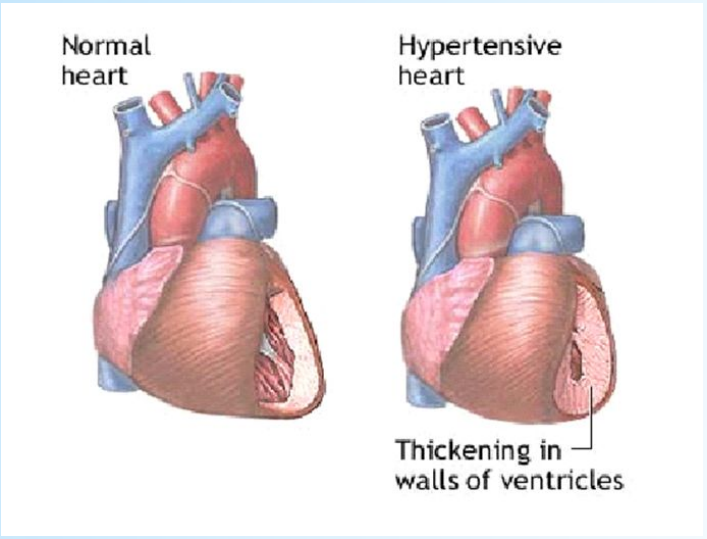

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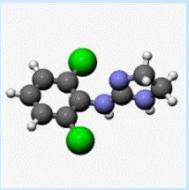
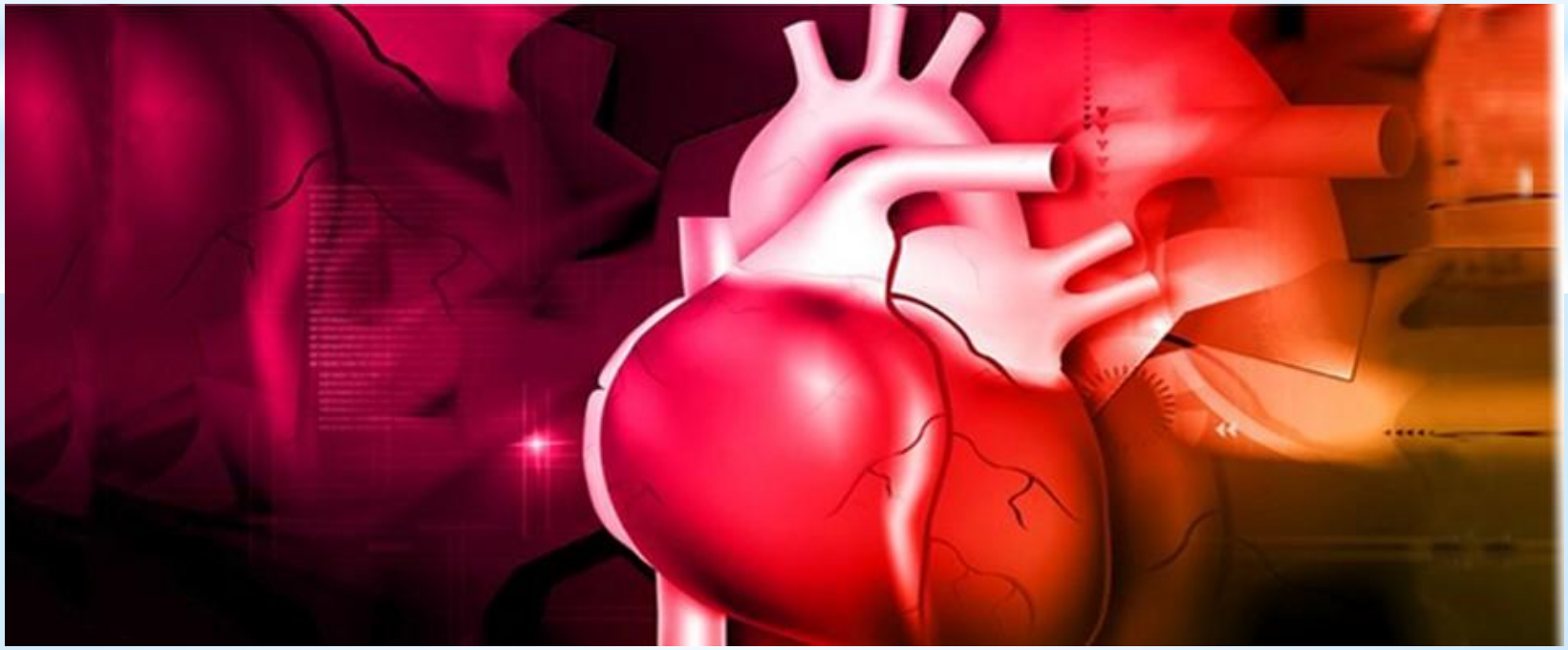
Pharmacology Department



Lecture N2

ANTIHYPERTENSIVE AND LIPID-LOWERING DRUGS

Lecturer: Assoc. Prof. Irina Borisovna Samura



Classification of arterial hypertension

By type of circulation:

- **Hyperkinetic** - increased contractile ability of the myocardium and normal or slightly decreased vascular tension. Tachicardia. BP is increased predominantly due to increase of systolic one. Diastolic pressure is normal or slightly decreased.
- **Hypokinetic** - increased activity of renin-angiotensin system increase the vascular tension and compensatory decrease of the myocardium contractile activity. Bradicardia. Blood pressure is increased predominantly due to increase of diastolic one. Systolic pressure is increased less.
- **Eukinetic** - normal contractile ability of the myocardium and increased vascular tension or equal activation of all pathogenetic links. Heart rate is normal or non-significant tachicardia. Systolic and diastolic pressure are equally increased.

Antihypertensive Drugs:

I. **Diuretics**:

Hydrochlorthiazide (*Dichlothiazide*) –
Tab. 0.025 and 0.1 g

Furosemide (*Lasix*) – Tab. 0.04 g ; amp 1%-2 ml

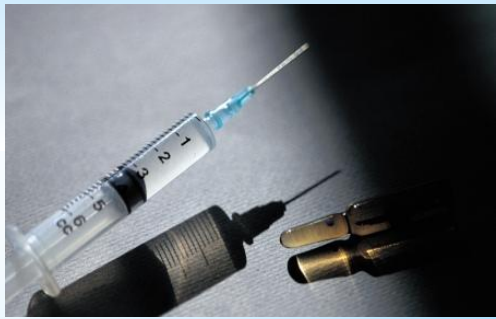
Bumetanide (*Burinexe*) –
Tab. 0.001 g; amp 0.025% - 2 ml

Indapamide – Tab. 2.5 mg (0.0025 g)

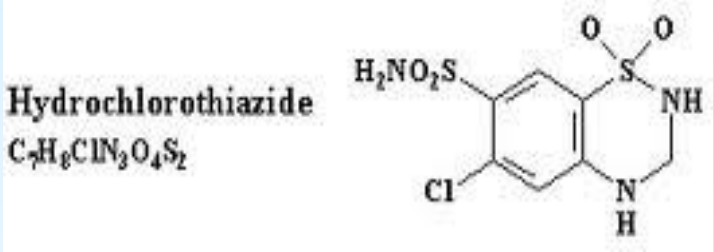
Verospirone (*Spironolactone*) – Tab. 25 mg

Amiloride – Tab. 2.5 and 5 mg

Triamteren – Caps. 50 mg (0.05 g)



Hydrochlorthiazide (*Dichlothiazide*)



=> inhibition Na^+/Cl^- cotransport

=> ↓ Na+ and Water Excretion =>

=> ↓ Extracellular Volume =>

↓Cardiac Output and Renal Blood Flower

Electrolyte disturbance: ↓K+ , ↓Mg2+, ↓Ca2+

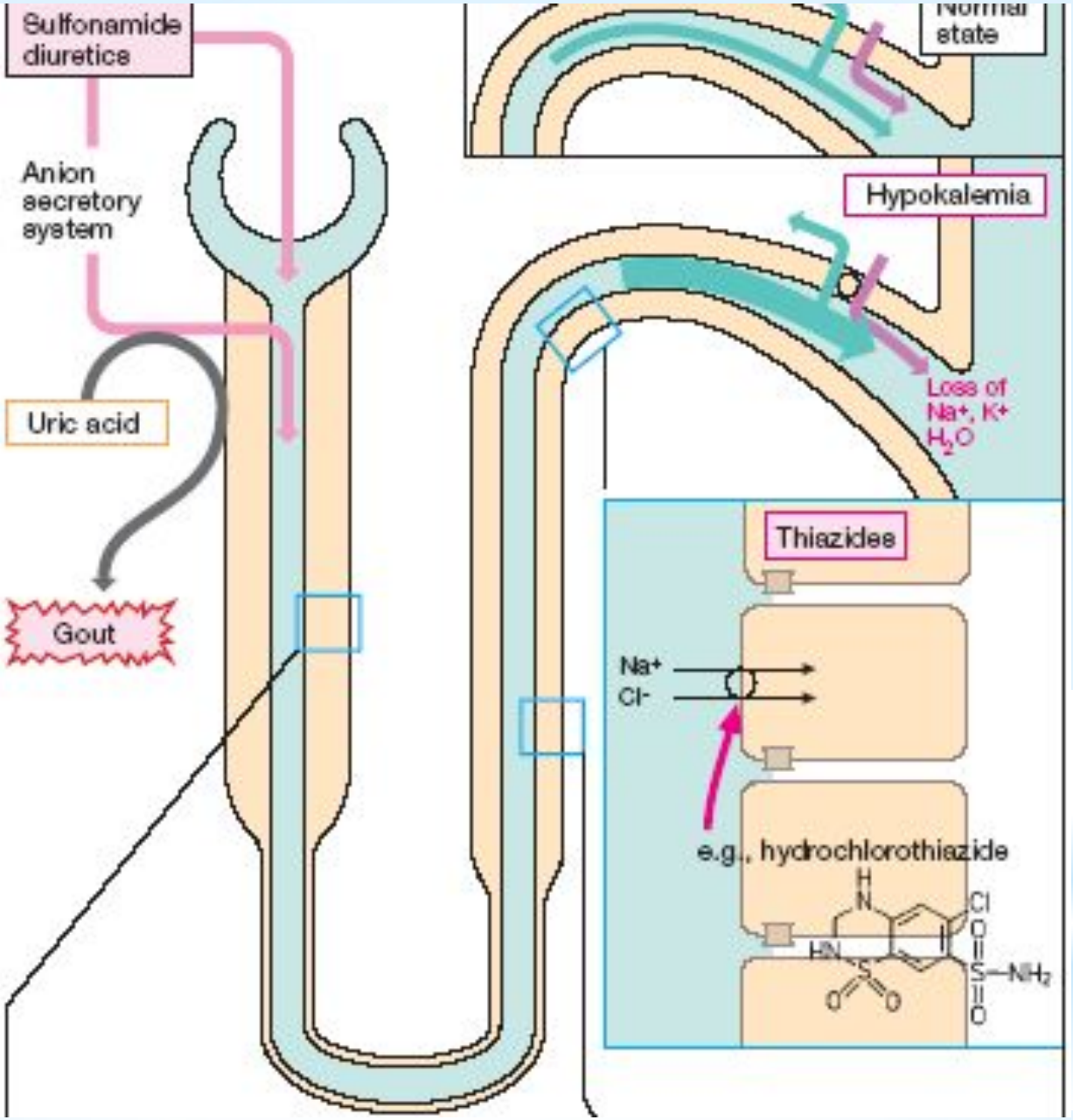
Thiazide diuretics counteract the Na^+ and water retention observed with other agents used in the treatment of hypertension.

Thiazide diuretics are useful in combination therapy with a variety of other antihypertensive drugs including β-blockers and ACE inhibitors.

Adverse effects:

Hypokalemia and Hyperuricemia – in 70% of patients,

Hyperglycemia - in 10% of patients



Thiazides: Inhibition a Na^+/Cl^- cotransport

CLINICAL USES OF THIAZIDES:

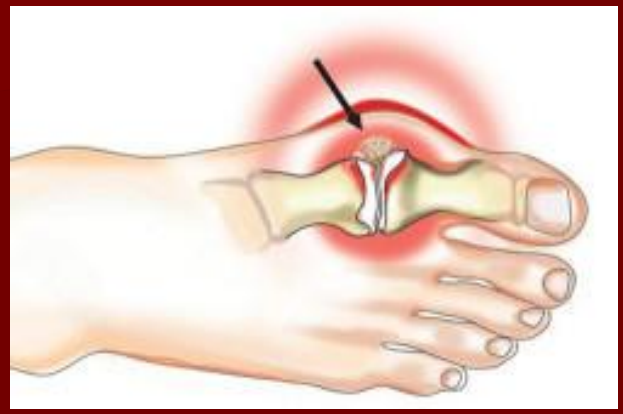
1. Hypertension
2. CHF. Thiazides can be the diuretic of choice
   in ⇓ *Extracellular Volume*
   If the *thiazide* fails - a *Loop diuretic*
3. Hypercalciuria:

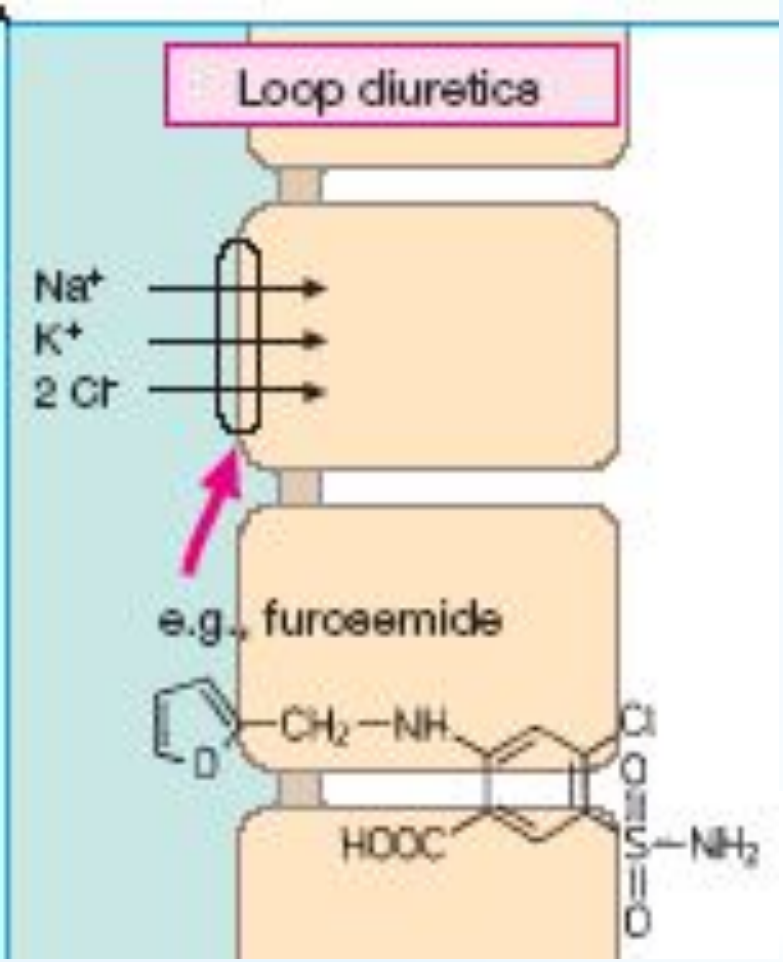
Thiazides inhibit urinary Ca^{2+} excretion

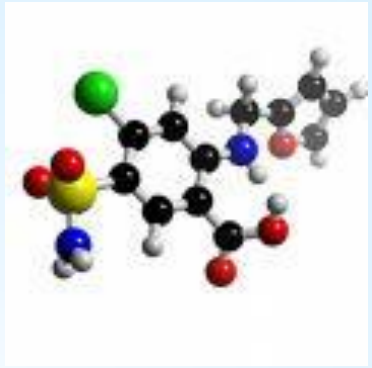
4. Diabetes Insipidus.

ADVERSE EFFECTS of THIAZIDES :

1. Hypokalemia
2. Hyperglycemia and Glucosuria.
3. Hyperuricemia - ☐ Plasma Urate Levels => **Gout**
4. Hyperlipidemia







Mechanism of action of Loop Diuretics:

They produce **Na+ / K+ /2Cl-** cotransport inhibition of **the Luminal Membrane** in the **Proximal Part** of **the Ascending Loop of Henle =>**

=> increase the excretion Na^+, H_2O, Cl^-, and **K^+**

II. Sympathoplegic Agents:

1. Centrally-acting Adrenergic Drugs:

α_2 Adrenomimetics:

Clopheline (*Clonidine*) -

Tab. 0.000 075 and 0.00015 g

amp. 0.01% - 1 ml

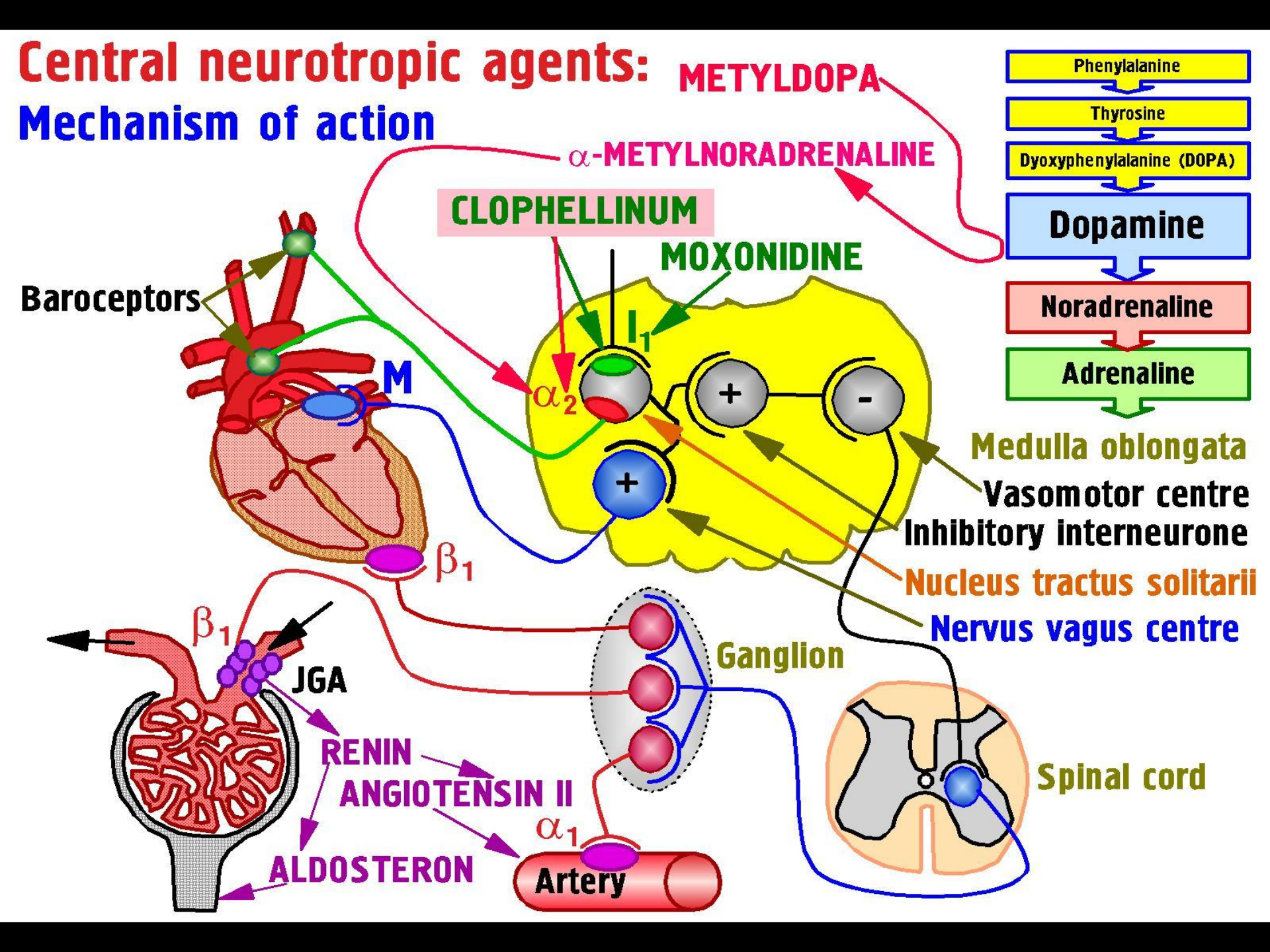
Methyldopa Tab. 0.25 g

Guanfacine Tab. 0.0005, 0.001 and 0.002 g

Moxonidine Tab. 0.0002 and 0.0004 g

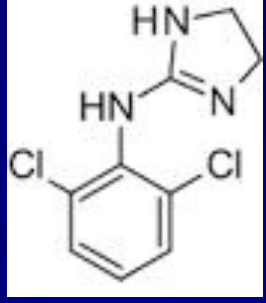
Central neurotropic agents:

Mechanism of action



Clopheline (*Clonedine*) – α_2 Adrenomimetic

- Central *A*drenergic Outflow.



- To treat mild to moderate hypertension that has not responded adequately to the treatment with diuretics alone.
- After IV injection, Clopheline → a brief BP followed by more prolonged hypotension.

The pressor response is due to direct stimulation of presynaptic α_2 adrenoreceptors in arterioles.

2. Centrally and Peripherally Acting Drugs:

a) Sympatholytics:

Reserpine – tab. 0.1 mg and 0.25 mg

Octadine (*Guanethidine*) – tab. 0.025 g (25 mg)

b) Ganglioblockers:

Benzohexonium – tab. 0.1 and 0.25 g, amp. 2.5% - 1 ml

Pentamine – amp. 5% - 1 ml

c) β-Blockers:

Propranolol (*Anaprilin*) – tab. 10 and 40 mg; amp. 0.1%-1 ml

Atenolol –tab. 50 and 100 mg

Metoprolol – Tab. 50 and 100 mg

d) α – Blockers:

Phentolamine – tab. 0.025 (25 mg)

Tropaphen – (amp. 20 mg)

Reserpine - blocks the **Mg $^{2+}$/ ATP – dependent transport** of **amines** - Noradrenaline , Dopamine and Serotonin from the **cytoplasm** into **storage vesicles** in the **adrenergic nerves** of all body tissues

=> depletion of Noradrenaline levels in the adrenergic neuron, since MAO degrades the Noradrenaline (NA)

=> Sympathetic function is impaired because of NA release

Reserpine Blood Pressure by a combination of :

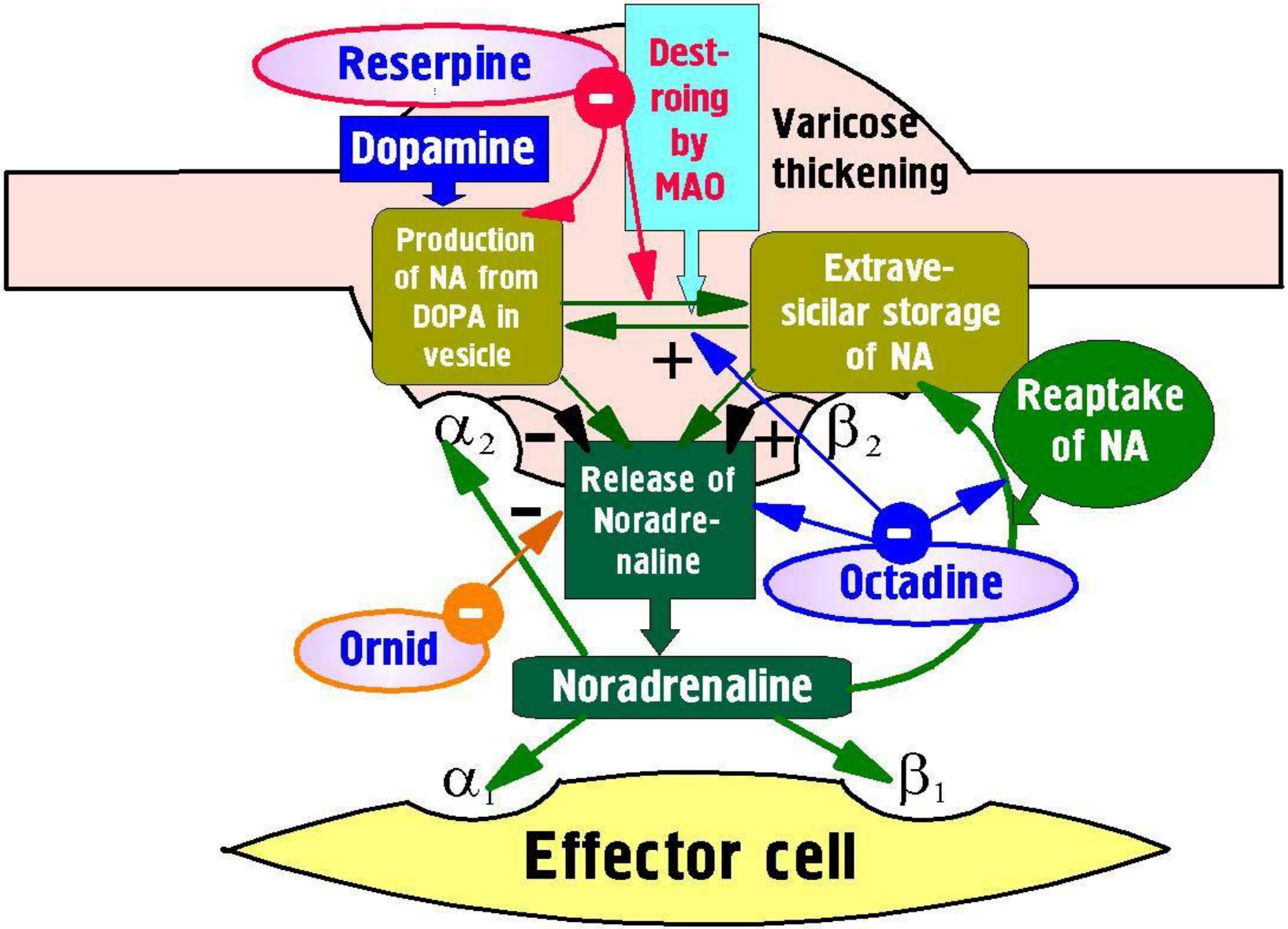
- Cardiac Output and
- Peripheral Vascular Resistance

Adverse effect:

Sedation, Lassitude, Nightmares, Mental Depression,
Extrapyramidal Effects resembling Parkinson's disease as a result of dopamine depletion in the *corpus striatum*

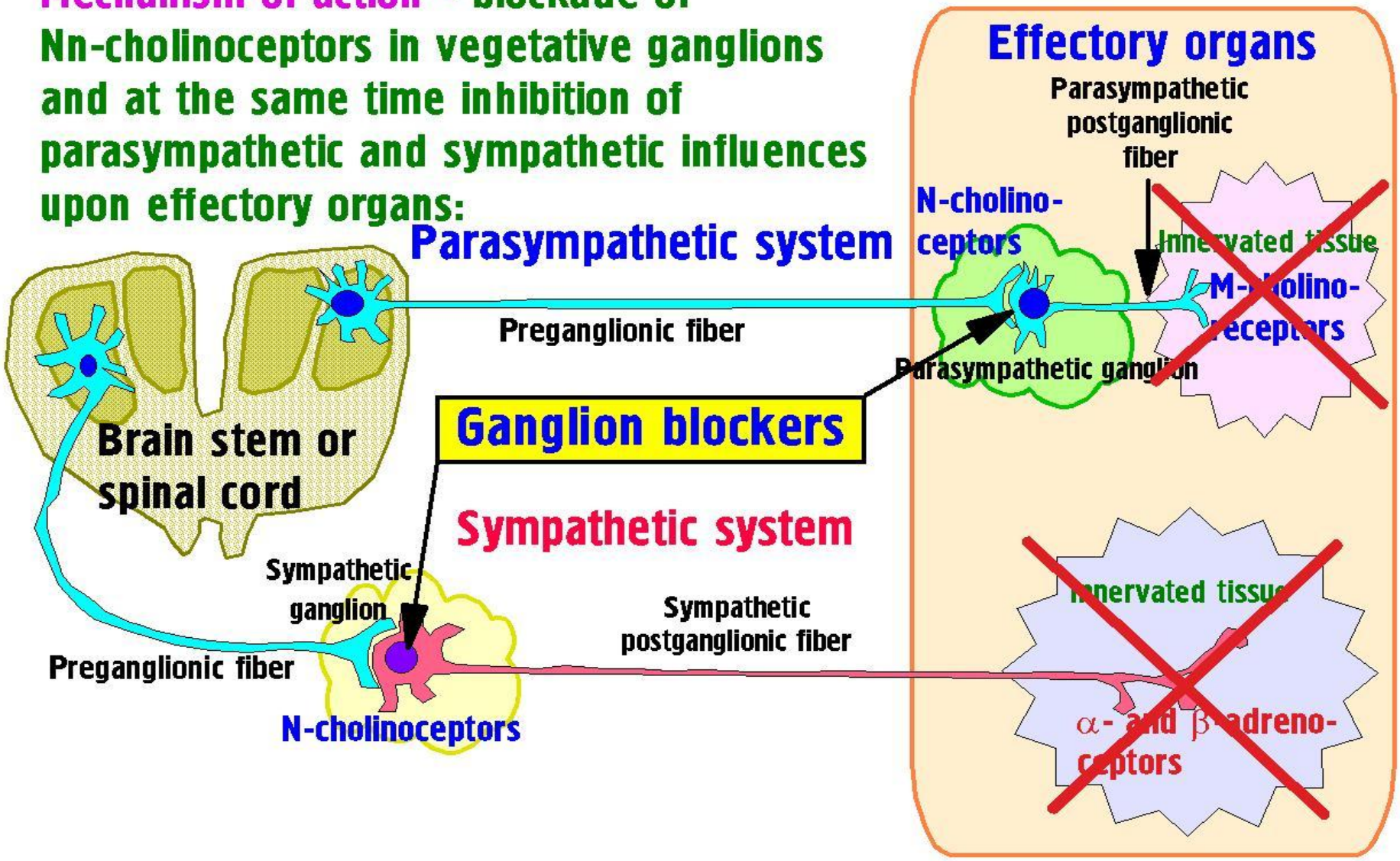
GIT abnormalities - diarrhea, gastrointestinal cramps, increase of gastric acid secretion, ulcer

Sympatholytics: Mechanism of Action



Ganglion blockers

Mechanism of action - blockade of Nn-cholinoceptors in vegetative ganglions and at the same time inhibition of parasympathetic and sympathetic influences upon effectory organs:



Propranolol - *a β-adrenoblocker, is useful for ↓BP in mild to moderate hypertension*

In Severe Hypertension, it is especially useful in preventing the reflex tachycardia that results from treatment with direct vasodilators

Propranolol ↓BP by:

- ↓ *Cardiac Output*
- ↓ *Sympathetic outflow from the CNS*
- ↓ *Renin Release and Renin-Angiotensin-Aldosteron system*

Adverse effect: Bradycardia, Bronchospasm, CHF, Vasoconstriction, Cold Extremities,

Intermittent Claudication, Fatigue, Lethargy,

Mental Depression, Memory Loss, Hallucination, Impotence,

Dislipidemia: ↑ **Cholesterol,** ↑ **Triglycerides** ,

↓HDL-cholesterol

III. Peripheral Vasodilators:

1. Direct Vasodilators:

Apressine (*Hydralasine*) – Tab. 0.01 and 0.025 g

$MgSO_4$ – amp. 25% – 10 ml IM

Dibazole (*Bendazole*) –

amp. 1% - 1 and 5 ml, Tab. 2 and 4 mg

No-spa - (*Drotaverine*) – amp. 2%-2 ml, Tab. 0.04 g

Papaverine hydrochloride – amp. 2%-2 ml, Tab. 0.04 g

Nanipruss (Na^+ *Nitroprusside*) –

amp. 25 and 50 mg

Euphylline (*Aminophylline*) –

tab. 0.15 g, amp. 2.4% - 10 ml, 24% - *1 ml*

Hydralazine (*Apressine – tab. 0.01 g and 0.025 g*)

- Direct Vasodilation, acting primarily on arteries and arterioles.
- ⇩Central Sympathetic Tonus
- Hydrazine Group inhibits NO inactivation.

=> Decreased Peripheral Resistance,

=> a reflex ⇧HR and cardiac output.

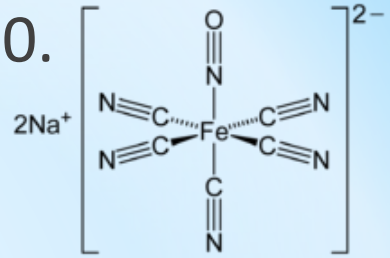
Clinical uses: moderately severe hypertension.

It is almost always administered in combination with a β-blocker such as *propranolol* (to balance the reflex tachycardia) and a *diuretic* (to decrease Na^+ retention).

Together, the three drugs decrease cardiac output, plasma volume, and peripheral vascular resistance.

Adverse effects: headache, nausea, sweating, arrhythmia, lupus-like syndrome.

Sodium Nitroprusside (*Nanipruss*) is known since 1850.



It was regarded as a **poison** because of its cyanide group **CN**.

Given in small, the drug has a specific, vascular-smooth-muscle relaxant action.

It dilates both arterial and venous vessels, resulting in reduced peripheral vascular resistance and venous return.

The drug dilates the Arterial Vessels => ⇩ *the Cardiac Afterload*;

dilates the Veins Vessels => ⇩ the *Cardiac Preload* .

=> ⇩ myocardial O_2 consumption and

=> improves myocardial function in low output states.

The fall in **AP** is accompanied by reflex tachycardia.

Nitroprusside ⇩ plasma renin activity.

Drugs which at the same time increase the coronary blood flow and decrease oxygen demand of the myocardium.

Mechanism of action of organic nitrates:

- Molecular level.

Nitrogycerin and other organic nitrates

↓

Release of nitric oxide (NO)

↓

Activation of guanylyl cyclase in the smooth muscle cells

↓

Increase of amount of cGMP

↓

Decrease of Ca^{++} in cytoplasm

↓

Dephosphorylation of the light chains of myosin

↓

Relaxation of smooth muscles in next priority:

1. Large veines.
2. Large arteries.
3. Venules, arterioles, precapillary sphincters.

2. Calcium Channel Blockers –

block high-threshold Ca^{2+} channels of L-type

A. Diphenylalkylamines:

Verapamil (*Isoptin*) – *Tab. 40, 80 mg*

B. Dihydropyridines:

1st Generation:

Nifedipine (*Phenigidin*) – *Tab. 10 mg*

2nd Generation:

Amlodipine (*Norvasc*) – *Tab. 2.5, 5, and 10 mg*

Isradipine – *Caps. 2.5 and 5 mg*

Nicardipine

C. Benzothiazepines:

Diltiazem – *Tab. 30, 60, 120 mg*

3. α_1 – Blockers: -

Prazosin – *Tab. 1, 3, 5 mg*

Doxazosin – *Tab. 2 and 4 mg*

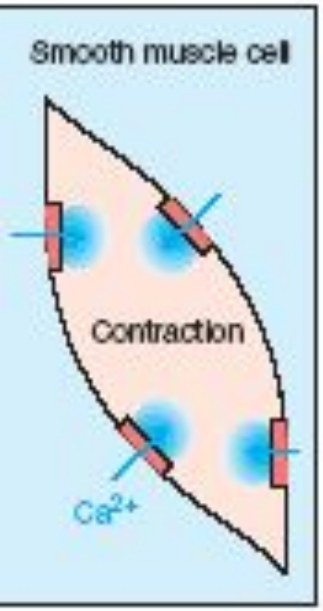
Terazosin – *Tab. 2 and 5 mg*

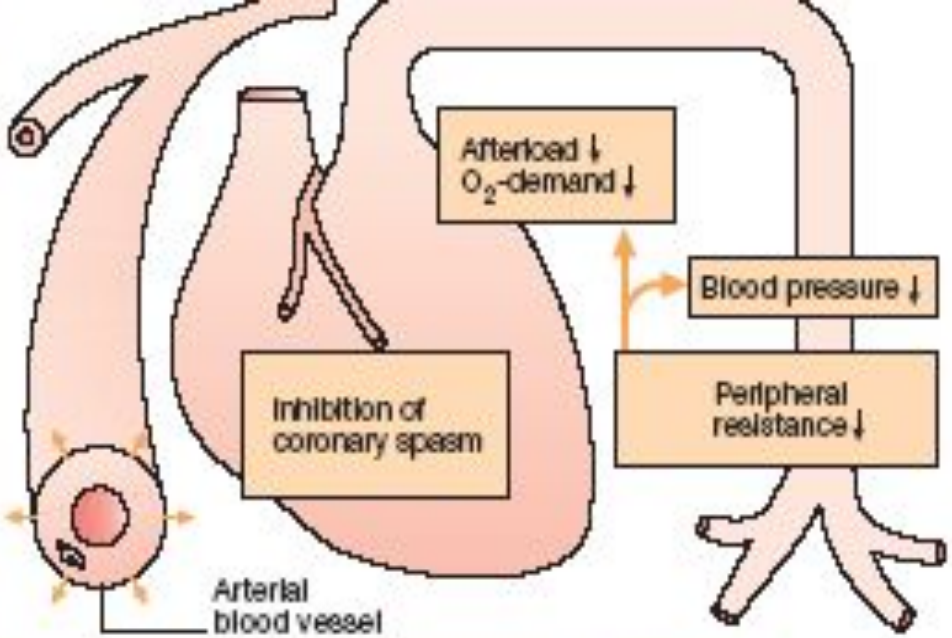
4. K^+ Channel Activator:

Diazoxide – *amp. 1.5% - 20 ml IV infusion*

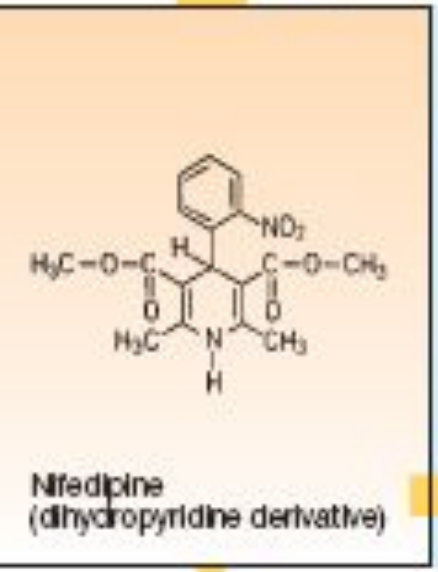
Minoxidil – *Tab. 5 mg*

Vial - 2%-10 ml IV infusion





Vasodilation in arterial bed



Inhibition of cardiac functions

Ca2+ Channel Blockers are useful in the Treatment of Patients with:

- **Asthma**
- **Diabetes**
- **Peripheral Vascular Diseases**

Verapamil appears to have antianginal, antihypertensive and antiarrhythmic action.

It manages unstable and chronic stable angina by:

□ *Afterload* => □ *O_2 Consumption*.

It also □ myocardial O_2 demand and cardiac work by:

- *Exerting Negative Inotropic Effect* - □ Heart Rate: the drug *slows Cardiac Conduction directly* .

In patients with Prinzmetal's Variant Angina:

Relieving coronary artery spasm => myocardial □ *O_2 Delivery*

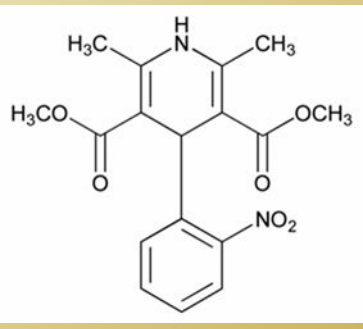
<u>Adverse Effects</u>:

Myocardial Depression, including *Cardiac Arrest*, Bradycardia, AV block, Hypotension, Heart Failure, Constipation, Peripheral Edema.

Nifedipine – functions mainly as an *arteriolar vasodilator*.

It dilates systemic arteries, resulting in:

- *Total Peripheral Resistance*
- Systemic AP with slightly Increased Heart Rate,
- *Afterload*, and increased cardiac index.



- The vasodilation effect of *Nifidipine* is useful in the treatment of *Variant Angina* caused by spontaneous coronary spasm.
- In *Prinzmetal's angina*, *Nifedipine* inhibits coronary artery spasm, increasing myocardial *Oxygen Delivery.*

Adverse effects: Flushing, Headache, Tachycardia, Hypotension , Dizziness, Nausea, Constipation, and Peripheral Edema as side effects of its *vasodilation activity*.

Amlodipine is a Dihydropyridine compound – the 2nd Generation long-acting Ca^{2+} antagonist.

It blocks the inward movement of Ca^{2+} by binding to L-type Ca^{2+} channels in the Heart and in Smooth Muscle of the Coronary and Peripheral Vasculature =>

=> vascular smooth muscle relaxation dilating mainly arterioles.

The drug has an Intrinsic Natriuretic Effect.

It has *Antianginal, Hypotensive, Vasodilative* and Spasmolytic *Action*

Clinical Uses:

- Arterial Hypertension,
- Stable and Unstable angina,
- Prinzmetal's or Variant Angina Pectoris.

Peak effects occur within 1-2 hours and persist for 24 hours.

Adverse effects: headache, peripheral edema.

Ca^{2+} channel blockers are useful in the treatment of patients who also have asthma, hypertension, diabetes, and/or peripheral vascular disease.

Minoxidil – Tab. 5 mg, vial - 2%-10 ml –

K^+ Channel Activator.

The effect results from the opening of K^+ channels in smooth muscle membranes.

This action Stabilizes the Membrane at its Resting Potential and makes contraction less likely.

Like *Hydralazine*, Minoxidil dilates **Arterioles** but not **Veins**.

Minoxidil is well absorbed from the GIT and is metabolized, primarily by conjugation, in the liver.

Clinical use: treatment of severe to malignant hypertension that is refractory to other drugs.

Reflex tachycardia may be severe and may require the concomitant use of a β-blocker.

Adverse effects: serious Na^+ and water retention, leading to volume overload, edema, and CHF.

Hypertrichosis – the Growth of Body Hair

Minoxidil is used topically to treat Male Pattern Baldness

IV. Agents affecting Renin-Angiotensin System:

1). **ACE Inhibitors**:

Captopril – Tab. 25 and 50 mg

Enalapril – Tab. 5; 10 and 20 mg

Lisinopril – Tab. 10; 20 and 40 mg

2**) Angiotensine II Antagonists**:

Losartan (*Cozaar*) – Tab. 50 mg

Valsartan – Tab. 80 mg

The Angiotensin-Converting Enzyme (ACE) Inhibitors: Captopril, Lisinopril, Enalapril

block the ACE that cleaves Angiotensin I to form Angiotensin II – a potent vasoconstrictor.

They also the rate of Bradykinin inactivation.

- Vasodilation occurs as a result of the combined effects of diminished levels of Angiotensin II and the potent vasodilating effect of increased Bradykinin.

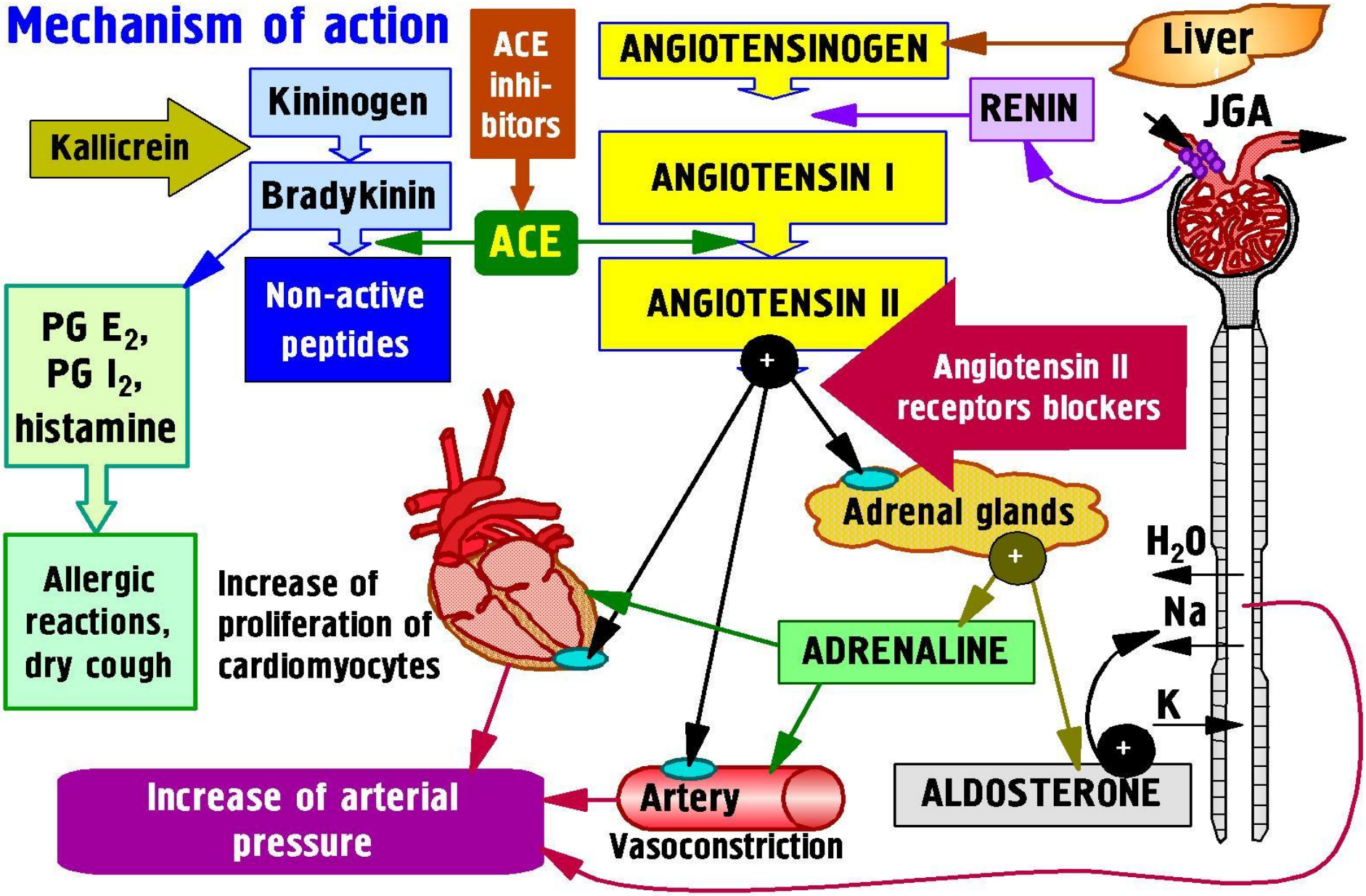
By reducing circulating angiotensin II levels, ACEIs:

 Aldesterone Secretion, resulting in decreased Na+ and water retention.

- Unlike β-blockers, ACEIs are effective in the management of patients with chronic CHF.
- ACE inhibitors are now a standard in the care of a patient following a Myocardial Infarction.

Drugs influencing upon the renin-angiotensin system:

Mechanism of action



Lipid-lowering Drugs

1. Hydroxy-Methyl-Glutaryl-CoA Reductase Inhibitors:

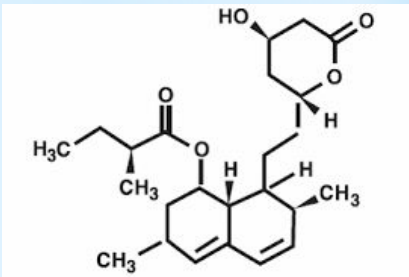
Lovastatin – tab. 20 and 40 mg

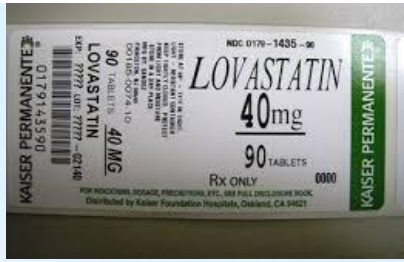
Pravastatin – tab. 10 and 20 mg

Simvastatin – tab. 20 and 40 mg

Fluvastatin - tab. 20 and 40 mg

Atorvastatin



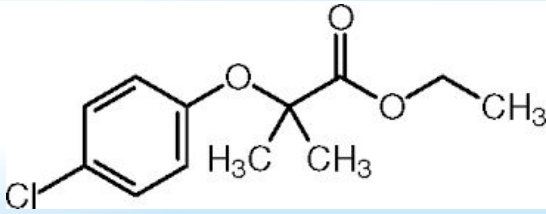


2. Fibrates:

Clofibrate – caps. 0.25 g

Fenofibrate

Gemfibrozil – caps. 0.3 g, tab. 0.6 g



3). Group of Nicotinic Acid :

Nicotinic acid (*Niacin*)

Tab. 0.05 g; 0.1 g and 0.5 g;
10% - 1 ml

Nicotinamid Tab. 50 mg, amp 1% - 1 ml

Xantinol nicotinate (*Complamin*)

4). Bile Acid Binding Resinse:

Cholestyramine – pulv. 16.0-18.0 g PO

Colestipol – pulv. 5.0-10.0 g PO

5). Antioxidants:

Probucol – Tab. 0.5 g

6). The others: Lipostabil, Pentoxiphylline

Hydroxy-methylglutaryl-CoA reductase Inhibitors (*Statins*):

Lovastatin, Simvastatin, Pravastatin Fluvastatin, and *Atorvastatin* –

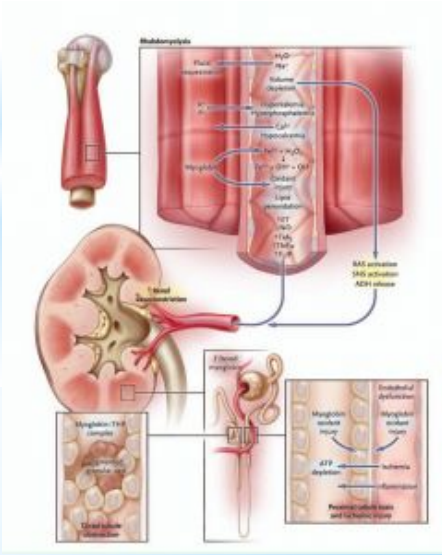
inhibit the 1st enzymatic step of Sterol Synthesis -

as structural analogs of the natural substrate,

3-hydroxy-3-methylglutaric acid (HMG),

they **compete** to block hydroxymethylglutaryl-CoA reductase (HMG-CoA reductase).

Adverse effects: Liver Failure, Myopathy, Rhabdomyolysis (disintegration and purulent melting of skeletal muscles).



Fibrates Clofibrate, Fenofibrate and Gemfibrozil – derivatives of fibric acid and are similar to Endogenous Fatty Acids.

Mechanism of Action:

 the activity of **Lipoprotein Lipase**, hydrolyzing **triglycerides** in **chylomicrons** and **VLDL =>**

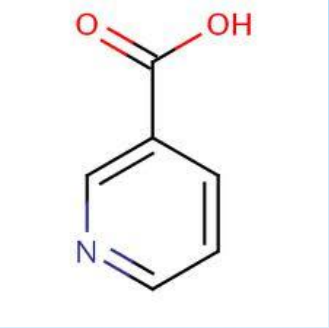
=> the removal of these particles from the plasma.

In contrast, **HDL** levels moderately.

Adverse Effects:

- **Lithiasis**: because **Biliary Cholesterol Excretion**, a predisposition to the formation of **Gallstones**
- **Malignancy**: Treatment with *Clofibrate* has resulted in a significant number of malignancy-related deaths
- **Myositis**

Nicotinic acid **–**



inhibits **Lipolysis** in adipose tissue –

the producer of circulating Free Fatty Acids

=> Eliminates the building blocks needed by the liver

to produce triglycerides and VLDL .

Adverse effects:

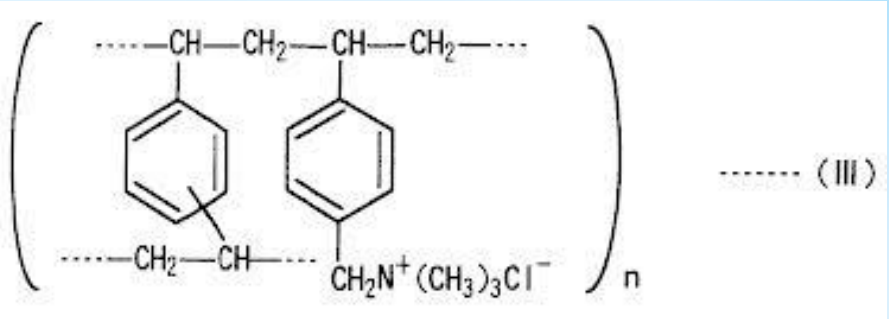
Pruritus, gastric irritation, hyperglycaemia, hyperuriacemia, elevated hepatic aminotransferase enzymes, and hepatitis.

Food sources of nicotinic acid, such as avocadoes and bananas, pose no health dangers.

Cholestyramine and

Cholestipol

are Anion Exchange Resins



that bind

Negatively Charged Bile Acid and **Bile Salts**

in the small intestine **=>**

=> the Bile Acids are **excreted** in faeces and

are not recirculated to the liver.

Adverse effects:

Abdominal Fullness

Flatulence

Constipation


THANK YOU FOR
ATTENTION