SNS COLLEGE OF ALLIED HEALTH SCIENCES

SNS Kalvi Nagar, Coimbatore - 35

Affiliated to Dr MGR Medical University, Chennai

DEPARTMENT OF CARDIO PULMONARY PERFUSION CARE TECHNOLOGY

COURSE NAME : Pharmacology Pathology and Clinical Microbiology

II nd YEAR

TOPIC : ANTI HYPERTENSIVE DRUGS

ANTIHYPERTENSIVE DRUGS

HYPERTENSION

Hypertension is defined as the elevated blood pressure from normal blood pressure. **(OR)**

Hypertension (BP >140/90 mm Hg) is defined as either a sustained SBP of > 140 mm Hg or a sustained DBP of > 90 mm Hg.)

Optimal healthy blood pressure is (<120/<80).

Classification for the purpose of RX

Category	Systolic Blood Pressure	Diastolic Blood Pressure
Normal	<120	<80
Pre-hypertension	120-139	80-89
Hypertension – Stage 1	140-159	90-99
Hypertension – Stage 2	≥160	≥100

INCIDENCE

✓Elevated blood pressure is a common disorder, affecting approximately 30% of adults in the United States.

✓Although many patients have no symptoms, chronic hypertension can lead to heart disease and stroke, the top two causes of death in the world.

✓Hypertension is also an important risk factor in the development of chronic kidney disease and heart failure.

ETIOLOGY OF HTN

Primary or essential (idiopathic) HTN >90% of all cases.

Risks Factors include:

- ✓ Hyperlipidemia
- ✓ Diabetes
- ✓ Genetic, Family History
- ✓ sex (males are at higher risk)
- ✓ Race (4X black than whites)
- ✓ Age
- ✓ Obesity
- ✓ Stressful life style
- ✓ cigarette smoking
- ✓ High dietary intake of Na^+

Secondary HTN (~10% of all cases)

Identifiable Cause:

- ✓ Renal Artery Constriction
- ✓ Coarctation of the Aorta
- ✓ Phaeochromocytoma
- ✓ Cushing's Disease
- ✓ Primary Aldosteronism
- ✓ Drugs

ANTIHYPERTENSIVE DRUGS

Drugs or agents which are used to treat elevated blood pressure are called anti-hypertensive drugs.

HOW TO TREAT HYPERTENSION?

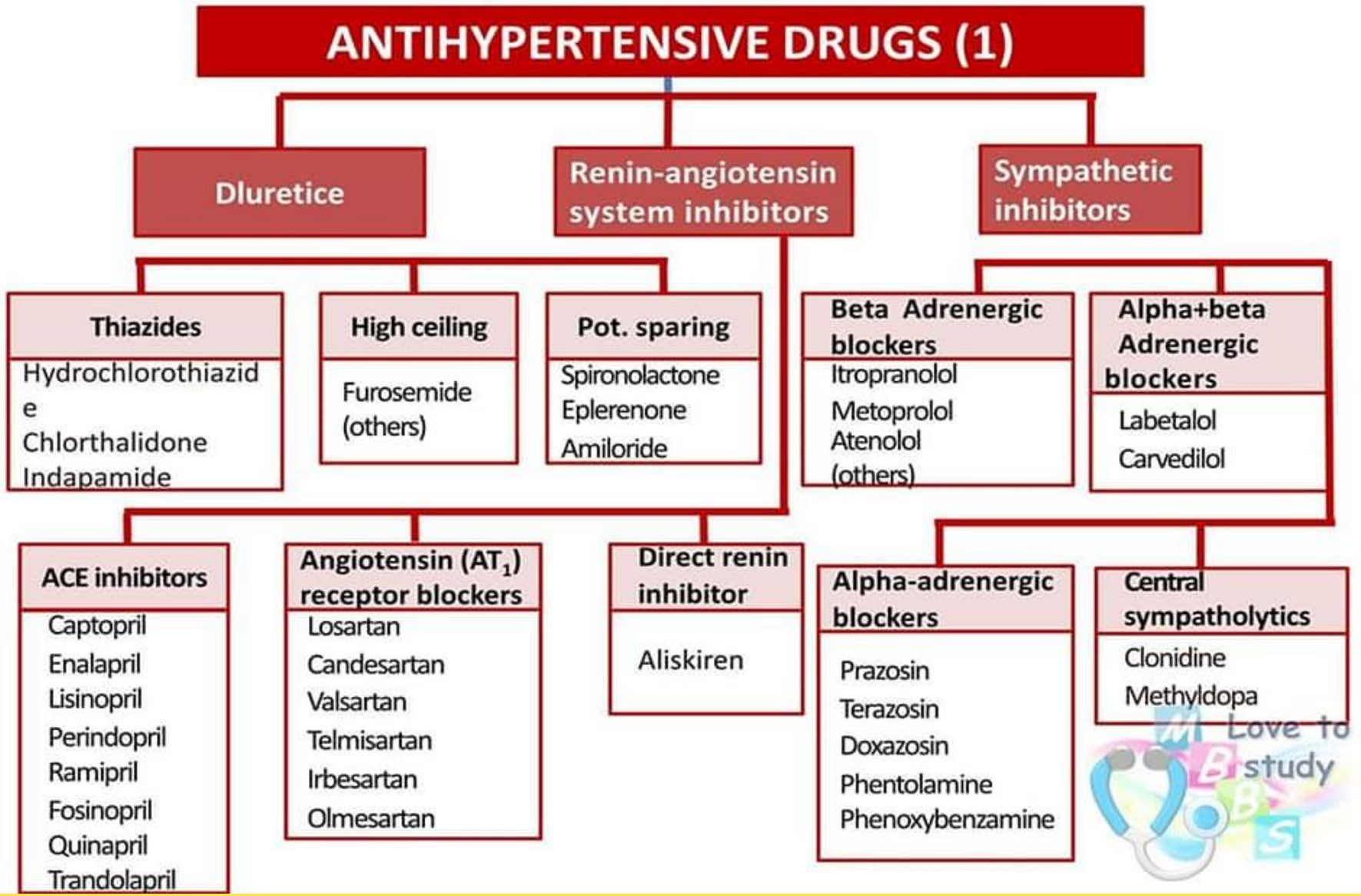
I. NON-PHARMACOLOGICAL

- Quitting cigarette smoking,
- regular exercise,
- restricting dietary intake of: salt, saturated fats, and calories

will improve peripheral circulation, prevent increases in blood volume, reduce plasma cholesterol levels and total body weight.

PHARMACOLOGICAL CLASSIFICATION

Cardiovascular Drugs



ANTIHYPERTENSIVE DRUGS (2)

- **Calcium channel blockers**
  - **Phenylalkylamine**
    - Verapamil
  - **Benzothiazepine**
    - Diltiazem
  - **Dihydropyridine**
    - Nifedipine
    - Felodipine
    - Amlodipine
    - Nitrendipine
    - Lacidipine
    - Lercanidipine
    - Benidipine
- **Vasodilators**
  - **Arteriolar dilator**
    - Hydralazine
    - Minoxidil
    - Diazoxide
  - **Arteriolar + Venodilator**
    - Nitroprusside sod

THIAZIDE DIURETICS:

✓Thiazide diuretics are a first-line therapy for hypertension.

✓They promote the elimination of water, sodium, potassium, magnesium, and chloride ions.

✓ Fluid loss decreases blood volume, yet this is not the primary mechanism of action for their effectiveness in decreasing blood pressure.

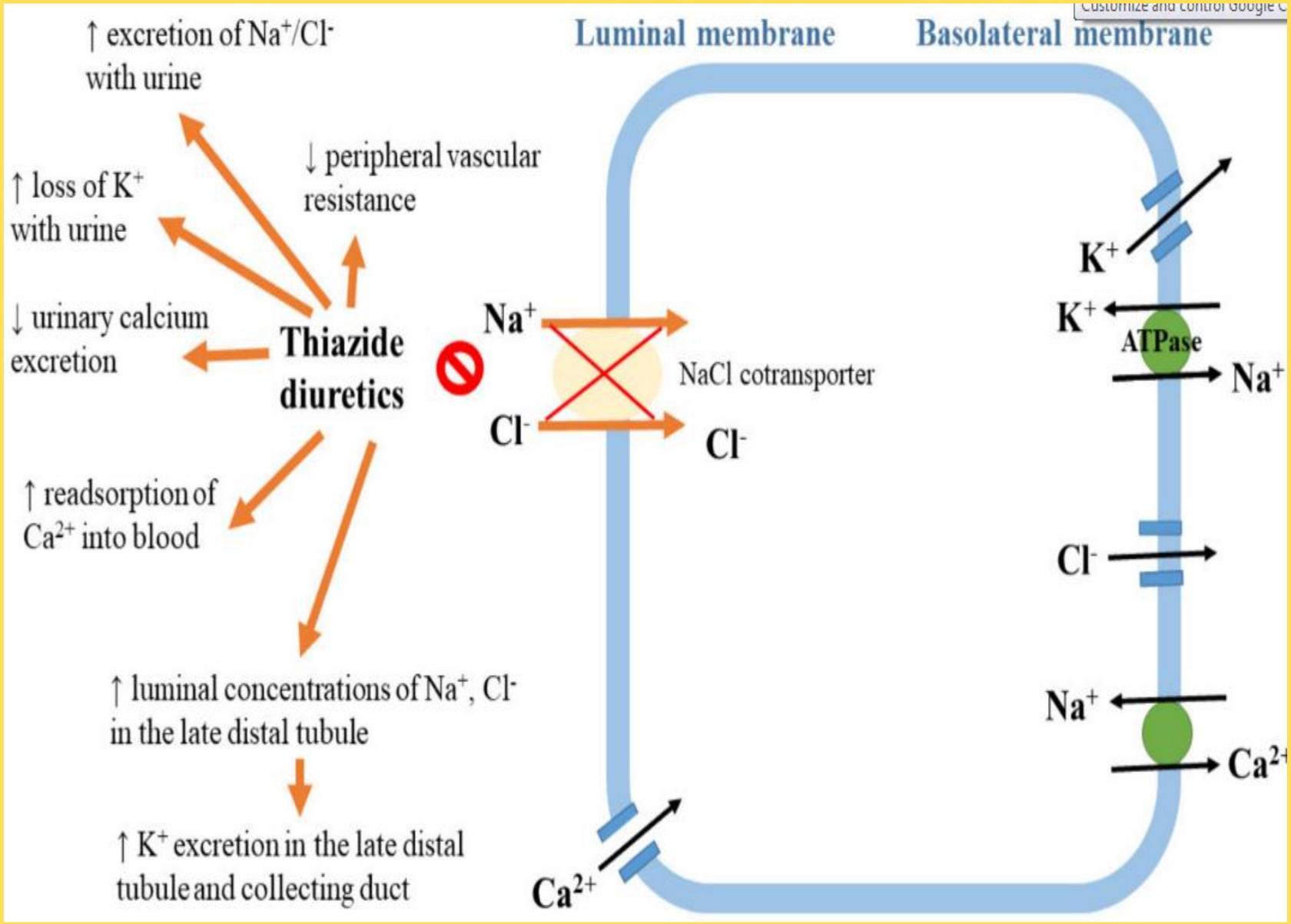
✓Thiazides act at the distal convoluted tubule, where they **block the sodium–chloride cotransporter .**

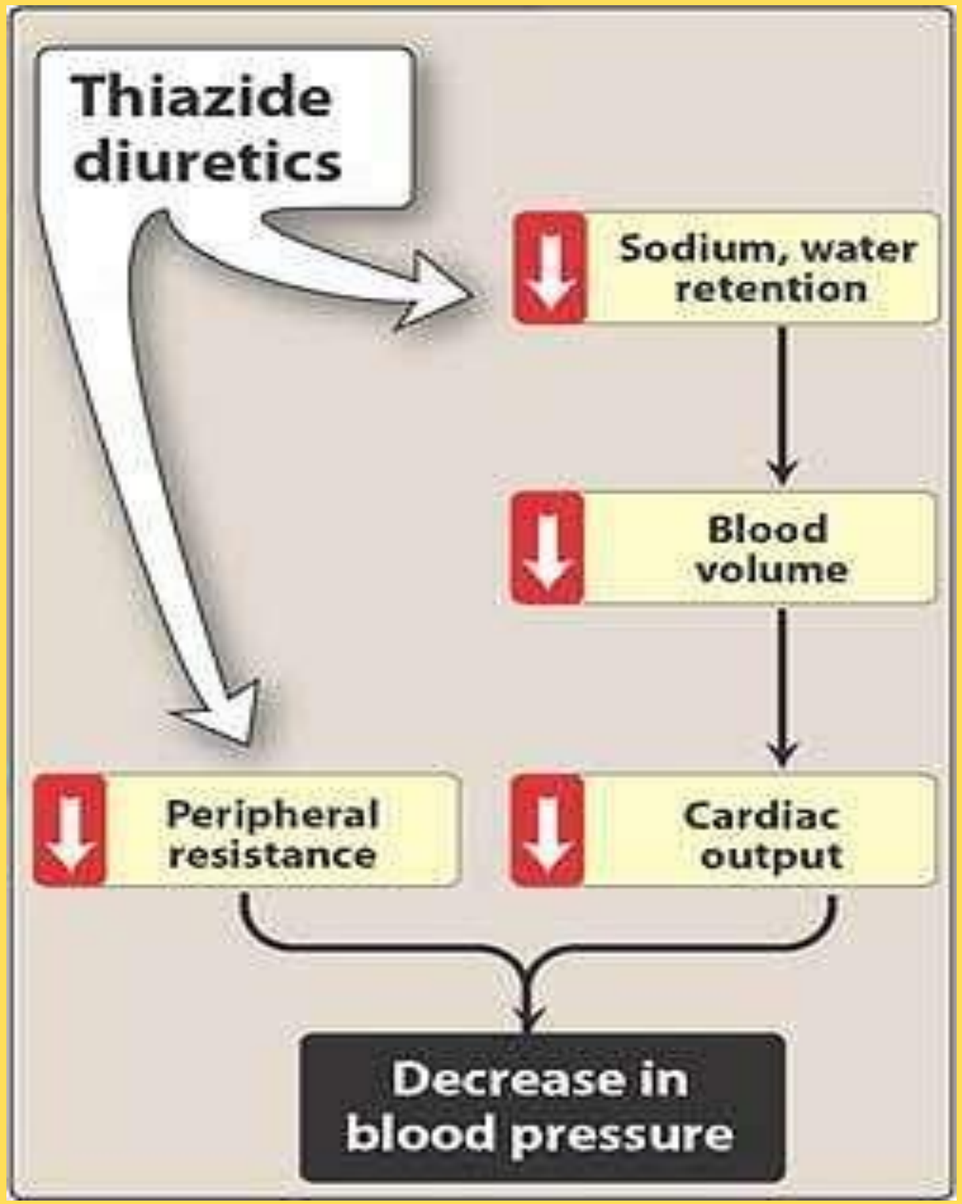
✓This interferes with calcium transport into arterioles, decreasing vasoconstriction.

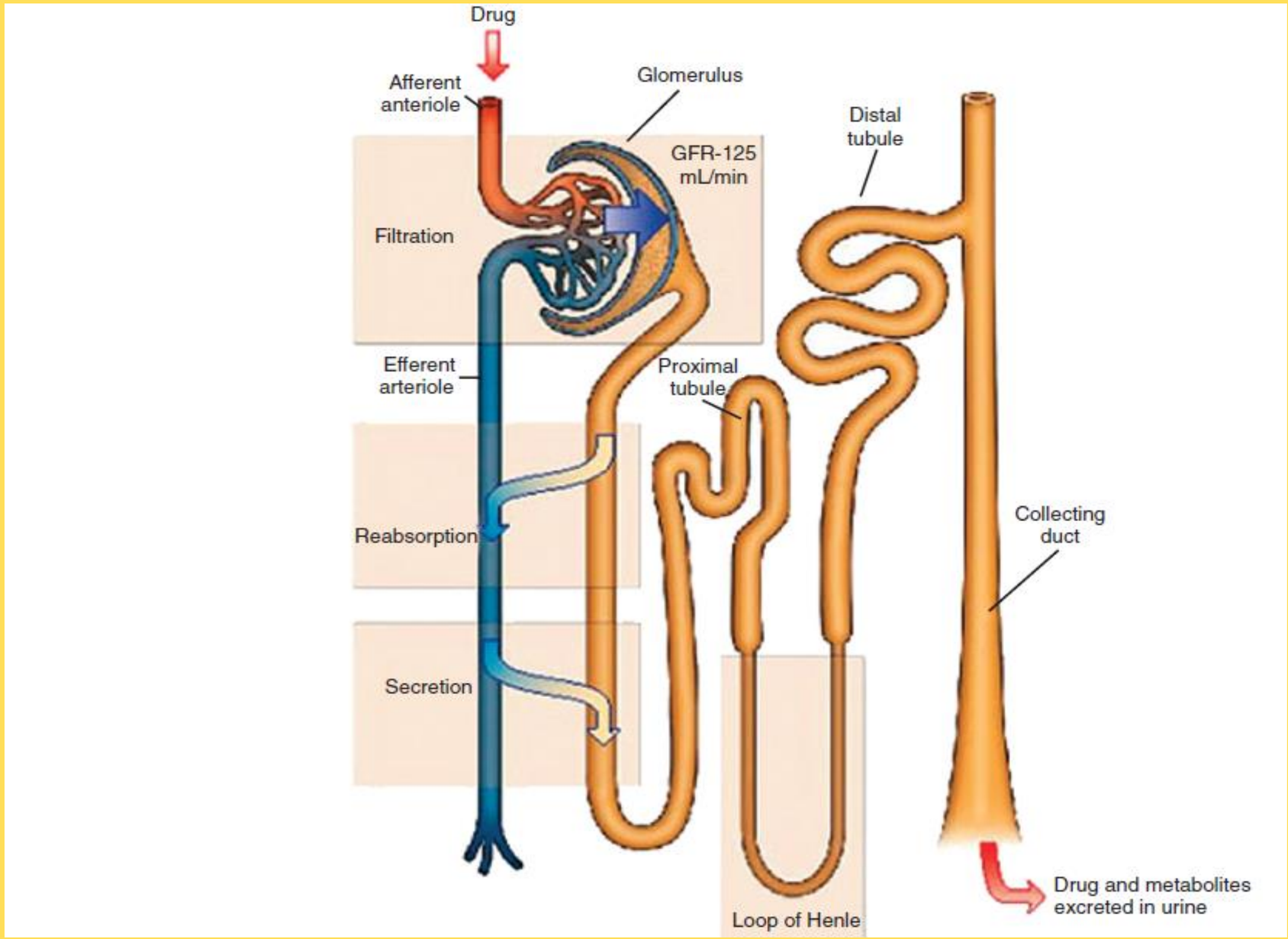
✓Peripheral resistance is lowered along with blood pressure. Thiazides indirectly stimulate aldosterone secretion, causing potassium excretion.

✓They stimulate calcium reabsorption, which makes them useful for the treatment of kidney stones that are caused by increased calcium in the urine (hypercalciuria) but at the expense of increasing blood calcium levels (hypercalcemia).

MECHANISM OF ACTION (THIAZIDE DIURETICS)




Thiazide diuretics
Sodium, water retention
Blood volume
Peripheral resistance
Cardiac output
Decrease in blood pressure


Drug
Afferent arteriole
Glomerulus
GFR-125 mL/min
Filtration
Distal tubule
Efferent arteriole
Proximal tubule
Reabsorption
Collecting duct
Secretion
Loop of Henle
Drug and metabolites excreted in urine

PHARMACOKINETICS:

✓Thiazide diuretics are readily absorbed by oral administration. They are weak acids and are highly protein bound.

✓After being transported into the proximal tubule of the nephron, tubular secretion is decreased. Their lipid solubility permits reabsorption along the distal nephron.

✓Their duration of effect varies from as little as 6 hours to as long as 48 hours depending on the drug.

✓ Most thiazide diuretics are dosed once a day.

ADVERSE REACTIONS:

- Dehydration,
- Hyponatremia (sodium loss),
- Electrolyte deficiency
- Hypokalemia (potassium loss),
- Hypomagnesemia (magnesium loss),
- Hypochloremia (chloride loss) and
- Photosensitivity.

Thiazide Diuretics

Generic Name	U.S. Brand Name / Canadian Brand(s)	Dosage Forms and Strengths
chlorothiazide*	Diuril	**Injection, powder for reconstitution:** 500 mg vial **Suspension, oral:** 250 mg/5 mL (237 mL) **Tablets:** 250 mg, 500 mg (generic only)
	Not available	
chlorthalidone*	Thalitone	**Tablets:** 15 mg† (Thalitone), 25 mg†, 50 mg†, 100 mg‡
	Generics	
hydrochlorothiazide*	Microzide. Oretic	**Capsules (Microzide):** 12.5 mg **Tablets:** 12.5 mg, 25 mg, 50 mg, 100 mg‡
	Generics	
indapamide*	Generics	**Tablets:** 1.25 mg, 2.5 mg
	Lozide	
metolazone*	Zaroxolyn	**Tablets, slow acting (Zaroxolyn):** 2.5 mg, 5 mg†, 10 mg†
	Zaroxolyn	

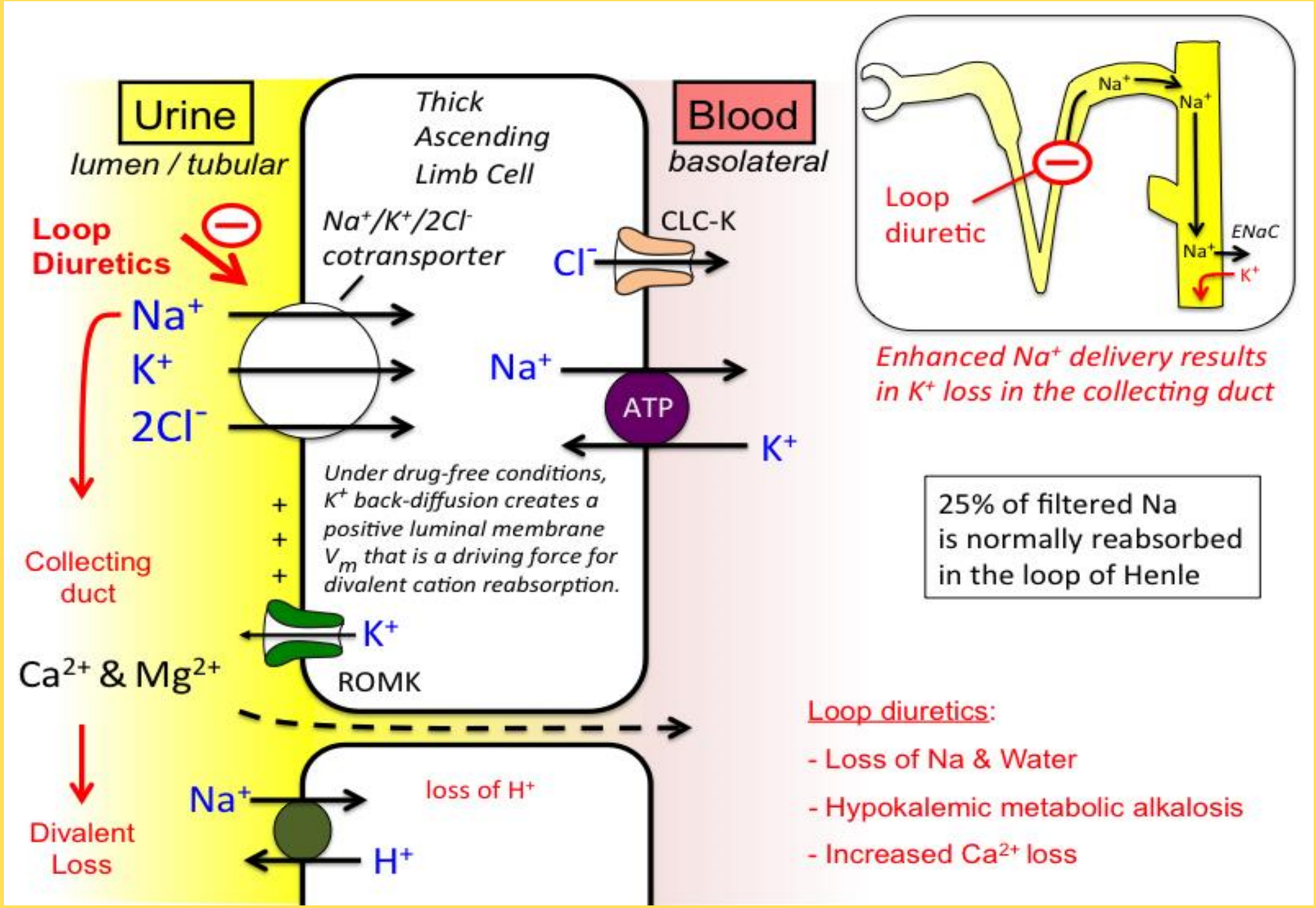
LOOP DIURETICS OR HIGH CEILING DIURETICS :

✓The loop diuretics also block the sodium–potassium 2 chloride cotransporter in the ascending loop of Henle.

✓They are the most potent diuretics because they inhibit the reabsorption of 20% to 30% of sodium load; the thiazides inhibit only 5% to 10%, and the potassium-sparing diuretics inhibit only 1% to 3% of the sodium load.

✓Loop diuretics increase potassium excretion and are often administered with a potassium supplement because of risk of hypokalemia. They also stimulate aldosterone secretion, similar to the thiazides, and increase calcium excretion

MECHANISM OF ACTION (LOOP OR HIGH CEILING DIURETICS)



PHARMACOKINETICS:

✓The loop diuretics are readily absorbed from the gastrointestinal tract. They are up to 98% protein bound.

✓Differences among the loop diuretics are associated with their degree of metabolism in the liver and the extent to which they are eliminated unchanged in the urine.

✓ Whereas bumetanide is partially metabolized in the liver, and 50% is excreted unchanged in the urine, torsemide's metabolism in the liver is greater and 20% is excreted unchanged.

✓Torsemide's long half-life permits once daily dosing.

ADVERSE REACTIONS:

✓ Dehydration,

✓ Severe hypotension,

✓Hypokalemia,

✓Hyperuricemia,

✓Photosensitivity and

✓Deafness has occurred when large doses are infused rapidly.

Potassium-Sparing Diuretics:

Mechanism of action (Triamtrene and amiloride)

The luminal membrane of late DT and CD cells expresses a distinct ***'amiloride sensitive' or 'renal epithelial' Na+* channel** through which Na+ enters the cell down its electrochemical gradient which is generated by Na+K+ ATPase operating at the basolateral membrane .

This Na+ entry partially depolarizes the luminal membrane creating a –15 mV transepithelial potential difference which promotes secretion of K+ into the lumen through K+ channels.

Though there is no direct coupling between Na+ and K+ channels, more the delivery of Na+ to the distal nephron—greater is its entry through the Na+ channel—luminal membrane is depolarized more—driving force for K+ secretion is augmented.

As such, all diuretics acting proximally (loop diuretics, thiazides, CAse inhibitors) promote K+ secretion

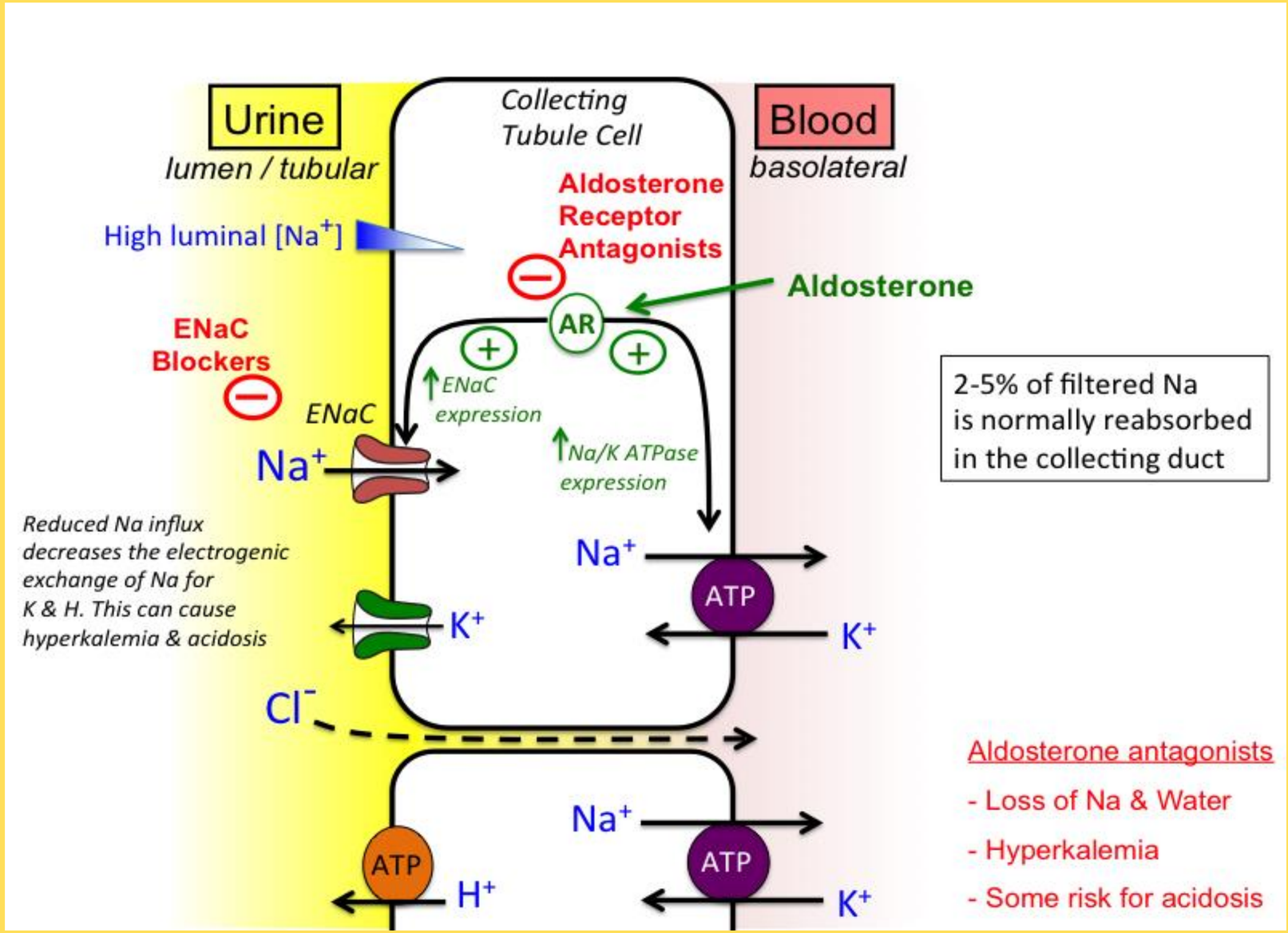
➢Amiloride and triamterene block the luminal Na+ channels—indirectly inhibit K+ excretion, while the net excess loss of Na+ is minor (most of it has already been reabsorbed).

➢The intercalated cells in CD possess an ATP driven H+ pump which secretes H+ ions into the lumen.

➢This pump is facilitated by lumen negative potential. Amiloride, by reducing the lumen negative potential, decreases H+ ion secretion as well; predisposes to acidosis.

➢Both triamterene and amiloride are used in conjunction with thiazide type or high ceiling diuretics: prevent hypokalaemia and slightly augment the natriuretic and antihypertensive response.

MECHANISM OF ACTION OF POTASSIUM SPARING DIURETICS



Triamterene

Pharmacokinetic :

- It is incompletely absorbed orally
- Plasma t½ is 4 hours

Side effects:

- *Nausea*,
- Dizziness,
- Muscle cramps ,
- Rise in blood urea.
- Impaired glucose tolerance and
- Photosensitivity.

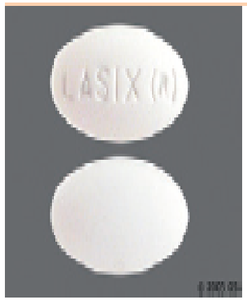
Dose:

50–100 mg daily;

DITIDE: *triamterene 50 mg* + benzthiazide 25 mg tab;

FRUSEMENE: triamterene 50 mg + furosemide 20 mg tab.

Loop Diuretics

Generic Name	U.S. Brand Name Canadian Brand(s)	Dosage Forms and Strengths
	Generics	
bumetanide*	Burinex	Injection, solution: 0.25 mg/mL Tablets: 0.5 mg†, 1 mg, 2 mg†, 5 mg‡
 furosemide*	Lasix	Injection, solution: 10 mg/mL Solution, oral: 10 mg/mL, 40 mg/5 mL Tablets: 20 mg, 40 mg, 80 mg
	Lasix	
torsemide*	Demadex	Injection, solution: 10 mg/mL Tablets: 5 mg, 10 mg, 20 mg, 100 mg
	Not available	

ALDOSTERONE RECEPTOR ANTAGONISTS(SPIRINOLACTONE)

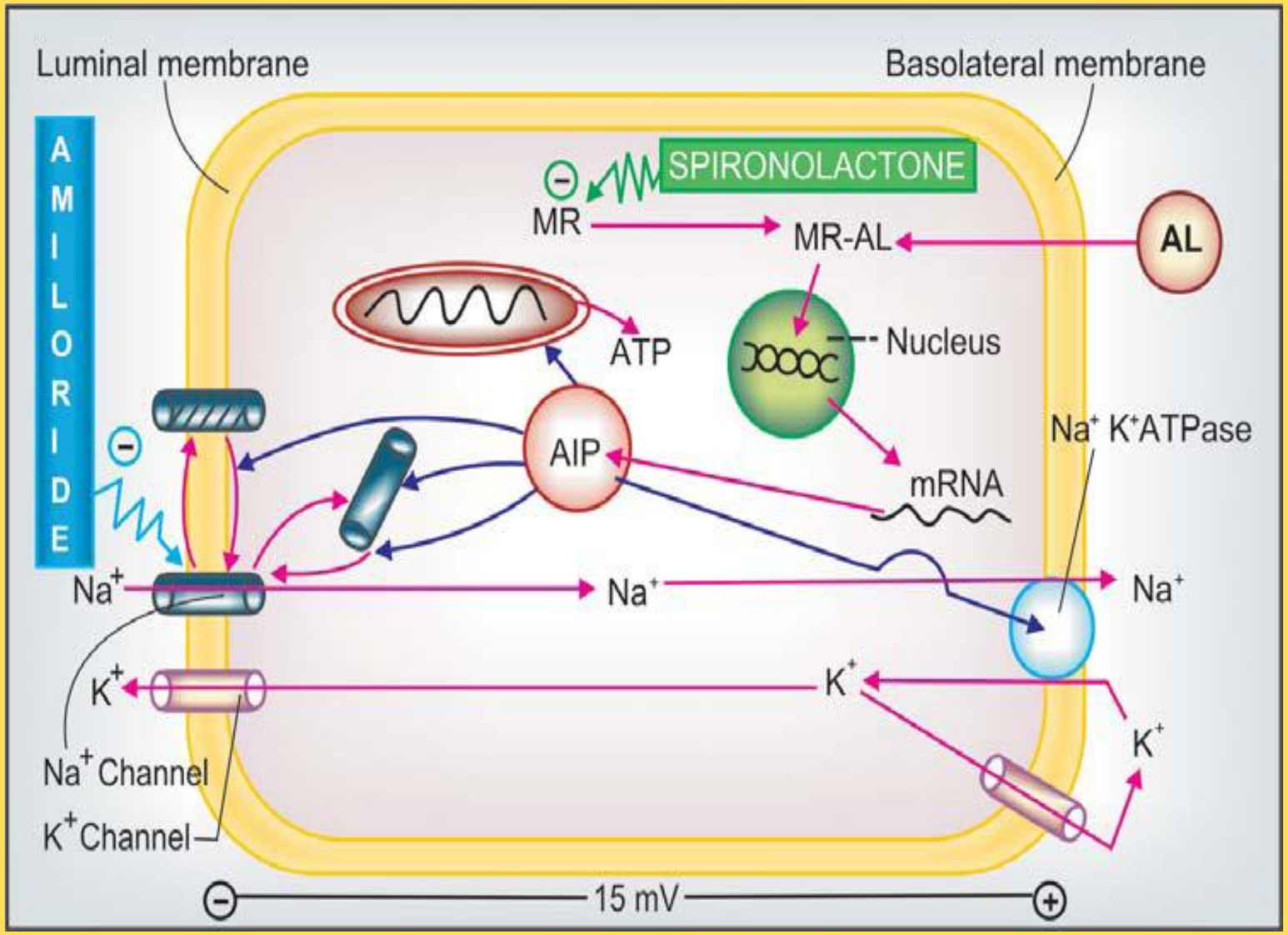
Mechanism of action:

➢**SPIRINOLACTONE** is a steroid, chemically related to the mineralocorticoid aldosterone.

➢Aldosterone acts on the late DT and CD cells by combining with an intracellular mineralocorticoid receptor → induces the formation of 'aldosterone-induced proteins' (AIPs) which promote Na+ reabsorption by a number of mechanisms and K+ secretion.

➢Spironolactone acts from the interstitial side of the tubular cell, combines with the mineralocorticoid receptor and inhibits the formation of AIPs in a competitive manner.

➢ It has no effect on Na+ and K+ transport in the absence of aldosterone, while under normal circumstances, it increases Na+ and decreases K+ excretion.


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

Use :

- Edema
- Hypertension
- Congestive heart failure

Pharmacokinetics :

- *The oral bioavailability of* spironolactone from microfine powder tablet is 75%.
- It is highly bound to plasma proteins and completely metabolized in liver;
- The t½ of spironolactone is 1–2 hours,

Adverse effects :

- *Drowsiness*,
- Confusion,
- Abdominal upset,
- Hirsutism,
- Gynaecomastia,
- Impotence and
- Menstrual irregularities.

Eplerenone: *is a recently developed more selective* aldosterone antagonist, that is less likely to cause hormonal disturbances like gynaecomastia, impotence and menstrual irregularities.

Dose:

25–50 mg .

➢ALDACTONE 25, 100 mg tabs.

ALDACTIDE: Spironolactone 25 mg + hydroflumethiazide 25 mg tab.

➢LACILACTONE, SPIROMIDE: Spironolactone 50 mg + furosemide 20 mg tab.

RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM

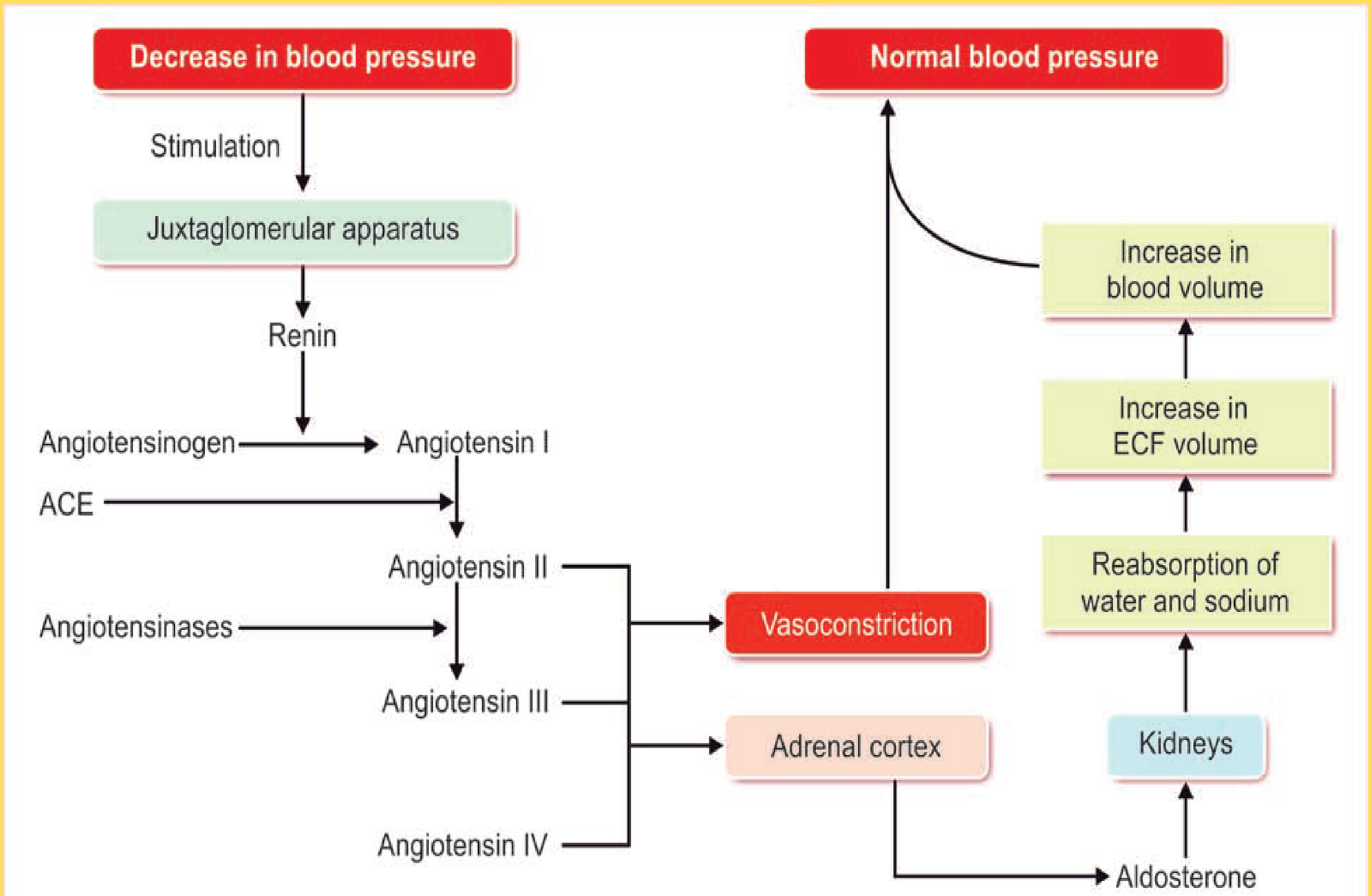
➢Kidney provides for long-term control of blood pressure by altering blood volume.

➢Renal Baroreceptors in kidney respond to reduced arterial pressure (and to sympathetic stimulation of adrenoceptors) by releasing the enzyme renin.

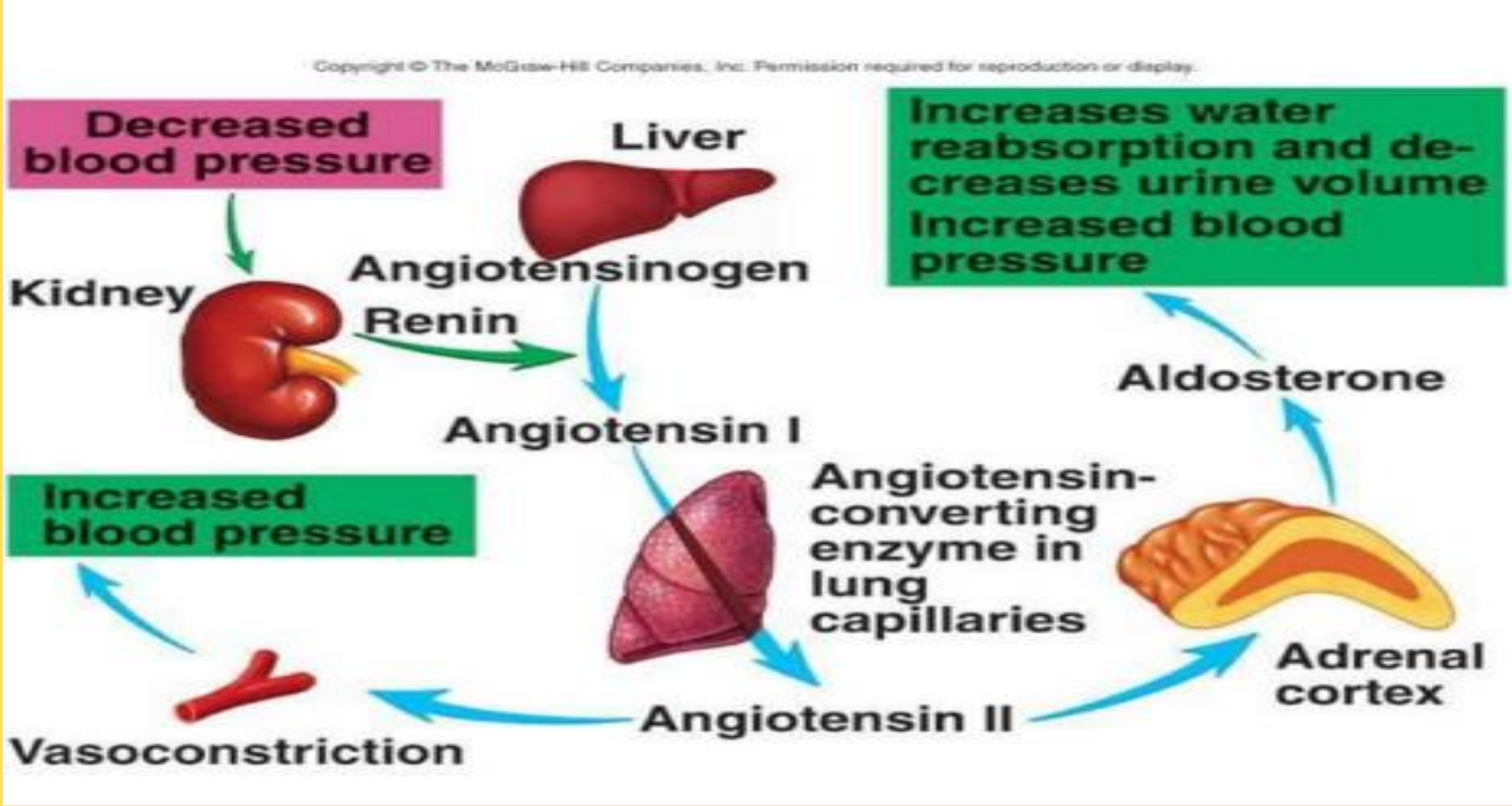
➢This peptidase converts angiotensinogen to angiotensin I, which is converted in turn to angiotensin II in presence of (ACE).

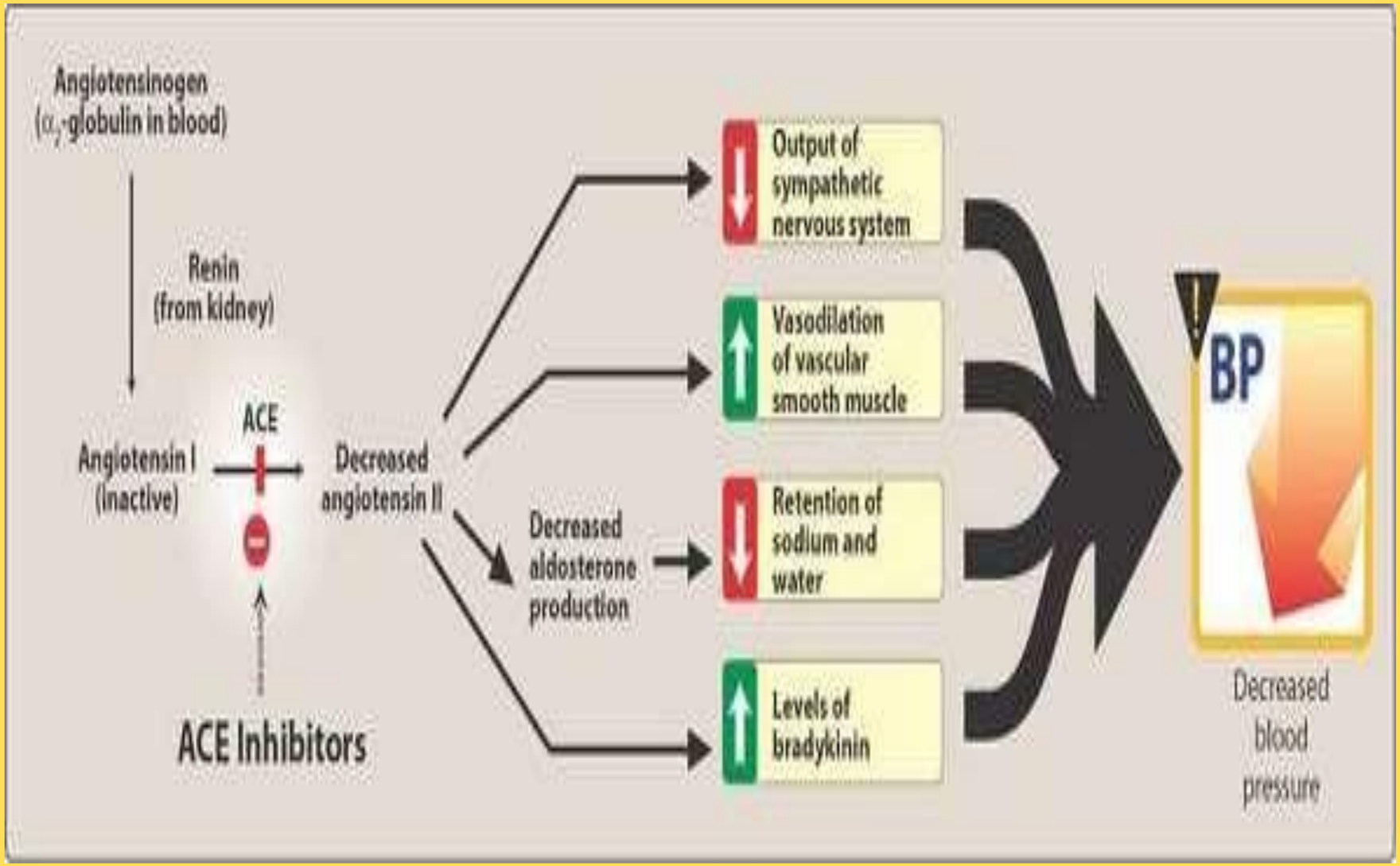
➢Angiotensin II is the body's most potent circulating vasoconstrictor, causing an increase in blood pressure.

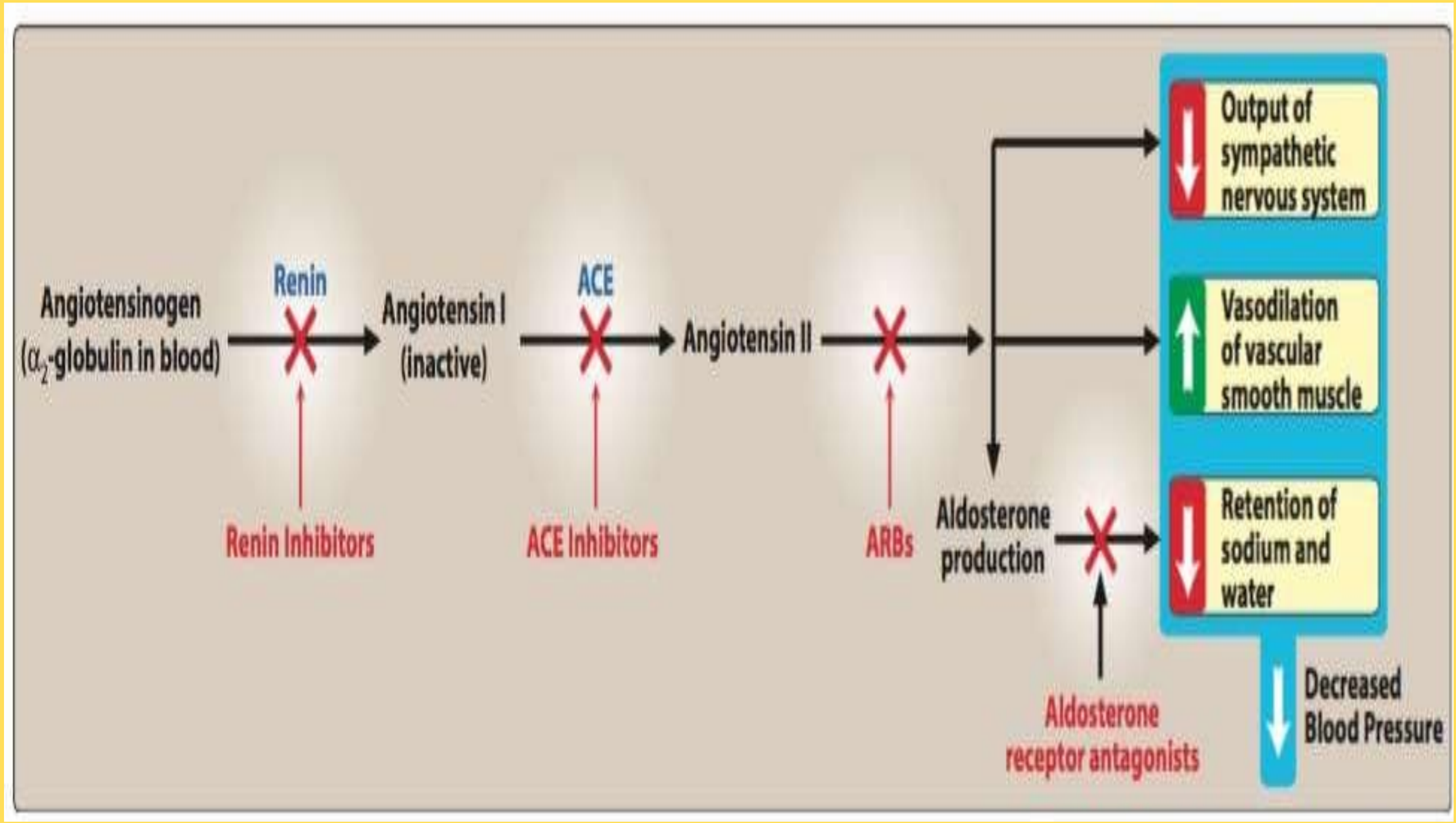
➢Furthermore, angiotensin II stimulates aldosterone secretion, leading to increased renal sodium reabsorption and increased blood volume, which contribute to a further increase in blood pressure.

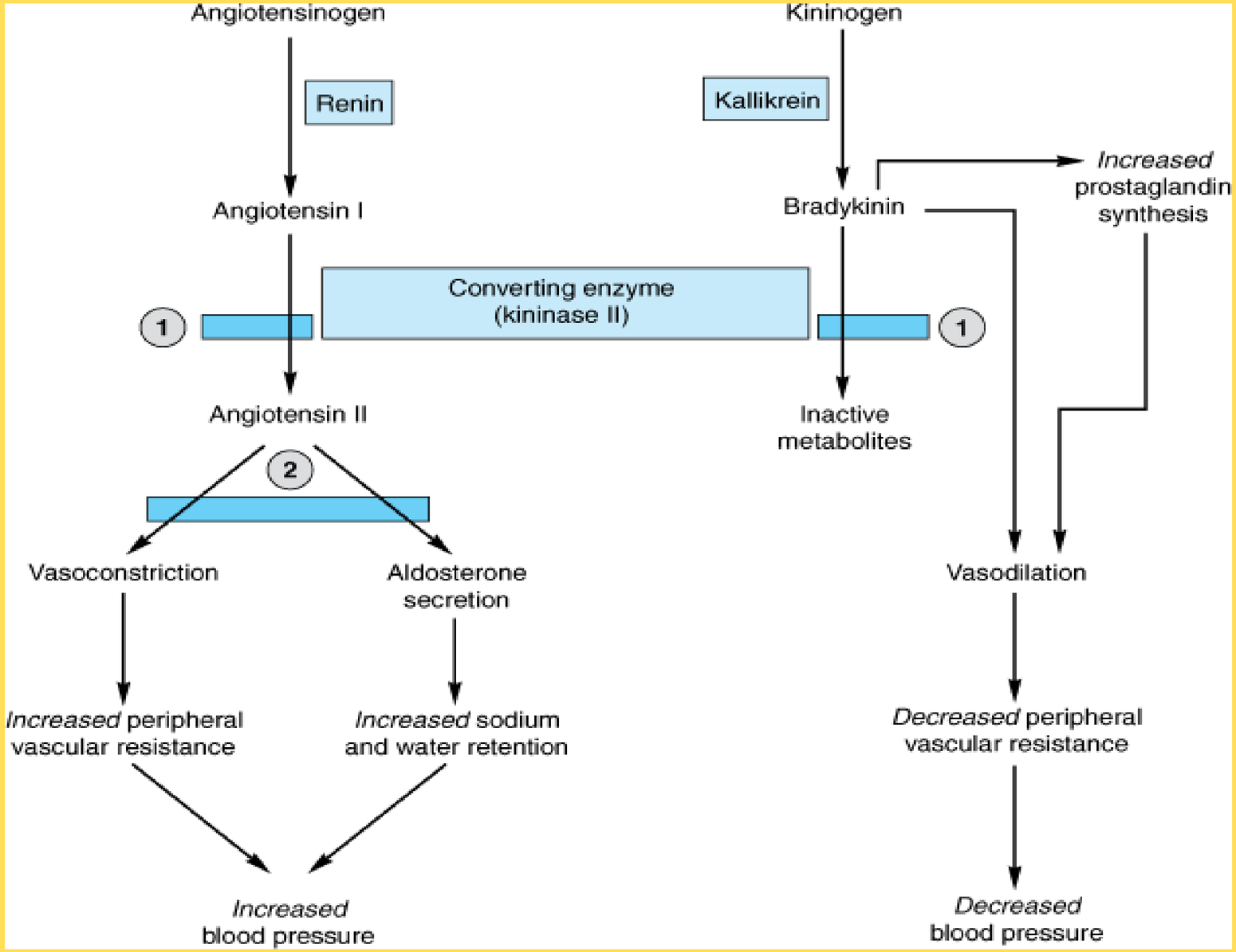

Decrease in blood pressure
Stimulation
Juxtaglomerular apparatus
Renin
Angiotensinogen
Angiotensin I
ACE
Angiotensin II
Angiotensinases
Angiotensin III
Angiotensin IV
Vasoconstriction
Adrenal cortex
Aldosterone
Normal blood pressure
Increase in blood volume
Increase in ECF volume
Reabsorption of water and sodium
Kidneys

Renin – Angiotensin Aldosterone System




Angiotensinogen
(α2-globulin in blood)
Renin
(from kidney)
ACE
Angiotensin I
(inactive)
Decreased
angiotensin II
ACE Inhibitors
Output of
sympathetic
nervous system
Vasodilation
of vascular
smooth muscle
Decreased
aldosterone
production
Retention of
sodium and
water
Levels of
bradykinin
BP
Decreased
blood
pressure


Angiotensinogen
(α_2-globulin in blood)
Renin
Angiotensin I
(inactive)
ACE
Angiotensin II
Output of sympathetic nervous system
Vasodilation of vascular smooth muscle
Retention of sodium and water
Decreased Blood Pressure
Aldosterone production
Aldosterone receptor antagonists
Renin Inhibitors
ACE Inhibitors
ARBs


Angiotensinogen
Renin
Angiotensin I
Converting enzyme
(kininase II)
1
Angiotensin II
2
Vasoconstriction
Aldosterone
secretion
Increased peripheral
vascular resistance
Increased sodium
and water retention
Increased
blood pressure
Kininogen
Kallikrein
Bradykinin
Increased
prostaglandin
synthesis
1
Inactive
metabolites
Vasodilation
Decreased peripheral
vascular resistance
Decreased
blood pressure

ANGIOTENSIN RECEPTOR BLOCKER

Pharmacokinetics:

➢The plasma half-life of individual ARBs vary.

➢Losartan, one of the first ARBs to be marketed, has a relatively short half-life (only 2 hours), but it has an active metabolite with a plasma half-life of up to 6 to 9 . **The drugs are administered as a single daily dose.**

Adverse Reactions:

➢Fatigue,

➢Abdominal pain,

➢Dizziness,

➢Dry mouth,

➢Constipation,

➢ Impotence, and muscle cramps.

DOSE OF ARB

Generic Name	U.S. Brand Name / Canadian Brand(s)	Dosage Forms and Strengths
candesartan	Atacand	Tablets: 4 mg, 8 mg, 16 mg, 32 mg
	Atacand	
eprosartan	Teveten	Tablets: 400 mg, 600 mg
	Teveten	
irbesartan	Avapro	Tablets: 75 mg, 150 mg, 300 mg
	Avapro	
losartan	Cozaar	Tablets: 25 mg, 50 mg, 100 mg
	Cozaar	

ACE INHIBITOR

Captopril:

Pharmacokinetic:

- Over 70% of orally administered drug is absorbed
- Plasma half life : 2 hours

Adverse effects:

- Hypotension
- Hyperkalemia
- Cough
- dygeusia

Uses:

- Hypertension
- Congestive heart failure
- Myocardial infarction
- Diabetic nephropathy
- Prophylaxis in high cardiovascular risk subjects

Dose:

- Angiopril -25mg tab
- Captoril -12.5,25mg tab

DIRECT RENIN INHIBITOR (Aliskiren)

Pharmacokinetic:

Orally administered,bioavailablity is low

Plasma half life > 24 hrs

Adverse effects:

Abdominal pain

Loose motion

Dizziness

Contraindicated during pregnancy

Dose:150 -300 mg

Rasilez 150 mg tab

Sympathetic inhibitors

α BLOCKERS (MOA)

Blockade of vasoconstrictor α1 (also α2) receptors reduces peripheral resistance and causes pooling of blood in capacitance vessels → venous return and cardiac output are reduced → fall in BP.

Postural reflex is interfered with → marked hypotension occurs on standing → dizziness and syncope. Hypovolemia accentuates the hypotension. The α blockers abolish the pressor action of Adr, which then produces only fall in BP due to β2 mediated vasodilatation— *vasomotor reversal of Dale. Pressor and* other actions of selective α agonists (NA, phenylephrine) are suppressed.

PHENOXYBENZAMINE

SIDE EFFECTS

- Postural hypotension,
- Palpitation,
- Nasal blockage and
- Miosis

DOSE:

- 20–60 mg/day oral; 1 mg/kg by slow i.v. infusion over 1 hour; used primarily in pheochromocytoma,
- FENOXENE 10 mg cap, 50 mg/ml inj.

PHENTOLAMINE :

➢**This is a** rapidly acting α blocker with short duration of action (in minutes). It equally blocks α1 and α2

➢It is used as a quick and short acting α blocker for diagnosis and intraoperative management of pheochromocytoma and for control of hypertension due to clonidine withdrawal, cheese reaction, etc.

DOSE:

5 mg i.v. repeated as required;

➢REGITINE, FENTANOR 10 mg/ml inj.

USES of alpha blocker:

- Pheochromocytoma
- Hypertension
- Benign hypertrophy of prostate (BHP)
- Secondary shock
- Peripheral vascular diseases
- Congestive heart failure (CHF)

β ADRENERGIC BLOCKERS (MOA)

➢Propranolol blocks vasodilatation and fall in BP evoked by isoprenaline and enhances the rise in BP caused by Adr—there is re-reversal of vasomotor reversal that is seen after α blockade.

➢ It has no direct effect on blood vessels and there is little acute change in BP.

➢ On prolonged administration BP gradually falls in hypertensive subjects but not in normotensive.

➢ Total peripheral resistance (t.p.r.) is increased initially (due to blockade of β mediated vasodilatation) and c.o. is reduced—little change in BP.

➢ With continued treatment, resistance vessels gradually adapt to chronically reduced c.o. so that t.p.r. decreases—both systolic and diastolic BP fall.

PROPRANOLOL:

PHARMACOKINETICS:

➢Propranolol is well absorbed after oral administration, but has low bioavailability due to high first pass metabolism in liver.

INTERACTIONS:

➢Additive depression of sinus node and A-V conduction with digitalis and verapamil — cardiac arrest can occur. However, propranolol has been safely used with nifedipine.

➢Propranolol delays recovery from hypoglycaemia due to insulin and oral antidiabetics

➢Indomethacin and other NSAIDs attenuate the antihypertensive action of β blockers

Dose:

➢*Oral—10 mg BD to 160 mg*

➢ INDERAL, CIPLAR 10, 40, 80 mg tab, 1 mg/ml inj,BETABLOC 10, 40 mg tab.S

CONTRAINDICATIONS:

➢Propranolol can accentuate myocardial insufficiency and can precipitate CHF/edema by blocking sympathetic support to the heart, especially during cardiovascular stress.

➢ Bradycardia: resting HR may be reduced to 60/min or less. Patients of sick sinus are more prone to severe bradycardia.

➢ Propranolol worsens chronic obstructive lung disease, can precipitate life-threatening attack of bronchial asthma: contraindicated in asthmatics

SIDE EFFECTS:

- G.I.T. Upset,
- Lack of drive,
- Nightmares,
- Forgetfulness,
- Rarely hallucinations.

USES of beta blockers:

- Hypertension
- Angina pectoris
- Cardiac arrhythmias
- Myocardial infarction (MI)
- Congestive heart failure
- Glaucoma

α + β ADRENERGIC BLOCKERS

➢**Labetalol It is the first adrenergic antagonist** capable of blocking both α and β receptors

➢Fall in BP (both systolic and diastolic) is due to α1 and β1 blockade as well

➢as β2 agonism (vasodilatation).

Side effect:

➢postural hypotension,

➢Rashes and

➢liver damage

Dose:

Start with 50 mg BD, increase to 100–200 mg TDS oral. In hypertensive emergencies 20–40 mg i.v. every 10 min till desired response is obtained.

NORMADATE 50, 100, 200 mg tab

Carvedilol :

➢It is a β1 + β2 + α1 adrenoceptor blocker; produces vasodilatation due to α1 blockade as well as calcium channel blockade, and has antioxidant property.

Dose:

➢*Hypertension/angina: 6.25 mg BD initially, titrate to max.* of 25 mg BD. CARVIL, CARLOC, CARVAS 3.125, 6.25, 12.5, 25 mg tabs; ORICAR 12.5, 25 mg tabs.

Vasodialators:

➢The mechanism of vascular smooth muscle relaxant action of hydralazine is not clearly known. It is partly endothelium dependent: may involve generation of NO (nitric oxide) and stimulation of cGMP. It is also an opener of ATP operated K+ channels;

➢Direct effects on membrane potential and on Ca2+ fluxes have also been Proposed.

Pharmacokinetics:

➢ *Hydralazine is well absorbed orally,* and is subjected to first pass metabolism in liver

➢t½ 1–2 hours.

➢*Dose: 25–50 mg OD–TDS; NEPRESOL 25 mg tab.*

Adverse effects

- Facial flushing,
- Throbbing headache,
- Dizziness,
- Palpitation,
- Nasal stuffiness,
- Fluid retention,
- Edema,
- CHF.
- Angina and MI may be precipitated in patients with coronary artery disease.

Use

➢*Hydralazine is used in moderate-to-severe* hypertension not controlled by the first line drugs.

➢ It is one of the preferred antihypertensives during pregnancy because of decades of experience and record of safety.

Minoxidil

Uses:

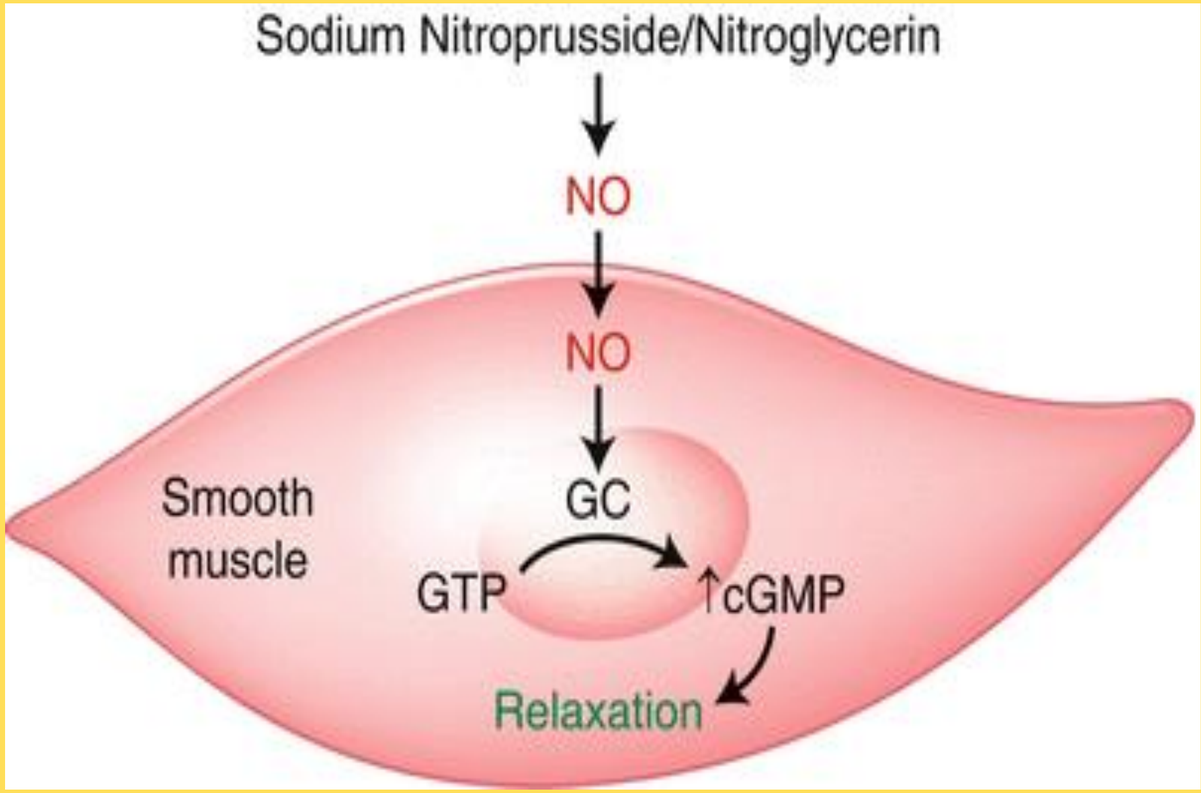
➢hypertension.

➢ *alopecia.*

Dose:

MINTOP, GROMANE 2% scalp lotion, MULTIGAIN 2% topical solution and metered spray, MANEXIL 5% gel; apply twice a day**.**

Sodium nitroprusside (MOA)



Nitroprusside:

Side effects

- Palpitation,
- Nervousness,
- Vomiting,
- Perspiration,
- Pain in abdomen,
- Weakness,
- Disorientation, and
- Lactic acidosis

Uses:

- controlled hypotension,
- in refractory CHF pump
- failure accompanying MI and
- acute mitral regurgitation.

Dose:

- SONIDE, PRUSIDE, NIPRESS 50 mg in 5 ml inj.

THANK YOU