal pain pain,

aggravation of peptic ulcer

ADR of Na ch inhibitors

Amiloride:

↓ Mg, Ca excretion, ↑urate excretion, hyperkalemia

Triamterene:

hyperkalemia

Photosensitivity,

impaired glucose tolerance,

megaloblastic anemia,

Compare and contrast

Loop diuretics	Thiazide diuretics

- Site and MOA
- examples
- Route of administration
- Duration of action
- Haemodynamic changes
- Uses
- Adverse effects

Pharmacotherapy Of Hypertension

DR PRADNYA ROTITHOR

definition

V common disorder

Mostly asymptomatic – silent killer

Primary hypertension -no cause found most common form

Termed as **essential hypertension**

Secondary hypertension less common

-1)Renal -renal artery stenosis

2)Endocrine –pheochromocytoma Primary or sec aldosteronism

3)Vascular disorders

Guidelines for BP measurements

Type	SBP	DBP	in mm of Hg
Normal	<120	<80	
Prehypertension	120-139.	80-89	
Stage 1 HTN	140-160	90-99	
Stage 2 HTN	>160	>100	

Hypertensive Crises

- -Hypertensive emergencies –BP 210/120 mm of Hg
- **WITH** target organ damage
- Malignant hypertension—Severe htn with vascular damage to arteriols- papilloedema retinal haemorrage and hy encephelopathy
- acute MI
- acute LVF With pulmonary oedema
- Pregnancy ecclampsia
- Pheochromocytoma induced uncontrolled HTN

- Hypertensive urgencies –high BP **WITHOUT** target organ damage

Pregnancy Hypertension

- Rise in BP after 20 wks of gestation more common in primigravida
- Prior to that –essential htn
- Complications of PET –pre eclamptic toxaemia –IUGR IUD PPH
- Eclampsia –high maternal mortality
- Treatment-
- Rest
- Drugs –alphamythyldopa -MCQ
- hydralazine CCB-Nifedipine
- Labetelol is now preferred
- Life saving drug –magnessium sulfate –magsulf—not mentioned in your textbooks

HOW TO QUANTIFY BLOOD PRESSURE

Factors involved
Baroreceptors
RAAS
Plasma volume
etc

$$BP = CO \times SVR\ (TPR)$$

$$CO = HR \times SV$$

$$BP = HR \times SV \times SVR$$

Treatment of Hypertension

- Confirmation of diagnosis – by correct method of blood pressure measurement
- Relaxed state of mind
- Sitting position with erect back feet NOT hanging
- Remember white coat hypertension –
- Ambulatory home measurement
- Now electronic BP apparatus is accepted
- Investigations –basic reports –ECG RFT Lipid profile

Lifestyle modification

- Mild hypertension can be treated WITHOUT drug therapy
- But close watch needed –patient compliance is most important
- Once a hypertensive is always a hypertensive –obsolete concept
- Obesity control
- DASH diet –dietary approach to stop hypertension
- low salt <2.4gm/day, fruits grains vegetables low fat dairy products ,restricted intake of pickles papads namkeens etc
- Regular moderate exercise
- lipid profile control
- Smoking alcohol XX
- Yoga meditation to control stress

Pharmacotherapy

- Monotherapy –diuretics –thiazide 12.5mg
- ACEI/ARB/CCB/Beta blockers
- Combination therapy –
- Mainly to overcome side effects of one another
- Sympatholytics and vasodilators cause retention of fluid –combine with diuretics
- Vasodilators like CCB esp short acting cause reflex tachycardia – combine with beta blockers
- ACEI and diuretics potentiate each other –synergistic

Resistant hypertension

- Uncontrolled BP with 3 drugs of different classes one of which is diuretic
- BP controlled but 4 or more drugs of different classes are needed

- Target BP –130/80 mm of Hg

Classification of antihypertensive drugs

- Diuretics
- ACEI
- ARB
- CCB
- Beta blockers
- Alpha blockers
- Alpha and beta blockers
- Vasodilators
- Centrally acting symoatholytics
- Ganglion blockers
- Adrenergic neurone blockers

homework – complete the chart by examples

MOA of each gr

ACEI ARB CCB already discussed

Diuretics –mild anti HTN drugs

MOA(persistent Na deficit →↓tpr)

1)Reduction in plasma volume and ecf -10%-↓CO

This ↓CO is restored by compensatory mechanism but eventual fall in BP is maintained by slow development of ↓tpr

Now how and why this tpr is reduced?

--why -small but persistent sodium and fluid volume deficit -5%

--how –low Na in vascular smooth muscle cells - ↓stiffness of vessel wall, ↓ response to vasoconstriction action of NA AII

In the long term Rx HR CO remain unaffected

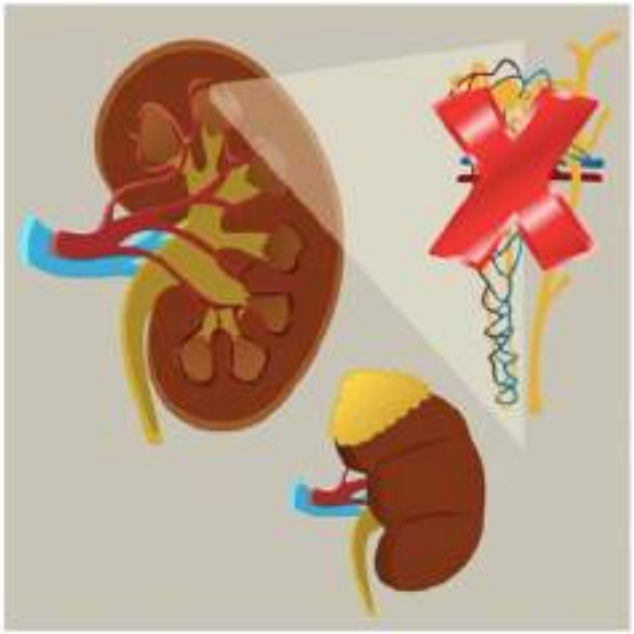
Thiazides-first doc alone or in combination

- Additional benefits-potentiate action of all other antiHTN drugs by keeping low plasma volume
- Per se 10 mm/Hg ↓ in mean arterial BP
- Dose – hydrochlorothiazide 12.5mg-25mg
- ADR – Hypokalaemia fatigue impotence dyslipidemia hyperuraecimia etc less seen at these doses

Antihypertensive Mechanism of Action

Diuretics

Facilitate Diuresis



Sodium Reabsorption
H2O Reabsorption

↓

Sodium Reabsorption
H2O Reabsorption
BP

Loop diuretics

- Not used for routine htn rx
- Used only when –
- 1)Chronic renal failure
- 2)htn with CHF

K sparing diuretics –are used in combination to decrease K loss

Inepamide –at antiHTN dose v little diuresis seen

Beta blockers

- On long term use tpr falls ,CO falls –both systolic and diastolic blood pressure falls
- Other contributory factors –
- Renin release fall due to blockade of B1 R in Kidneys
- Reduced central and peripheral NA flow
- Cardioselective beta blockers like atenolol or labetalol with additional alpha blocker action are preferred

Antihypertensive Mechanism of Action

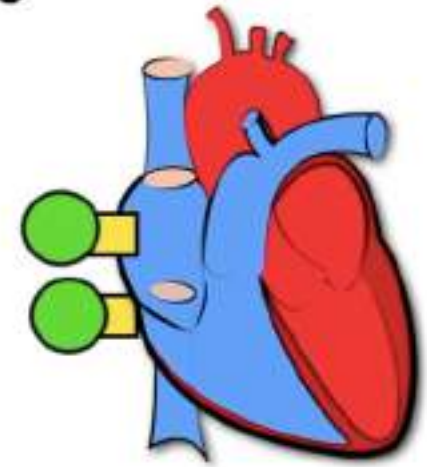
Beta Blockers

Beta-1 Receptor

Norepinephrine
Epinephrine

Block Beta Receptors

Fight or Flight Response
(Sympathetic)



HR

SV

CO

BP

BP

Advantages of beta blockers

- No postural hypotension
- No salt and water retention
- No action on bowel
- Possible cardioprotection
- OD dosage
- Low cost

Combined action on alpha and beta blockage

- Labetelol- intravenous for emergency use for rapid reduction in BP
- Indications –cheese reaction rebound HTN of clonidine withdrawl

- Carvedilol- nonselective beta and selective alpha 1 bloker and additional antioxidant property

Alpha blockers

- Alpha one blockers dialates both resistance and capacitance vessels
- Reduced tpr

- Prazosin- postural hypotension with first dose effect
- terazosin tamsulosin-additional benefit of action on prostate
- Nonselective alpha blockers –
- ***Phenoxybenzamine and phentolamine – pheochromocytoma***

Central Sympatholytics – clonidine and alpha methyl dopa

- Clonidine –imidazoline derivative, orally active
- complex action
- 1)alpha2 R in brainstem
- Stimulation of alpja2 R in vasomotor centre –→↓sympathetic outflow→fall in BP and bradycardia
- 2)action on specific imidazoline R in brain also reduces sympathetic outflow

ADR of Clonidine

- Common and disturbing side effects
- Impotence
- Disturbed sleep
- Dryness of mouth.eyes.nose
- Sedation
- Salt and water retention
- Rebound hypertension on sudden withdrawal MCQ

Alpha methyl dopa

- Selective alpha 2 agonist
- Action on central alpha2 R to reduce sympathetic outflow
- Probably acts on different set of neurons than clonidine

✓**Safe in pregnancy**

✓**Dose -250mg -750mg**

Vasodilators

- **Hydralazine-**directly acting arteriolar vasodilators
- Little or no action on venous capacitance vessels
- Tpr reduced
- Greater fall in diastolic BP than systolic BP
- Compensatory tachycardia –marked

✓**Safe during pregnancy**

minoxidil

- Directly acting arteriolar dilator
- Prodrug
- Opens up K channels in muscles-causes efflux of K leading to hyperpolarization and thus muscle relaxation
- Used for htn not responding to other drugs
- Also used for androgenic alopecia
- While unacceptable in women –hypertrichosis

- Diazoxide –related to thiazide diuretic
- Potent arteriolar vasodilator
- May cause hyperglycaemia –inhibits insulin secretion from pancreas

Sodium Nitroprusside

- Rapidly acting powerful vasodilator
- Relaxes both resistance and capacitance vessels--MCQ
- Reduces tpr
- Reduces CO
- Reduces cardiac work
- Infusion needs to be protected from light –dark room /bottle covered with black cloth
- BP needs to be closely watched as it falls v v rapidly
- Previously used for hypertensive emergencies but now labetalol is preferred

Antihypertensive Drug Names

Suffixes

ACE Inhibitors "pril"

ARBs "sartan"

Alpha Blockers "osin" "zosin" (Selective Alpha-1 Blockers)

Nonselective "mine"

Beta Blockers "lol"

Phentolamine, Phenoxybenzamine

Calcium Channel Blockers "dipine" (Dihydropyridines)

Non-dihydropyridines

Diuretics "ide"

Verapamil and Diltiazem

HOW TO QUANTIFY BLOOD PRESSURE

Factors involved
Baroreceptors
RAAS
Plasma volume
etc

$$BP = CO \times SVR\ (TPR)$$

$$CO = HR \times SV$$

$$BP = HR \times SV \times SVR$$

Antihypertensive Drug Classes

	Classes	Drug Names	Examples	Mechanism of Action	Main Effect on BP
A	ACE Inhibitors	"pril"	Lisinopril Enalapril	Inhibit ACE	↓ SVR, SV
A	ARBs	"sartan"	Losartan Valsartan	Block Angiotensin II Receptors	↓ SVR, SV
A	Alpha Blockers	"osin"	Doxazosin Terazosin	Block Alpha Receptors	↓ SVR
B	Beta Blockers	"lol"	Metoprolol Labetalol	Block Beta Receptors	↓ HR, SV
C	Calcium Channel Blockers (CCBs)	"dipine"	Amlodipine Nicardipine	Block Calcium Channels	↓ SVR
D	Diuretics	"ide"	Furosemide Hydrochlorothiazide	Facilitate Diuresis	↓ SV

**Alpha blockers refer to selective alpha-1 blockers, and calcium channel blockers refer to dihydropyridines

MUHS QUESTIONS

- LAQ –classify antihypertensive group of drugs with examples
- Sub question mostly on ACEI
- Lots of SAQs on MOA uses and ADR of each class mainly diuretics, ACEI ARB CCB
- Compare and contrast loop diuretics with thiazides
- Compare and contrast ACEI with ARB
- Lots and lots of MCQ –
- Clonidine –rebound hypertension
- ACEI –dry cough
- Vasodilator –sodium nitroprusside