Unit-I → Introduction to Haemodynamic & Electrophysiology of Heart →

✡ **Heart →**
- It is a myocular organ
- Made up of specialised cardiac tissue that allows it to act as pump & circulate the blood throughout the body with the help of blood vessels.
- It has the property of autorhythmicity which means it generates all electrical impulse.

Ex → SA node, also K/as Pacemaker.

✡ **function of heart →**
- Delivery of blood
- Delivery of O_2 & nutrient

✡ **factors affecting heart rate →**
- Autonomic activity
- Circulating hormone
- Physical Activity
- Age
- Emotions
- Baroreceptors

✡ **Electrophysiology of heart →**

Cardiac muscles have property of –
- Excitability
- Contractility
- Automaticity

✡ **Myocardium has two types of cell or tissue →**

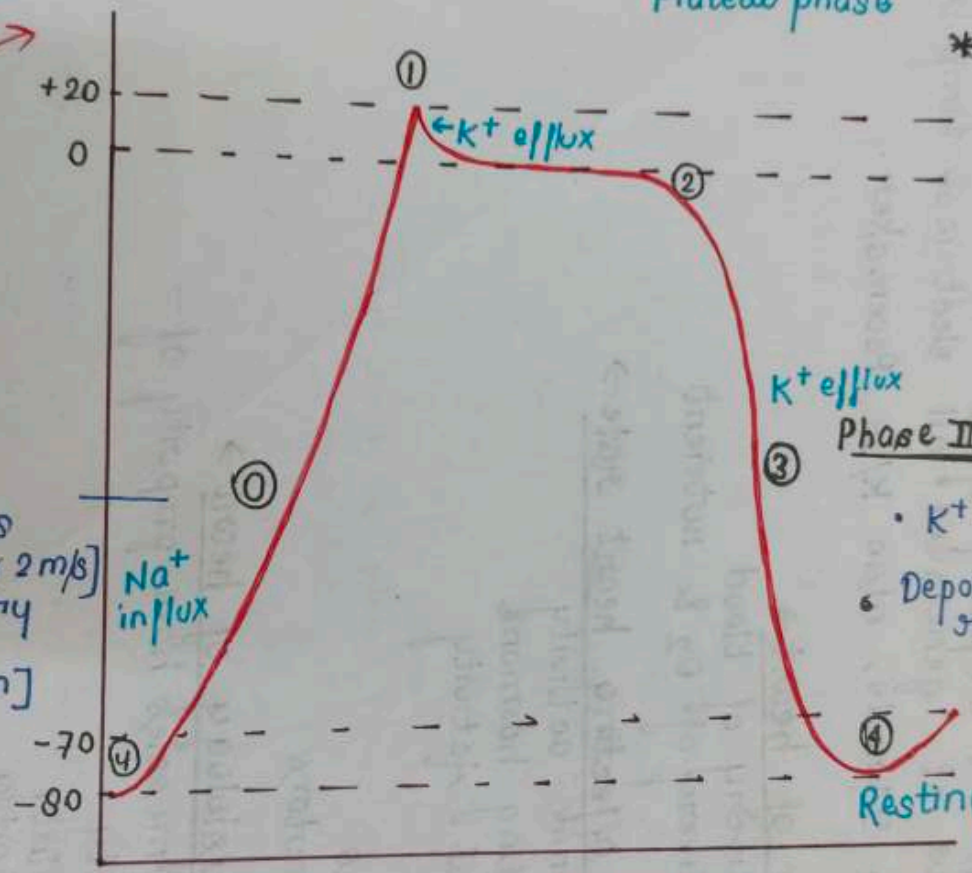
① Contracting cells → Participate in pumping action of heart.

② Conducting cells → Conduct impulse to another part.

Ex → SA node, AV node, Bundle of his & Purkinje Fibre.

* Phase-I → Short initial, rapid period.
• K^+ ion efflux occur, resulting rapid repolarisation.

Cardiac Action potential →



* Phase II →
• There is slow entry of Ca^{++} ion resulting in prolong plateau phase
• does not depolarise with another impulse

* Phase 0 → Voltage
• Na^+ channel opens [for 2 m/s]
• There is fast entry of Na^+ ions. [depolarisation]

Phase III → It is 2nd period of rapid repolarization.
• K^+ efflux occur [repolarization]
• Depolarization may occur in respond to strong stimuli.

* Phase-IV →
• K^+ ion returns to the cell.
• Na & Ca move out of the cell & resting membrane potential is retained.

* Congestive Heart failure [CHF] →

→ Heart failure is a complex, progressive disorder in which the heart is unable to pump sufficient blood to meet the needs of the body.

→ Its symptoms are –
- Shortness of breath
- fatigue or fluid retention
- Heart failure is due to an impaired availability of the heart to the adequetly filled with and or inject the blood.
- Heart failure may primarily be due to systolic dysfunction or diastolic dysfunction.

Other cause is –
- Arterioschloretic heart disease.
- Myocardial infarction [heart attack]
- Hypertension.
- Valbular heart disease.

* Systolic dysfunction →

- Ventricals r dilated an enable to develop sufficient wall tension.
- This occurs in ischimic heart disease, valbular heart disease.

* diastolic dysfunction →

- Ventricular wall are thicker & unable to relax during diastole, ventricular filling is impaired becoz of its output flow.

Compensentory Physiological Response in CHF →

- The failing heart evokes 3 major compensentory mechanism to enhance cardiac output —

① ↑ sympathetic activity →

- Baroreceptor sense ↓ in bp. & activates the sympathetic nervous system.
- The stimulation of β-adrenergic receptors results in ↑ Heart rate. & a greater force of contraction of the heart muscle which in turn, ↑ cardiac output
- These compensentory meachain or response ↑ the work of the heart, which in the long term, contributes to further decline in cardiac function.

② Activation of Rennin Angiotensin-aldosterone System

- fall in cardiac output ↓ blood flow to the kidney, promoting the release of renin, & resulting in ↑ formation of angiotensin II
- This results in ↑ periferal resistance [after load] & retention of Na & H_2O.
- Blood vol. ↑ & more blood if return to the heart
- If the heart is unable to pump this extra vol., pulmonary edema occurs.
- which in the long term contribute to further decline in cardiac function.

③ Myocardial hypertrophy →

- The heart ↑es in size & the chambered dilated.
- Stretching in the heart muscles leads to a stronger contraction of the heart.
- However, excessive elongation of the fibre, results in weaker contraction & reduces the ability to eject the blood.

✡ Drug used in CHF →

① ACE inhibitors → Captopril, Ramipril, Enalapril

MOA → [Liver]

Angiotensinogen
↓ ← Renin [kidney]
AT-I [inactive]
↓ ← ACE [Angiotensinogen Converting enzyme]
AT-II
↓ ↓
Vasoconstriction | Na^+ + water retention

② ARB – Angiotensin Receptors blocker inhibitor →

- Losartan
- Telmesartan
- Candesartan

Mechanism →

① → Angiotensin
receptor
Smooth muscle cell

② Angiotensin + receptor complex
- Vasoconstriction
- Na^+ + water retention

③ ARB
→ No effect

③ **Beta blocker →**

- Aterinol
- Metaperinol
- Carvidalol
- Propanalol

Action →

- Beta blocker improve systolic function of the heart.
- It reverse cardiac remodeling.
- It reduces sympathetic outflow from CNS.

* β-Adrenoreceptor blocker → Activation of β-receptor on heart ↓ → ↓ Pre-load & After load

Activation of β-receptor on kidney ↓ → ↓ Renin → A T-II ↓ → ↓ Na^+ + water retention → ↓ vasoconstriction

④ **Diuretic →**

- Hydrochlorothiazide
- furosemide

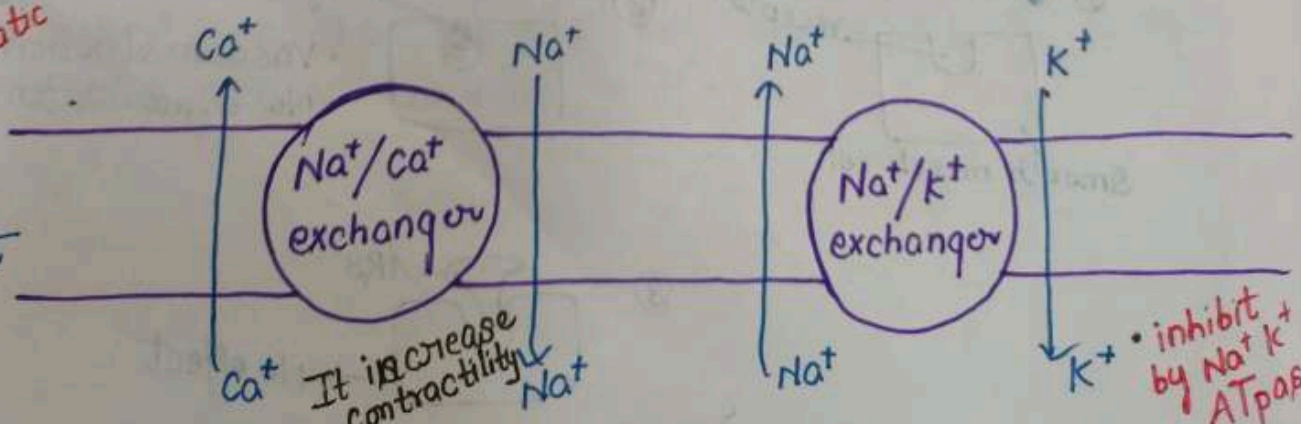
→ They increases Na^+ & water elimination by preventing the reabsorbtion process in urine formation.

This results in reduce blood volume & venous pressure. & ultimately reduces the preload & after load.

⑤ **Inotropic agents [Drug] →**

- Digitalis or Cardiac glycosides
- Digoxin

maintain homeostatic



- By inhibiting the Na^+ K^+ ATpase enzyme.
- Digitalis reduces the ability of myocytes to actively pump Na^+ from the cell.
- This ↓es the Na^+ concentration gradient & the ability of Na^+ Ca^+ exchanger to move Ca^+ outside the cell.
- This results in ↑es intracellular calcium ion.

⑥ Vasodilator →
- Hydralazine
- Isosorbidedinitrate

- Dilation of venous blood vessel leads to a ↓es in cardiac preload by ↑ing venous capacitance.

Ex-. Nitrate
- Arterial dilator such as hydralazine reduces arterial resistance & ↓es afterload.

Antihypertensive Drugs

Hypertension is defined as either a sustained systolic BP of greater than 140 mm Hg or a sustained diastolic BP of greater than 90 mm Hg.

↑BP = ↑ Systolic or ↑ diastolic

→ Types : ① Primary (or) essential — Causes are Unknown
② Secondary Hypertension — Causes are known

Secondary →
- Kidney problem
- Thyroid problem ↑↓ → ↑ Ca^+
- Adrenal gland tumor — Aldosteronism

→ Risk factors

(i) Age — Risk ↑ with Age (65 yrs)
(ii) family history
(iii) Obesity - Blood vol. ↑ — puts pressure on artery
(iv) Tobacco / Smoking
(v) Diet
(vi) Alcohol

→ Classification

		Systolic	Diastolic
①	Normal	<120	<80
②	Pre Hypertension	120-139	80-90
③	Stage - I	140-159	90-99
④	Stage - II	>160	>100

→ Mechanism for controlling Blood pressure

① Baroreceptors and the sympathetic nervous system

② Renin - angiotensin - aldosterone system

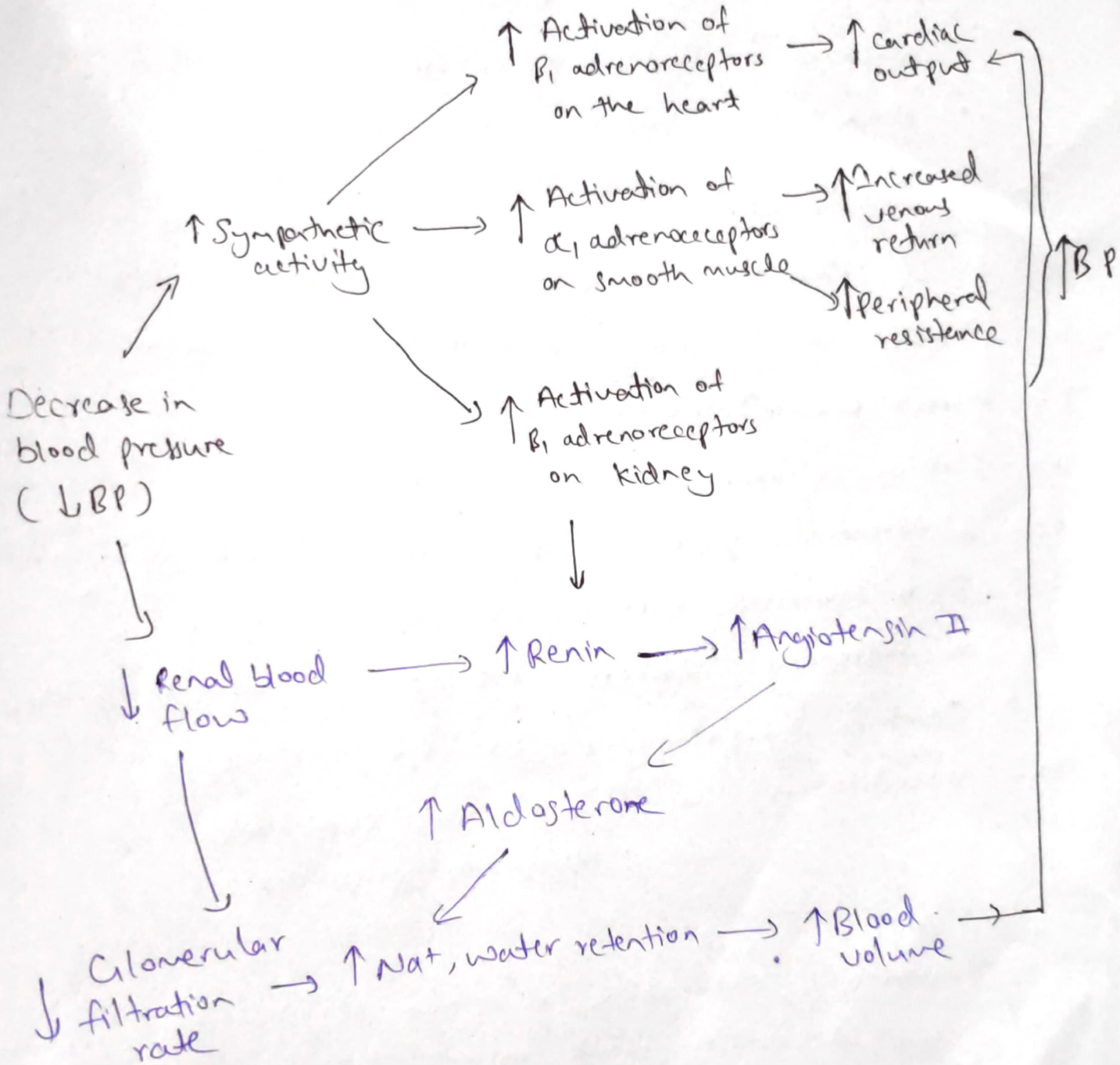
① - Baroreceptor & the sympathetic nervous system

~~Baroreceptor~~ Baroreflexes act by changing the activity of the Sympathetic nervous system. Therefore, they are responsible for the rapid, moment-to-moment regulation of blood pressure. A fall in BP causes baroreceptors to send impulses to cardiovascular centers in the spinal cord this ~~results~~ in increased sympathetic and decreased parasympathetic output to the heart, resulting in vasoconstriction & increased cardiac output. These changes result in rise in BP.

② Renin - angiotensin - aldosterone system

The kidney provides long-term control of BP by altering the blood volume. Kidney release renin in response to low BP. The renin converts the Angiotensin I to Angiotensin II which causes vasoconstriction & stimulates the aldosterone secretion, leading to increased ~~blood~~ Na^+, water retention & blood volume which contribute to further increase in blood pressure.

Response mediated by the sympathetic nervous system



Response mediated by the renin-angiotensin-aldosterone system

→ Classification

1. Diuretics
   - Thiazides – Hydrochlorothiazide, Chlorthalidone
   - High ceiling (loop) – furosemide
   - K^+ sparing : Spironolactone, Amiloride

2- ACE Inhibitors – Captopril, Enalapril, Ramipril

3- ARBs – Losartan, Telmisartan, candesartan

4- Direct Renin Inhibitor – Aliskiren

5- Calcium channel blockers – Amlodipine, Nifedipine, verapamil

6- β Adrenergic blockers – Propranolol, Atenolol, Metoprolol

7- β + α Adrenergic blakers – Labetalol, Carvedilol

8- α Adrenergic blockers – Prazosin, Terazosin, Doxazosin

9- Central sympatholytics – Clonidine, Methyldopa

10- vasodilators – Hydralazine, Minoxidil
Sodium nitroprusside

1- Diuretics – Mechanism of action of diuretics is based upon decreasing blood volume, which ultimately leads to decreased blood pressure.

- Thiazide diuretics → ↓ Na^+, water retention
  - ↓ Blood volume
    - ↓ Cardiac output
  - ↓ Peripheral Resistance

Decrease in blood pressure

- Thiazide diuretics lower blood pressure initially by increasing Na^+ and water excretion. This causes a decrease in extracellular volume, resulting in a decrease cardiac output & reduces blood pressure.
- Thiazide diuretics are not effective in patients with inadequate kidney function.
- Adr — Hypokalemia (low potassium), Hyperuricemia (↑ uric acid)

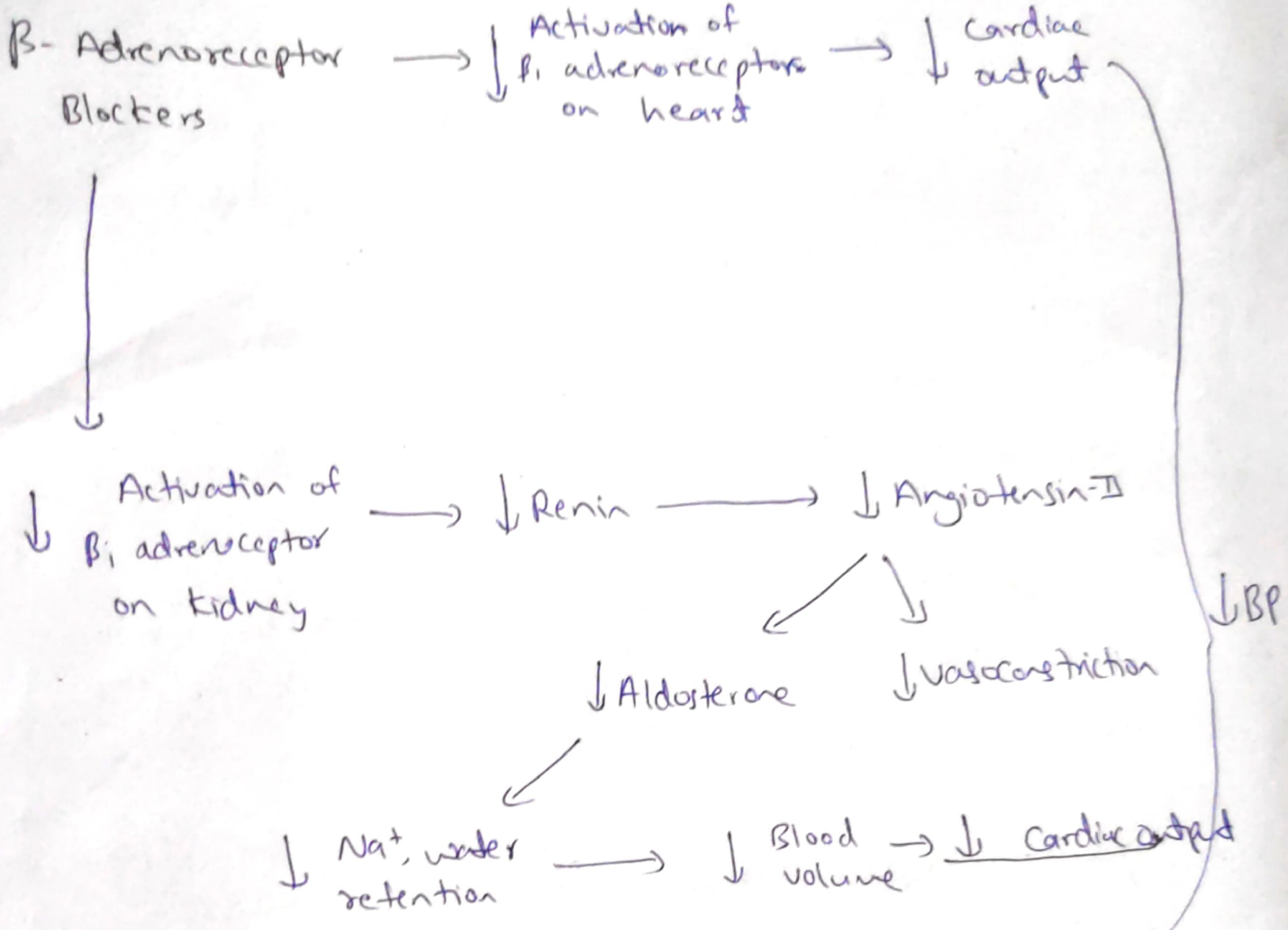
* Loop diuretics — Act promptly by blocking sodium and chloride reabsorption in the kidneys.

  Adr — Hypokalemia

* Potassium sparing diuretics — They reduce potassium loss in the urine. Potassium sparing diuretics are sometimes used in combination with thiazides & loop diuretics to reduce the amount of potassium loss induced by these diuretics.

2- β-Adrenoreceptor blocking Agents

The β-blockers reduce blood pressure primarily by decreasing cardiac output. They also decrease sympathetic outflow from the CNS and inhibit the release of renin from the kidneys, thus decreasing the formation of Angiotensin-2 & secretion of aldosterone, which reduces the vasoconstriction & Na^+, water retention & ultimately reduces blood pressure.



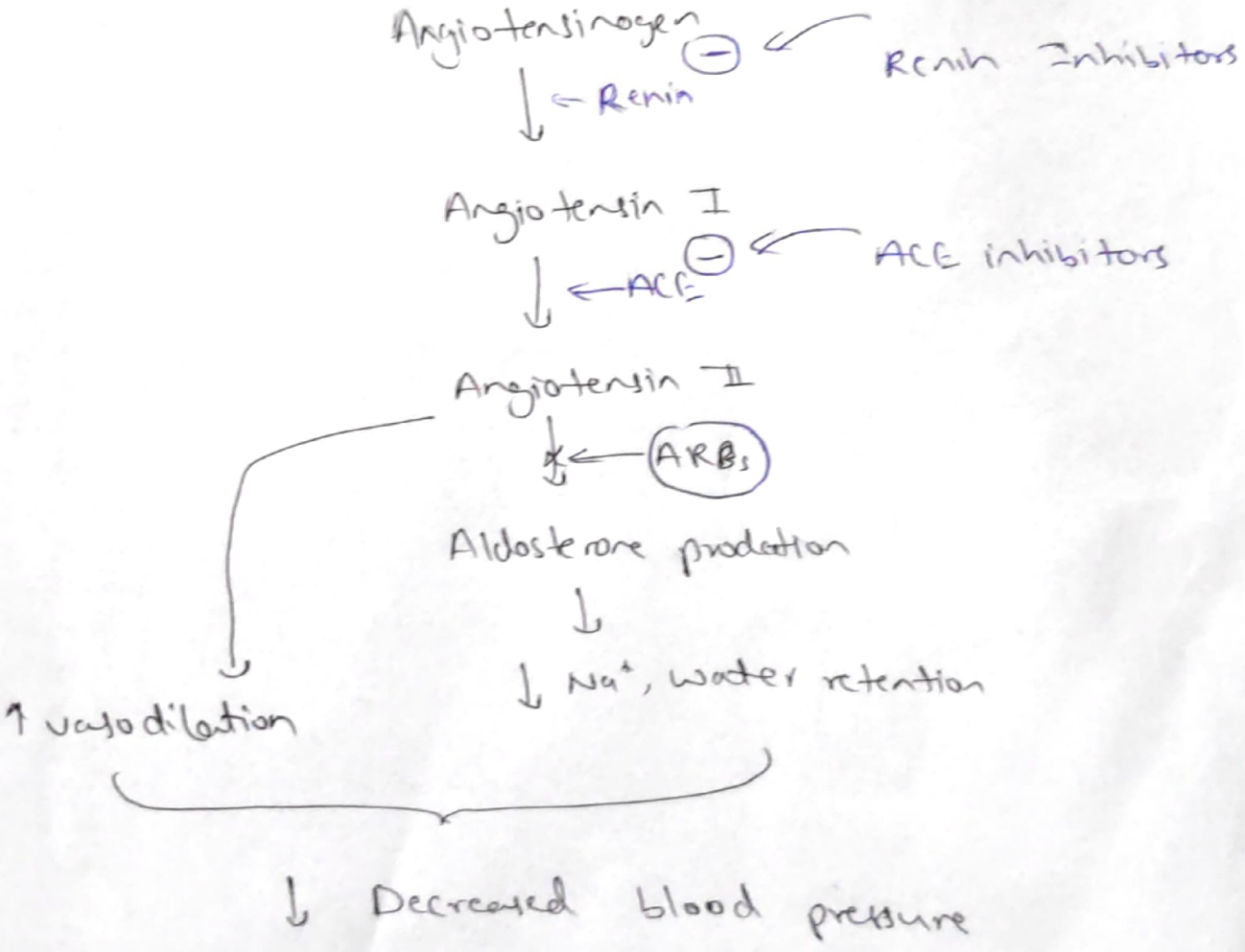
Adr —
- Bradycardia
- Hypotension
- fatigue

Uses —
- Hypertension
- Myocardial infarction
- Angina pectoris
- CHf (congestive heart failure)

3- ACE Inhibitors

These drugs block the enzyme ACE (Angiotensin converting enzyme) which convert Angiotensin I to Angiotensin-II (vasoconstrictor).

- ACE inhibitors decrease angiotensin II & increase bradykinin levels. vasodilation of both arterioles and veins occurs as a result of decreased vasoconstriction (Due to decrease in ↓ AT-II) & enhanced vasodilation (from ↑ bradykinin).



Effect of various drugs on Renin-angiotensin-aldosterone System (RAAS)

Adv- Dry Cough, rash, fever, Hypotension

Adv- Dry Cough, rash, fever, Hypotension

④- ARBs (Angiotensin II receptor blockers)

These drugs block the angiotensin receptor & inhibit the further action of angiotensin

They produce similar pharmacological effect to ACE inhibitors, produces arteriolar & venous dilation & block aldosterone secretion, thus lowering blood pressure & decreasing salt & water retention.

⑤ Renin Inhibitor

Renin Inhibitor directly inhibits renin and, thus acts earlier in the renin-angiotensin-aldosterone System than ACE inhibitors or ARBs.

It lowers blood pressure about as effectively as ARBs, ACE inhibitors & thiazides.

⑥ Calcium channel blockers

The intracellular conc of calcium plays an important role in maintaining the tone of smooth muscle & in the contraction of myocardium.

Calcium channel blockers block the inward movement of calcium by binding to L-type calcium channels in the heart & smooth muscle of coronary arteries

This causes vascular smooth muscle to relax & dilate mainly arterioles.

4) α- Adrenoreceptor blockers

These drugs or agents block the α_1 adrenoreceptor and decrease peripheral vascular resistance and lower arterial blood pressure by causing relaxation of both arterial & venous smooth muscle.

Antianginal drugs

Angina pectoris - is a pain syndrome due to induction of an adverse oxygen supply/demand situation in a portion of the myocardium.

Angina pectoris is a characteristic sudden, severe, crushing chest pain that may radiate to the neck, jaw, back & arm.

— Types of angina

1. Classic angina (effort induce or stable angina)
2. Prinzmetal, variant or rest angina
3. Unstable angina

① - Classic (stable angina)

- Most common form of angina
- Characterized by short-lasting burning, heavy, squeezing feeling in the chest.
- Caused by the reduction of coronary perfusion due to obstruction of a coronary artery produced by atherosclerosis.
- Related to workout & emotion.

② Prinzmetal (rest angina)

- Uncommon pattern of episodic angina that occurs at rest
- Caused by decreased blood flow to the heart muscle from the spasm of the coronary artery.
- Unrelated to physical activity

(3)- Unstable angina

- Classified b/w stable angina & Myocardial Infa
- Chest pain occurs with increased frequency, durati & intensity.
- Any episode of rest angina longer than 20 min, any new-onset angina or even sudden develop of shortness of breath is suggested as unstebe angina.

→ Treatment

→ Anti anginal drugs

Anti anginal drugs are those that prevent, abort or terminate attacks of angina pectoris.

→ Classification

1- Nitrates - (a) Short Acting - • Glyceryl trinitrate (Nitroglycerine)

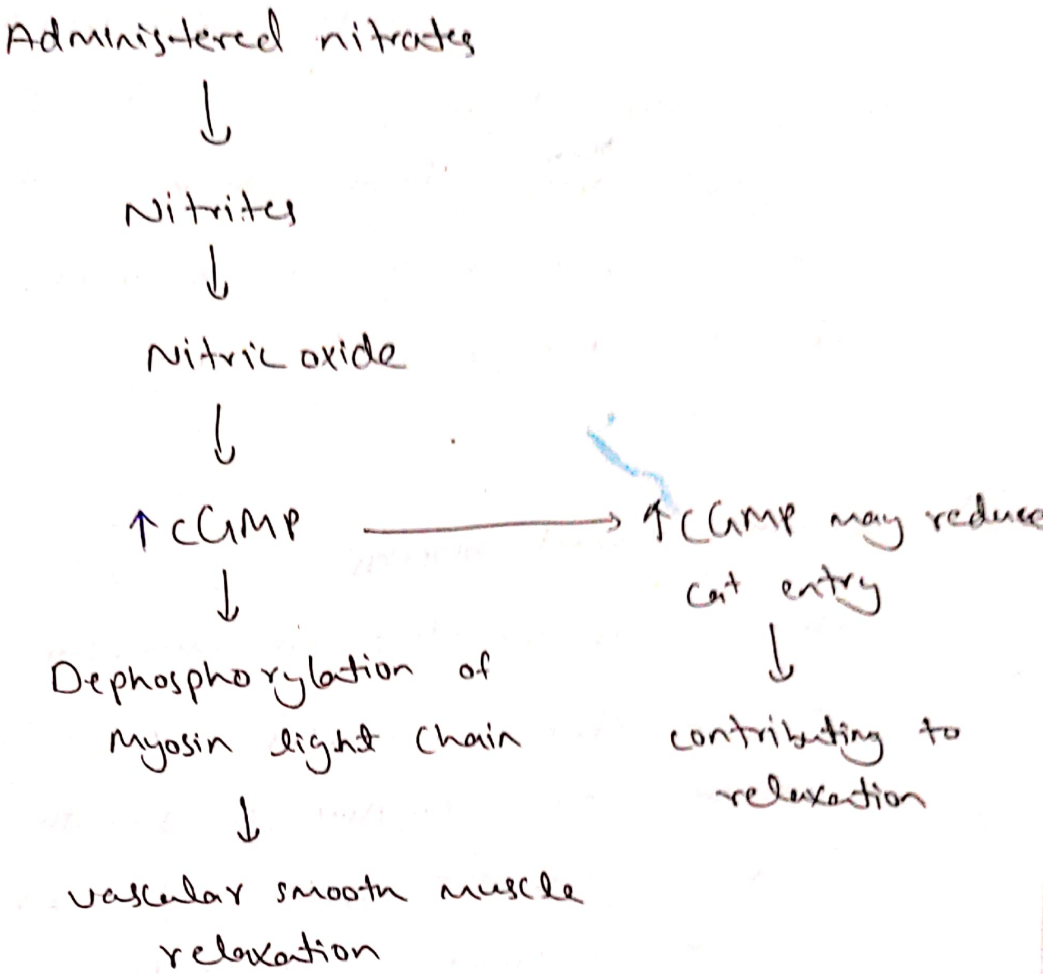
(b) long Acting - • Isosorbide dinitrate
• Isosorbide mononitrate

2- β- Blockers - Atenolol, metoprolol, propranolol

3- Calcium channel blockers -
(a) Phenyl alkylamine - verapamil
(b) Benzothiazepine - Diltiazem
(c) Dihydropyridines - Nifedipine, Amlodipine

④ - K+ channel opener - Nicorandil

Nitrates



Organic nitrates relax vascular smooth muscle by their intracellular conversion to nitrite ions and then to nitric oxide, which activates guanylate cyclase & increases the cells' cyclic guanosine monophosphate (cGMP). Elevated cGMP ultimately leads to dephosphorylation of myosin light chain, resulting in vascular smooth muscle relaxation.

Adr –
- Headache
- High dose can cause postural hypotension.
- Tachycardia

(2) β- blockers

The β-blockers decrease the oxygen demand of the myocardium by blocking β_1 receptors, resulting in decreased heart rate, contractility, cardiac output & blood pressure. These agents reduce the oxygen demand during exertion & at rest. They can reduce both the frequency & severity of angina attacks.

(3) Calcium channel blockers

Calcium is essential for muscular contraction.

The Ca^+ channel blockers inhibit the entry of Calcium into cardiac & smooth muscle cells. These agents cause a decrease in smooth muscle tone & vascular resistance resulting in decrease myocardial oxygen consumption.

(4) Potassium channel opener

K^+ channel openers
↓
Open K_{ATP}
↓
↑ K^+ efflux
↓
Membrane Hyperpolarization
↓
↓ Ca^+ entry.
↓
↓ Calcium (intracellular
↓
Smooth muscle relaxation

✡ Anti-Arrhythmic Drug →

- Arrhythmia – Abnormal heart rhythym
- Other causes → Myocardium Hypoxia, Drugs, ANS effect Trauma, Electrolyte imbolance, Ischaemia.
- Symptoms → Headache, Breathlessness, palpitation [heart rasing] fatigue

* Types →

- Bradycardia [↓ automaticity, H.R. below 60 beats/min]
- Tachycardia [↑ automaticity, H.R above 100 beats/min]
- Ventricular Tachycardia [H.R increase becoz of ventricle]
- Artial flutter [H.R. above 200 b/m]
- A-fibrillation [350 above]

* Primary Causes →

① Abnormalities in impulse generation
- → Altered automaticity
- → Abnormal automaticity
- → After

② Abnormalities in conductance of impulse
- Reentry & blockage

* Classification →

① Class I – Na^+ channel blocker
② Class II – β-Blocker (eg) - Propranol, Esmolol, Atenolol
③ Class III – K^+ channel oppener/ blocker (eg) · Sotalol · Amiodorone
④ Class IV – Ca^+ channel blocker (eg) · Verapamil · diltiazem

① Class I → Na^+ channel blocker [membrane stabilizing agent]

- I-A
- I-B
- I-C

- Quinidine
- Lidocaine
- Propafenone

✡ Abnormalities in impulse generation →

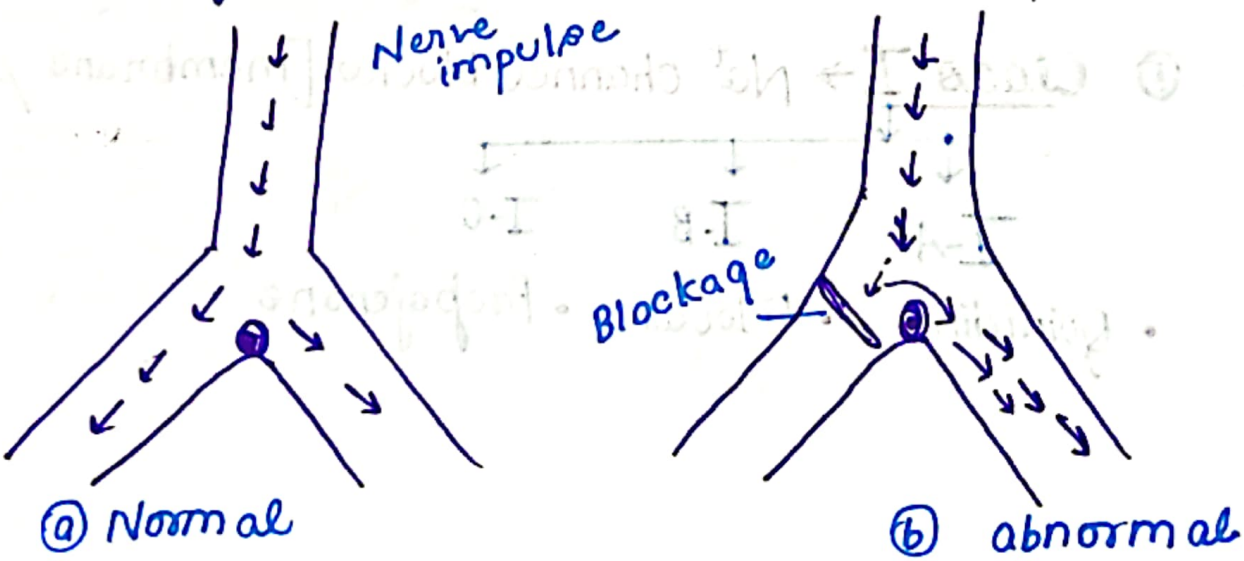
① Abnormal automaticity –

② Altered Automaticity –

- The S.A node show the fastest rate of phase 4 for depolarisation &, therefore, accelerate a higher rate of discharge then that occuring in other pacemaker cells accelerating automaticity.
- Thus, the S.A node normally set the pac of contraction for the myocardial.
- If cardiac site other than the SA node shows enhance automaticity, they may generate competing stimuli, & arrhythmia may occur!

✡ Abnormalities in impulse generation →

- A phenomena called reentry can occur if a unidirectional block cause by myocardial injury or a prolong refractory period results in an abnormal conduction pathway.
- Reentry is the most common cause of arrhythmia.
- This short circuit pathway result in re-excitation of ventricular muscles, causing premature contraction of sustained ventricular arrhythmia.



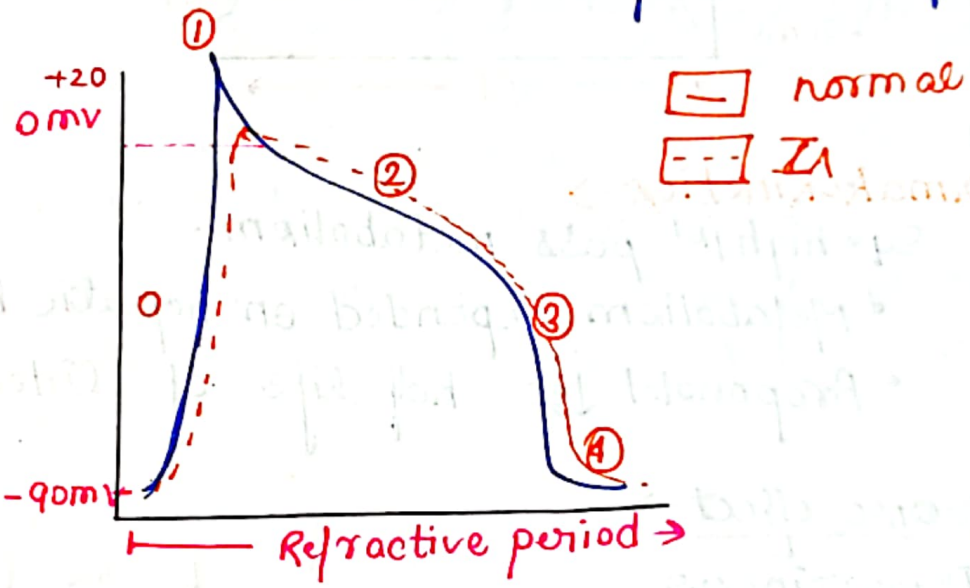
* Anti arrhythmic drug →

- These drug are used to treat irregularity of cardiac arrhythmia.

✡ Mechanism of action Class I [Na^+ Blocker]

* IA →

- Quinidine binds to open & inactivated Na^+ channel. & prevent sodium influx, Thus slowing the rapid of stroke during phase 0.
- It ↓eses the slope of phase 4 depolarisation, inhibit K^+ channel & act higher conc^n it also inhibit Ca^+ channel. becoz of these action, it slow conductance velocity & ↑es refractoriness



* Pharmakokinetics →

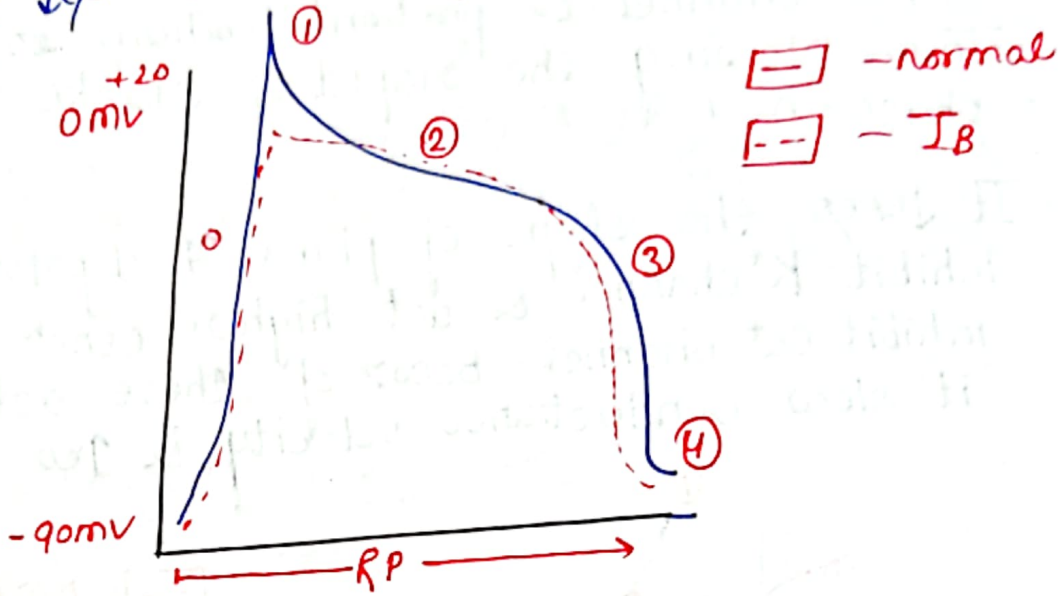
- well absorb.
- 90% bound to plasma protein.
- Short duration of action 2-3 hr.

* Uses →

- Use in wide range of arrhythmia including atrial, AV junctional & ventricular trachyarrhythmia.

* Adverse effect-
  - Hypotension
  - Diarrhea

* I_B →
  - In addition to Na^+ channel blockage, lidocaine & mexiletine shorten phase 3 repolarisation & less duration of action potential.



* Pharmakokinetics →
  - High 1st pass metabolism.
  - Metabolism depended on hepatic blood flow.
  - Propanolol less half life of lidocaine.

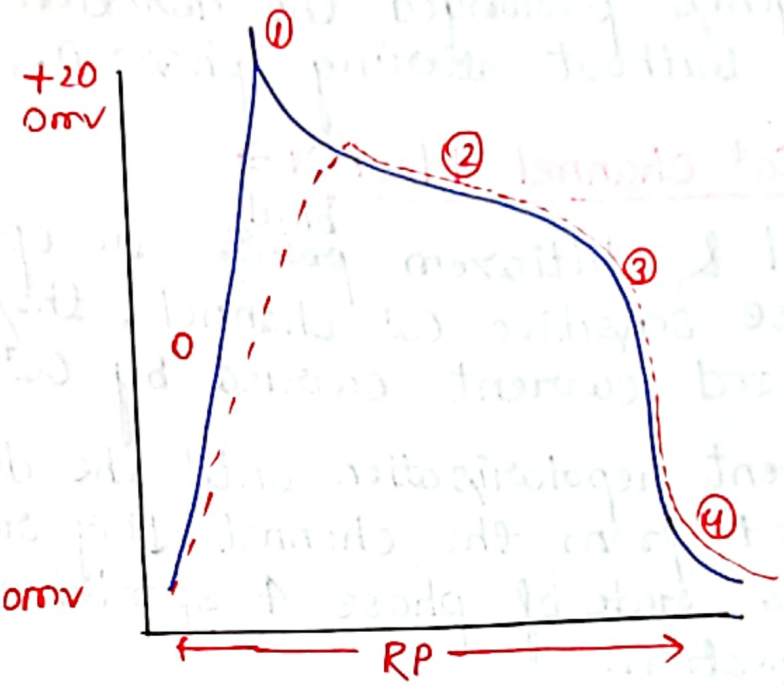
* Adverse effect →
  - Drowziness
  - Slurred speech
    Confusion

* Uses →
  - Tachycardia
  - Fibrillation

* Ic →
- Flecainide supresses phase 0 upstroke in mayocardial fibres & Purkinje.
- This causes marked flowing of conduction in all cardiac tissue, with a minor effect on the duration of action potential & refractive period.

- Flecainide also block K^+ channel leading to ↑ duration action potential.

- Propaferone — like flecainide, it slows conduction in all cardiac tissue but doesnot block K^+ channel.



* Adverse effect →
- Visual disturbance
- Headche

* Uses →
- V. Tachycardia
- Atrial flutter
- Atrial fibrilation

* **Class II x β-Blocker →**

- These drugs diminish phase 4 depolarisation & thus, depress automaticity, prolonged AV conduction & ↓es heart rate & contractility.
- β-Blockers are useful in tachyarrhythmia cause by ↑es sympathetic activity.

* **Class III x K^+ channel blocker →**

- Class 3rd agent block K^+ channel & thus, diminish the outward K^+ current during repolarisation of cardiac cells.
- These agents prolonged the duration of action potential without altering phase 0.

* **Class IV x Ca^+ channel blocker →**

- Verapamil & diltiazem binds to open depolarise sensitive Ca^+ channel, thus ↓ing the inward current carried by Ca^+.
- They prevent repolarisation until the drug dissociated from the channel, resulting in a ↓es rate of phase 4 spontaneous depolarisation.
- They also slow conduction in tissue that are depandent on Ca^+ current such as SA & AV node.

Anti Hyperlipidemic Drugs

Hyperlipidemia → Hyperlipidemia is also called hyperlipoproteinemia. It is a result of abnormalities in lipid metabolism or plasma lipid transport or a disorder in the synthesis and degradation of plasma lipoprotein. It is a major cause of coronary heart disease.

* **Causes or Risk factors**
  - Obesity
  - Not exercising
  - Smoking
  - Diabetes

* Coronary heart disease is due to ↑ level of LDL (low density lipoprotein) & ↓ level of HDL.

* Cholesterol, Triglycerids and phospholipid transported by Lipoproteins.

* **Lipoprotein:** Lipid + protein

→ **Types of lipoproteins**
  - LDL – formed as a result of catabolism of IDL (Intermediate Density lipoprotein).
  - VLDL – Synthesized in liver
  - Chylomicron – Largest and least dense. formed in intestine
  - HDL – formed in liver + intestine

Classification

1 - HMG CoA reductase inhibitors → Atorvastatin, Lovastatin, Pravastatin

2- Nicotinic Acid – Niacin

3- fibrates – fenofibrate, Gemfibrozil, clofibrate

4 - Bile acid sequestrants - Colestipol, Colesevelam

5 - Cholesterol Absorption inhibitor - Ezetimibe

1- HMG CoA reductase Inhibitors

Acetyl CoA and Acetoacetyl CoA

↓

HMG-CoA

Statins → × ↓ HMG CoA reductase

Mevalonate

↓

farnesyl pyrophosphate

↓

Squalene

↓

Cholesterol

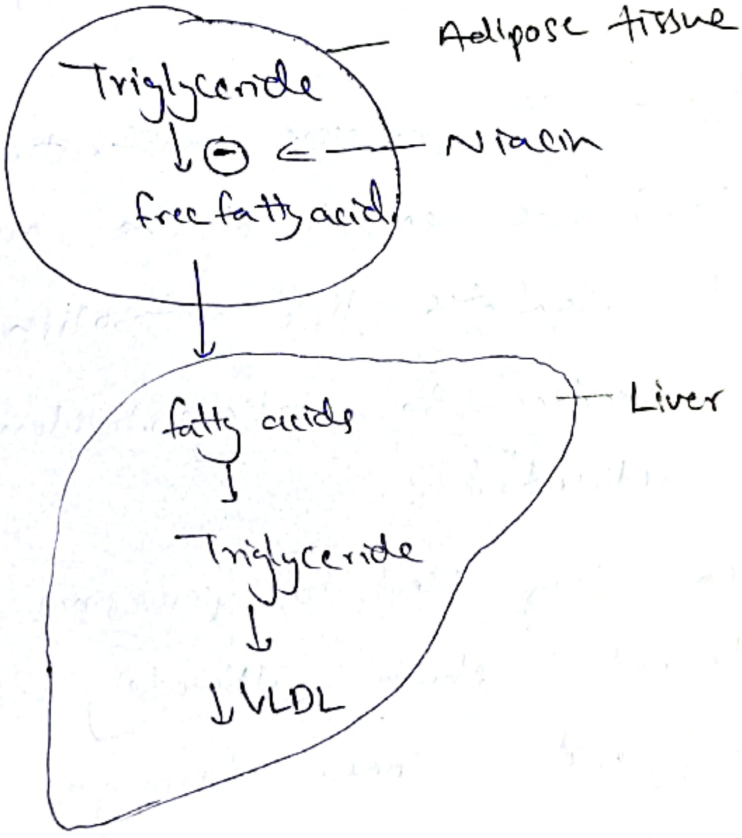
* Pharmacokinetic

- Absorption of statins is variable (30% to 85%) following oral administration.
- All statins are metabolized in the liver.
- Excretion takes place through bile & feces.

* Advs – • Liver failure
  • Myopathy
  • Contraindicated in pregnancy

* Uses: Effective in lowering plasma cholesterol levels in all types of hyperlipidemias.

2- Niacin (Nicotinic acid)



Niacin inhibits lipolysis in adipose tissue, thereby reducing production of free fatty acids. The liver normally uses circulating free fatty acids as a major precursor for triglycerides synthesis. Reduced liver triglyceride level decrease hepatic VLDL production, which in turn reduce LDL-C plasma concentrations.

* Adr

- Nausea
- Abdomen pain
- Hyperuricaemia
- Gout

* Use : It is useful in the treatment of familial hyperlipidemias. It is also used to treat other severe hypercholesterolemias, often combination with other agents.

3- fibrates - The peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor family that regulates lipid metabolism.

- Upon binding to antihyperlipidemic drugs, PPARs get activated.
- Then they bind to peroxisome proliferator response element which ultimately leads to decreased triglyceride conc. through increased expression of lipoprotein lipase.

fibrate
↓
PPARs activate
↓
↑ Lipoprotein lipase
↓
↓ Triglyceride conc.

4- Bile acid sequestrants

Bile acid helps in digestion and made from cholesterol by liver.

Bile acid sequestrants binds to negatively charged bile acid in the small intestine and formed insoluble complex.

↓

This prevent reabsorption & lead to excretion of bile acid complex. thus lowering the bile acid concentration.

↓

To compensate this, liver increases the number of LDL receptors to bring more LDL cholesterol

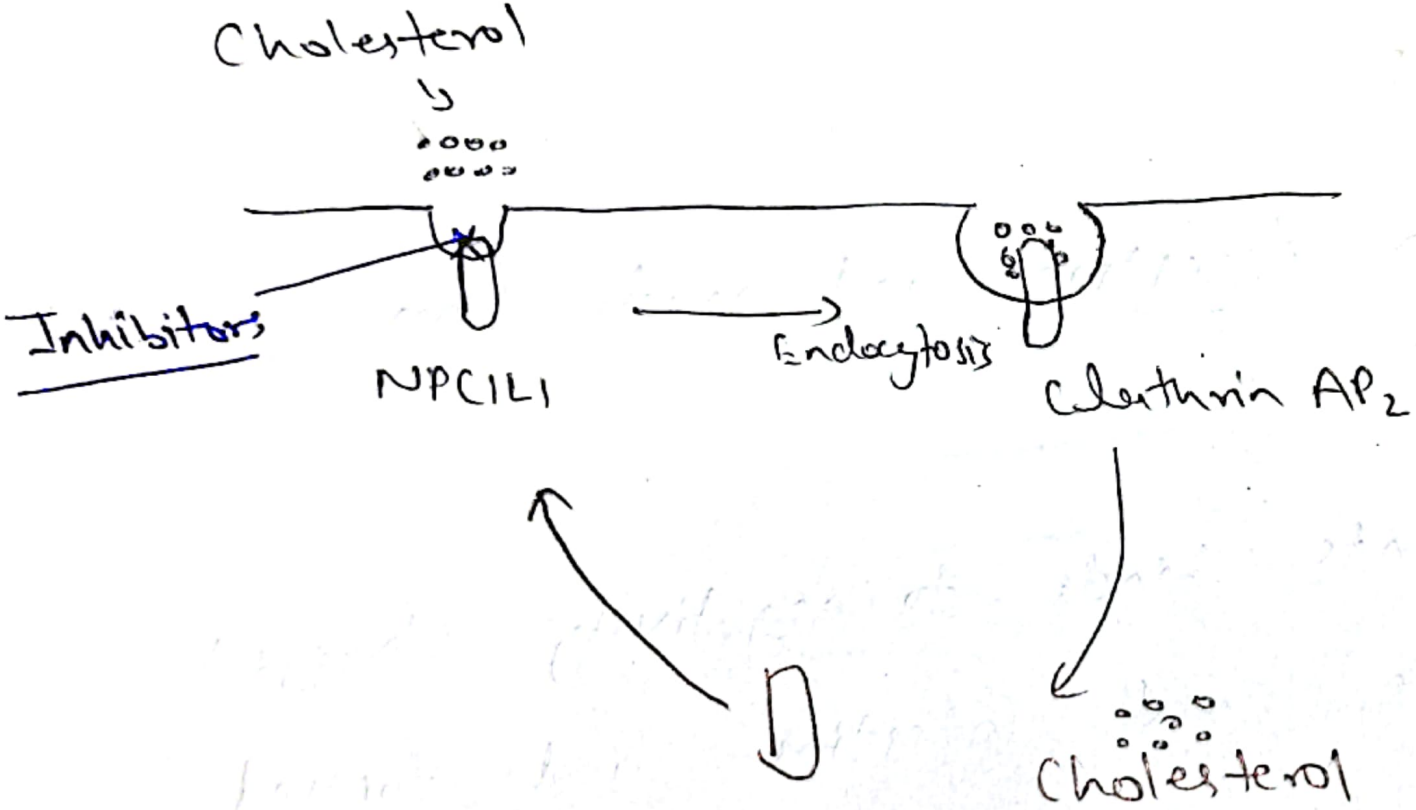
↓

This causes fall in plasma LDL cholesterol

(↓ LDL)

5- Cholesterol absorption inhibitor

Ezetimibe selectively inhibits absorption of dietary and biliary cholesterol in the small intestine, leading to a decrease in the delivery of intestinal cholesterol to the liver.


Cholesterol
Inhibitors
NPC1L1
Endocytosis
Clathrin AP2
Cholesterol