Regulation of Blood Pressure

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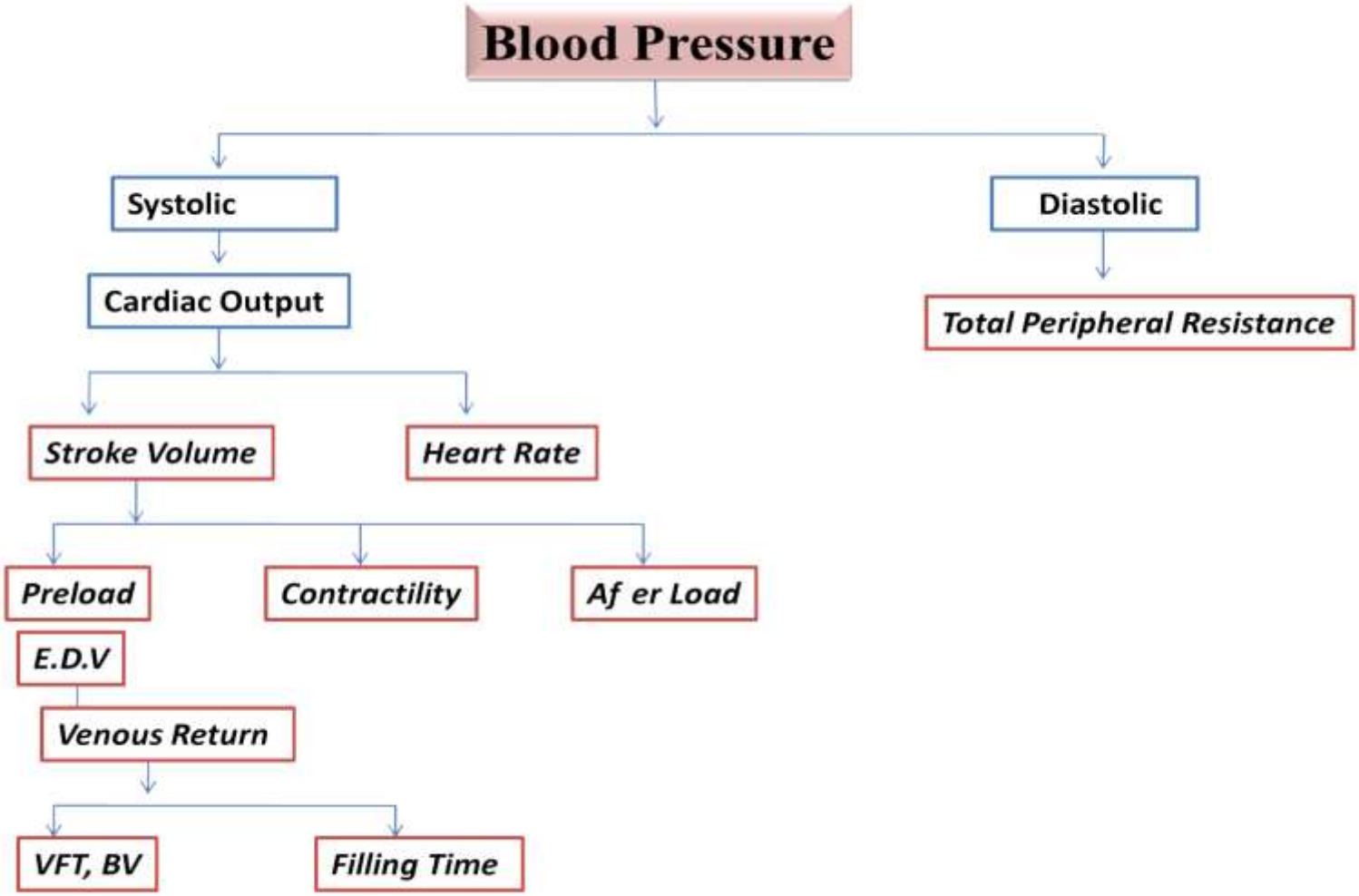
Content

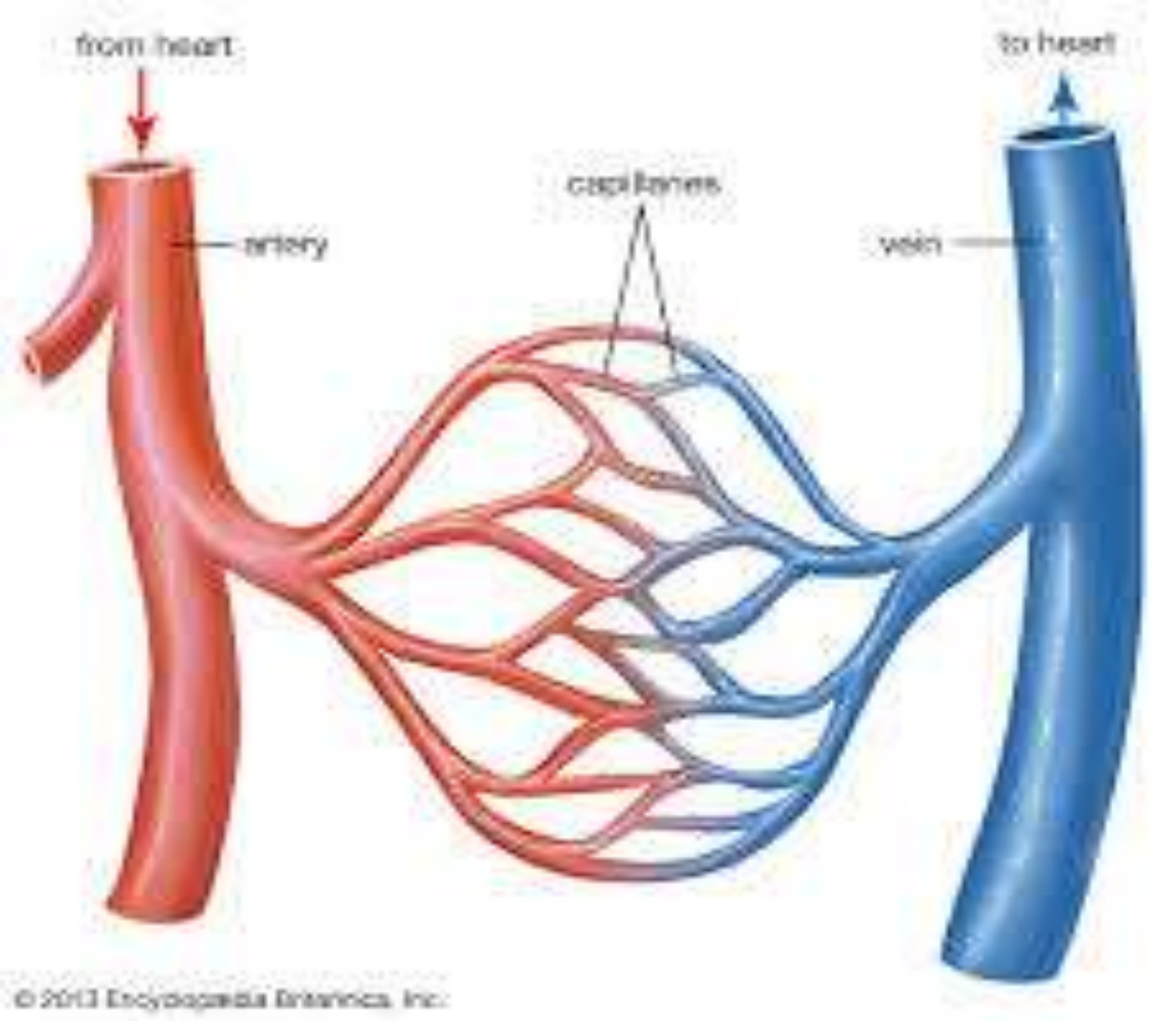
- Introduction
- Baro Receptor
- Chemo Receptor
- RAAS

Introductions

Blood pressure is the force exerted in the arteries by blood as it circulates. It is divided into systolic (when the heart contracts) and diastolic (when the heart is filling) pressures.

$$\text{B. P.} = \frac{120}{80} = \frac{\text{Systolic}}{\text{Diastolic}} \; \alpha \; \frac{\text{C.O.}}{\text{T.P.R.}}$$


Blood Pressure
Systolic
Diastolic
Cardiac Output
Total Peripheral Resistance
Stroke Volume
Heart Rate
Preload
Contractility
Af er Load
E.D.V
Venous Return
VFT, BV
Filling Time


from heart
to heart
capillaries
artery
vein
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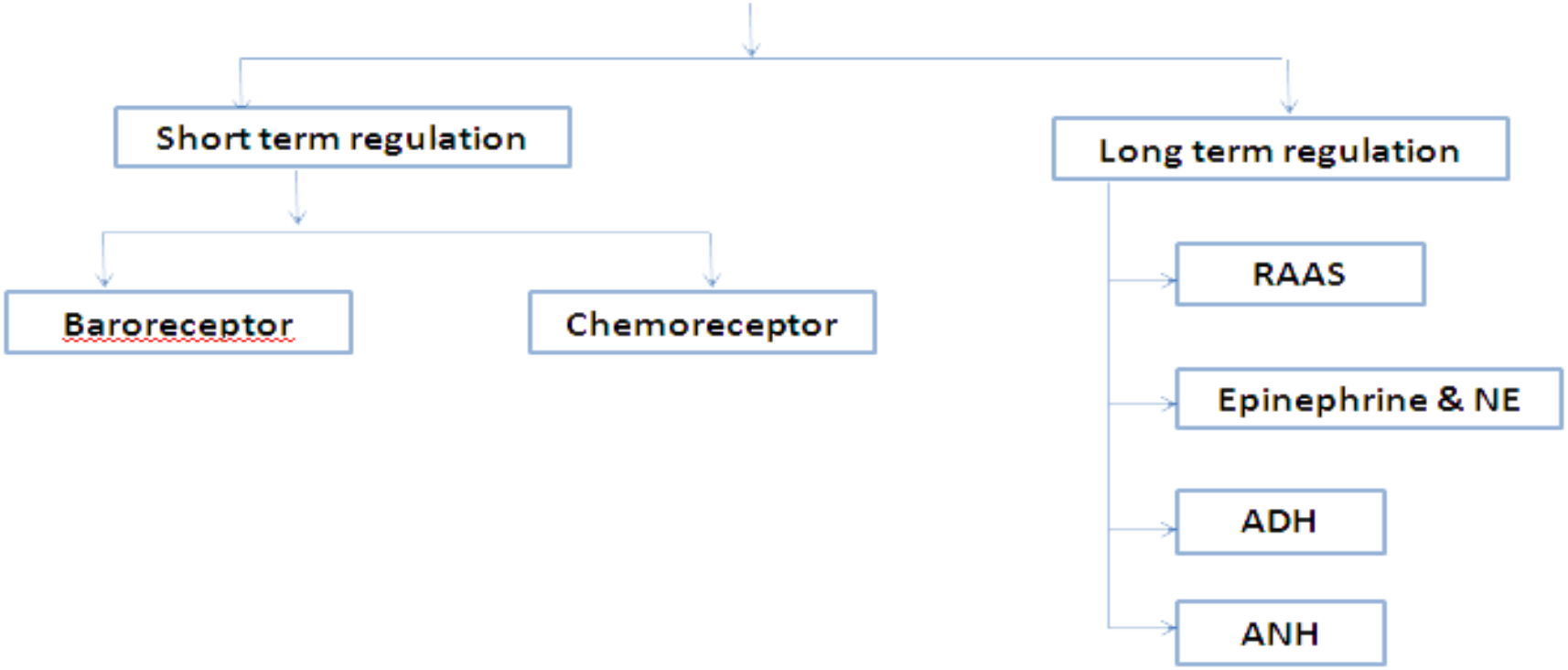
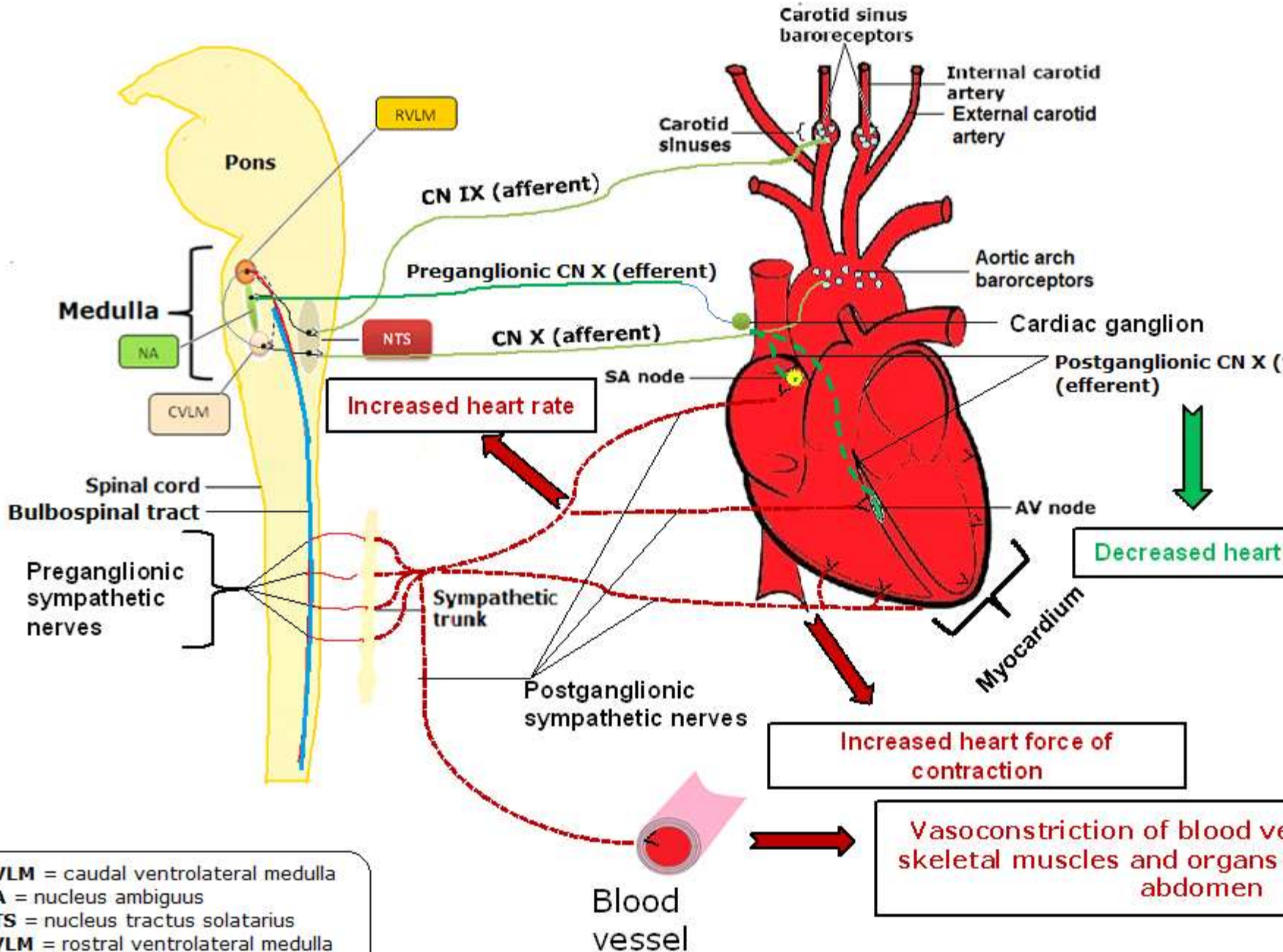
Regulation of Blood Pressure

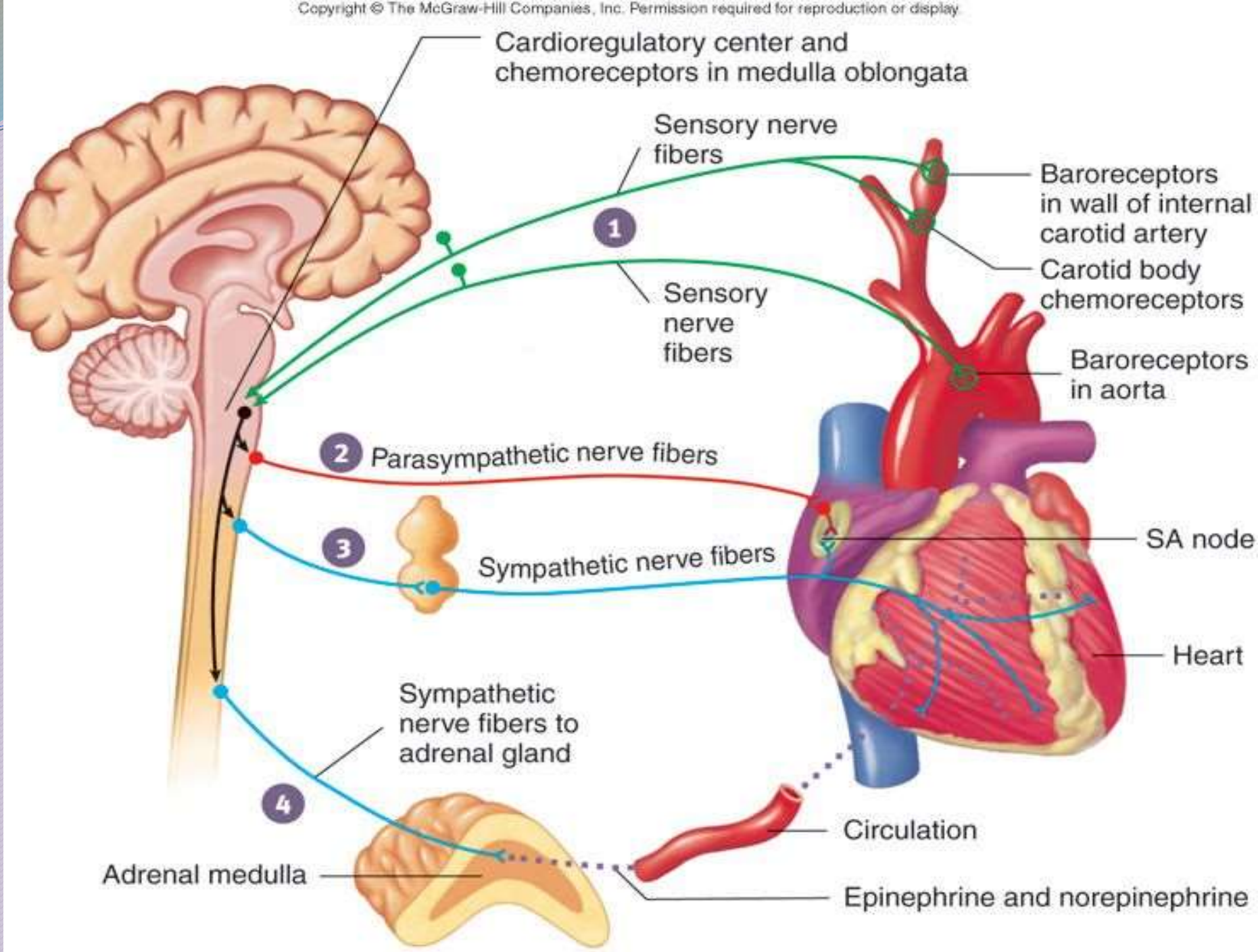


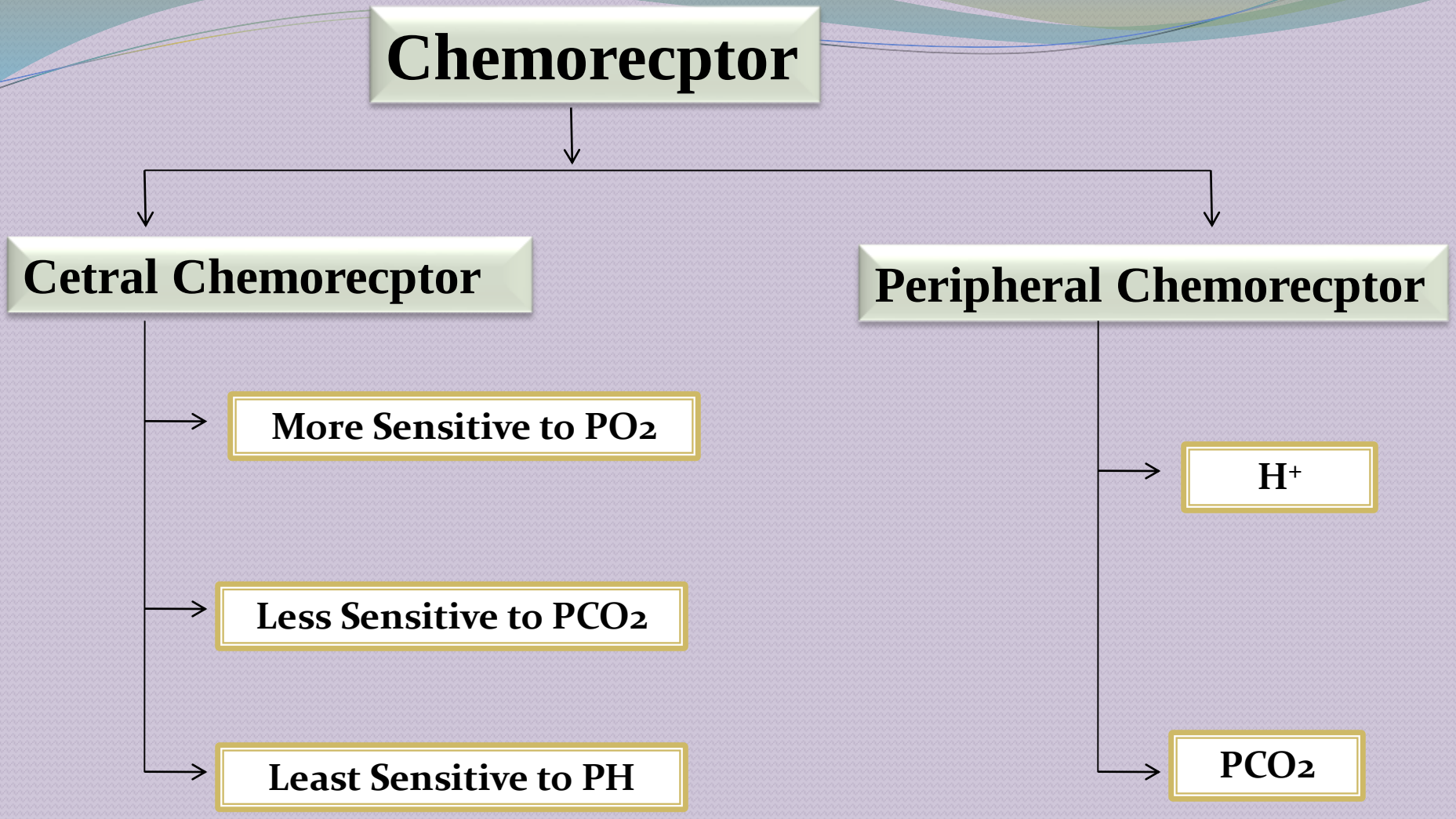
Baroreceptor

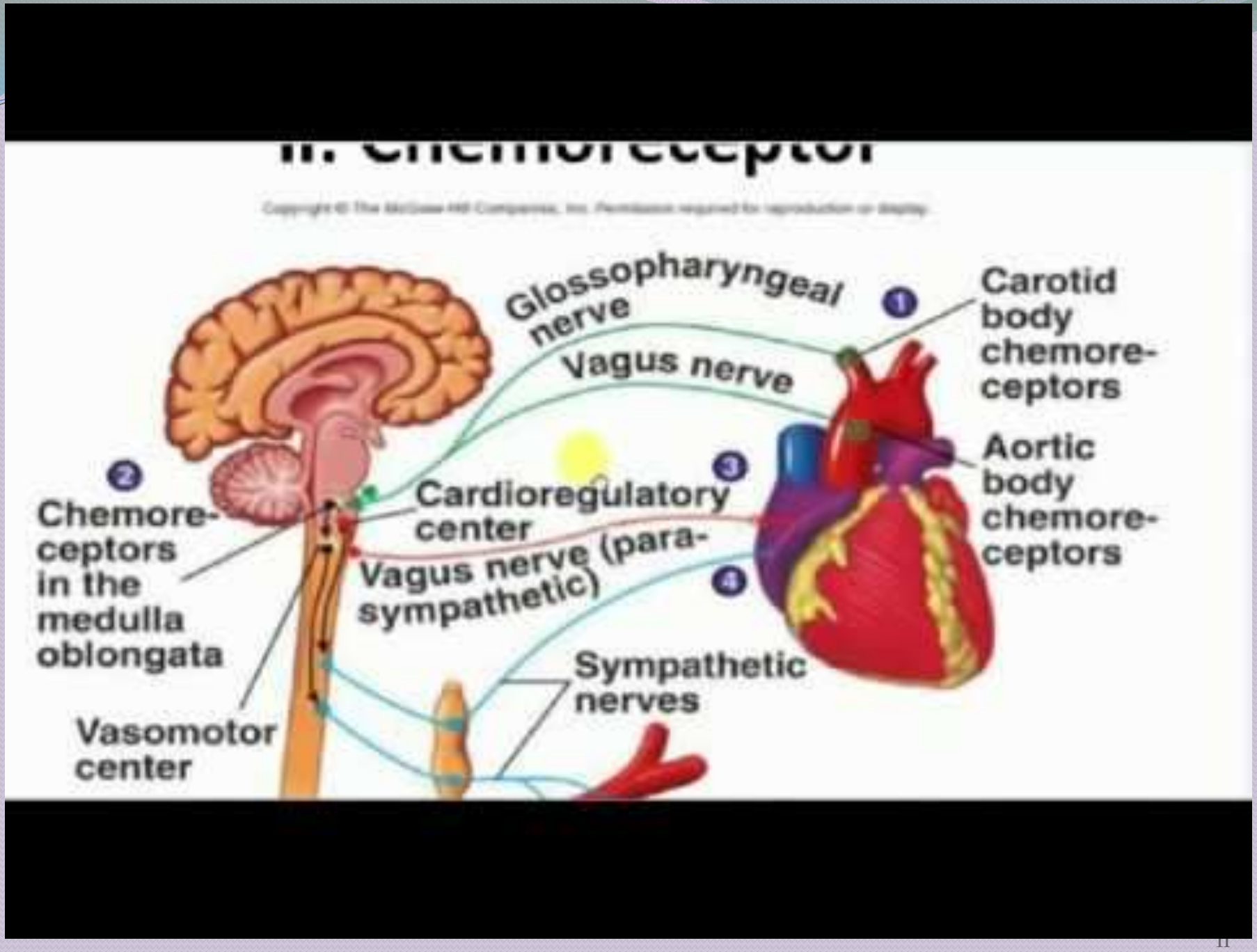
Arterial Baroreceptor Reflex Pathways



CVLM = caudal ventrolateral medulla
NA = nucleus ambiguus
NTS = nucleus tractus solatarius
RVLM = rostral ventrolateral medulla

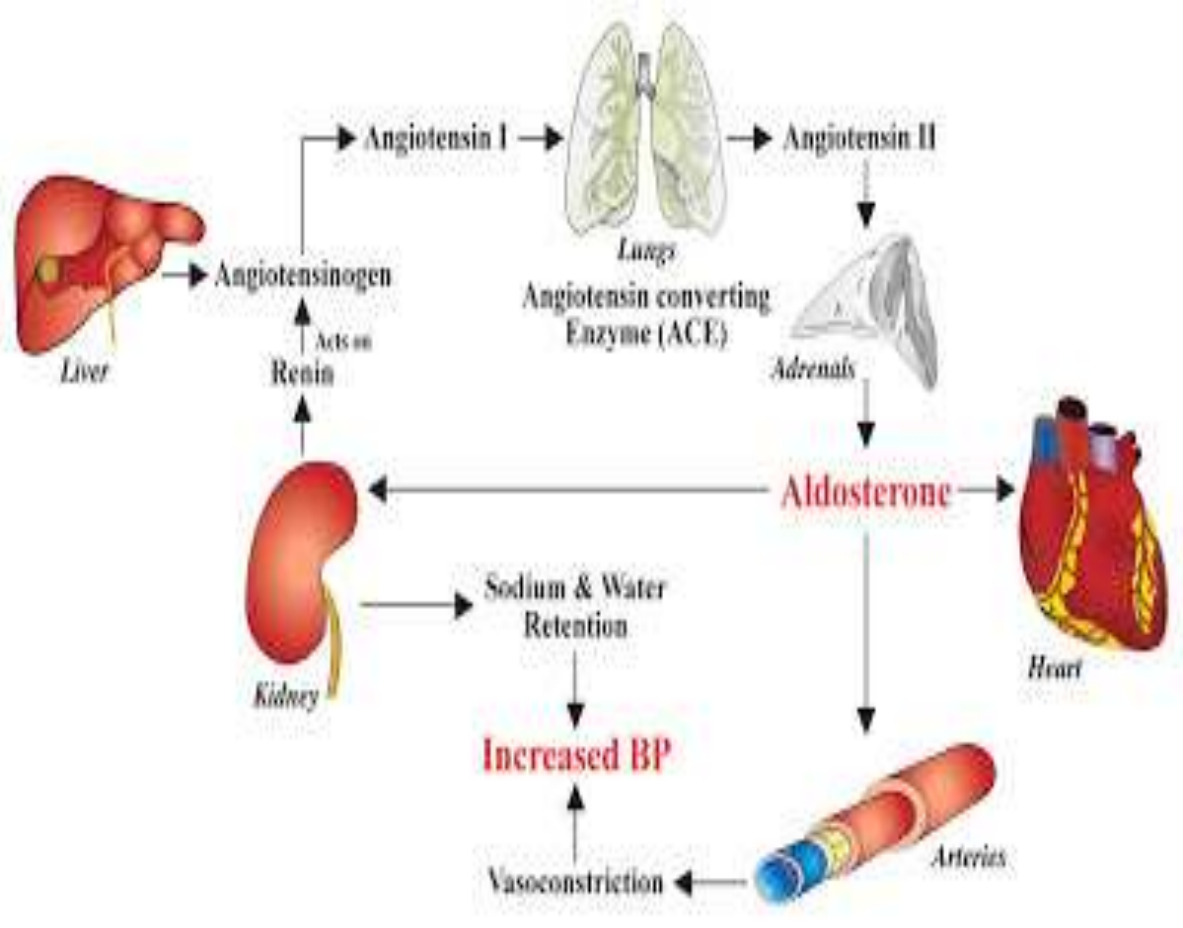



Chemorecptor
Cetral Chemorecptor
Peripheral Chemorecptor
More Sensitive to PO2
Less Sensitive to PCO2
Least Sensitive to PH
H+
PCO2

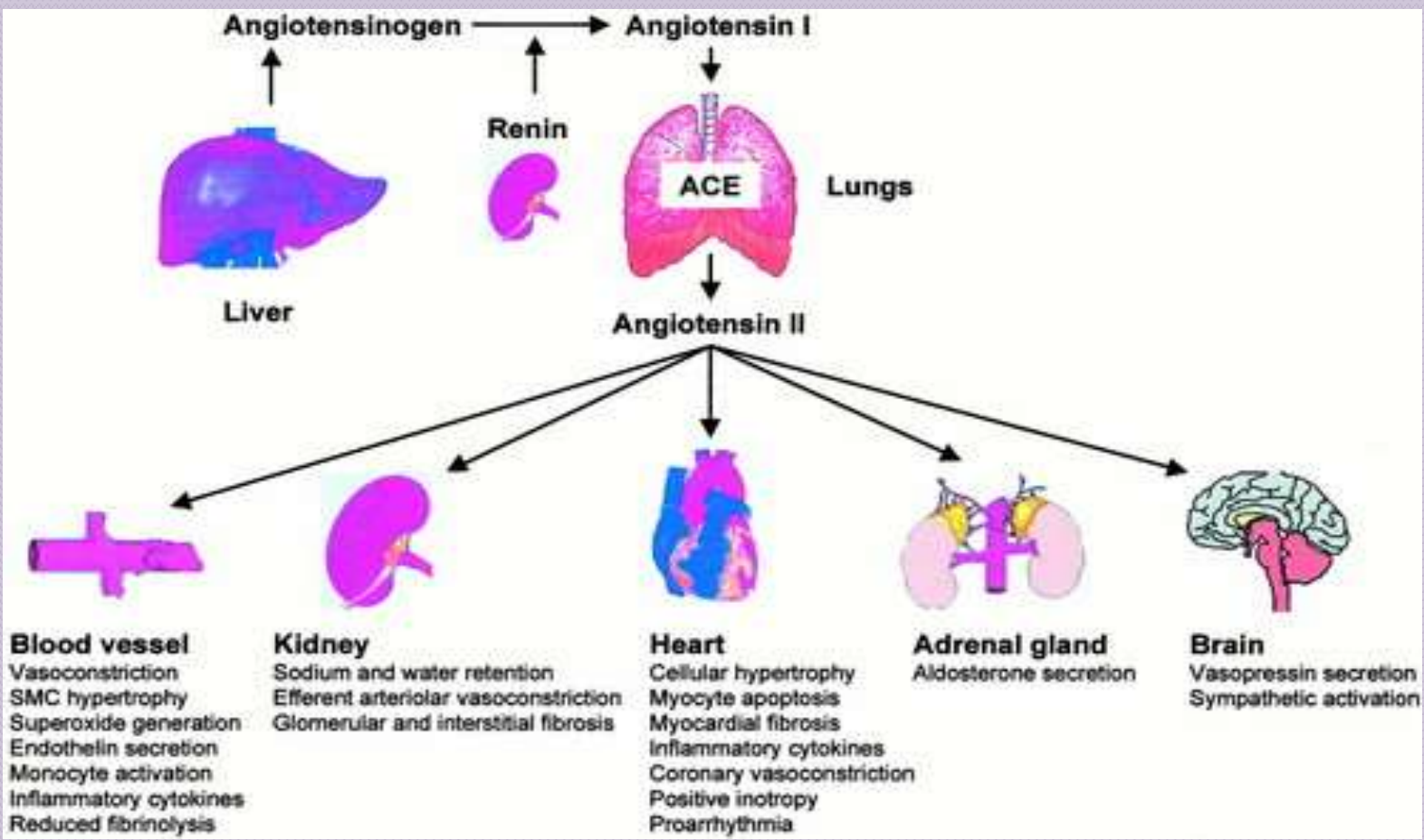

Glossopharyngeal nerve
Vagus nerve
Carotid body chemore-ceptors
Aortic body chemore-ceptors
Cardioregulatory center
Vagus nerve (para-sympathetic)
Chemore-ceptors in the medulla oblongata
Sympathetic nerves
Vasomotor center
1
2
3
4

Renin Angiotensin Aldesterone System (RAAS)

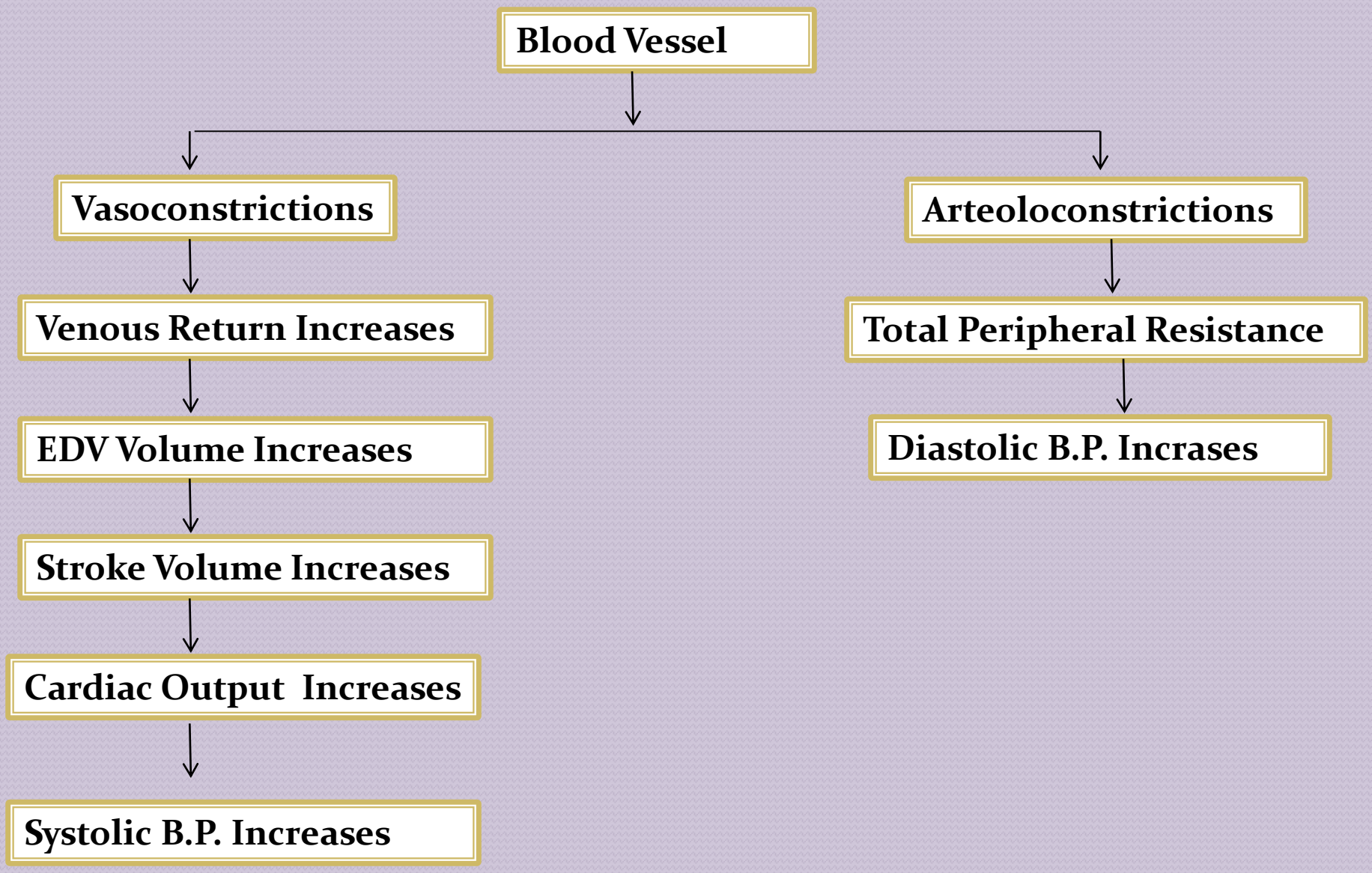
- ↓ B.P
- ↓ in ECF volume
- ↑ Sympathetic Activity
- ↓ load of Na^+ & Cl^- in MD



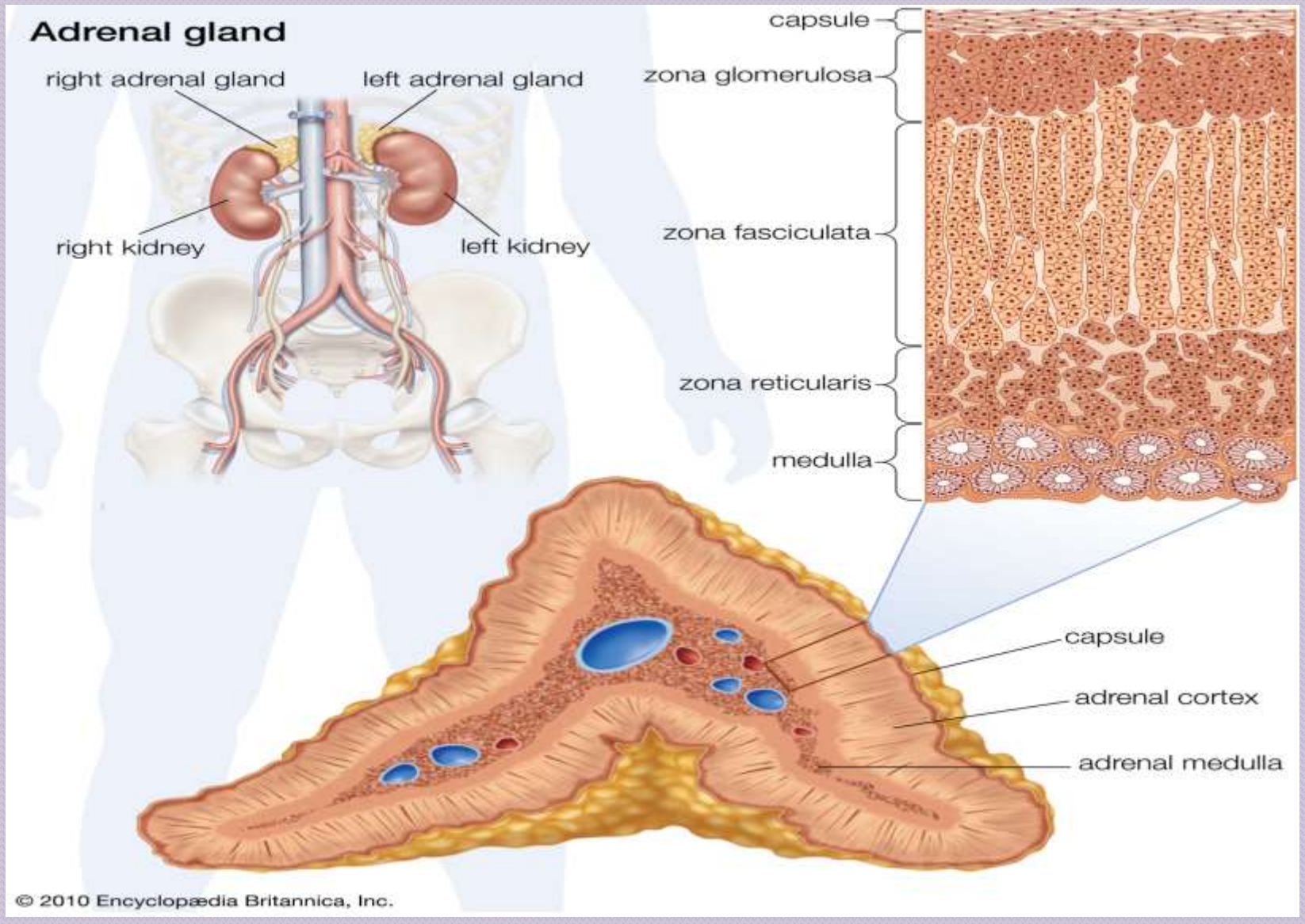
Pharmacological Actions



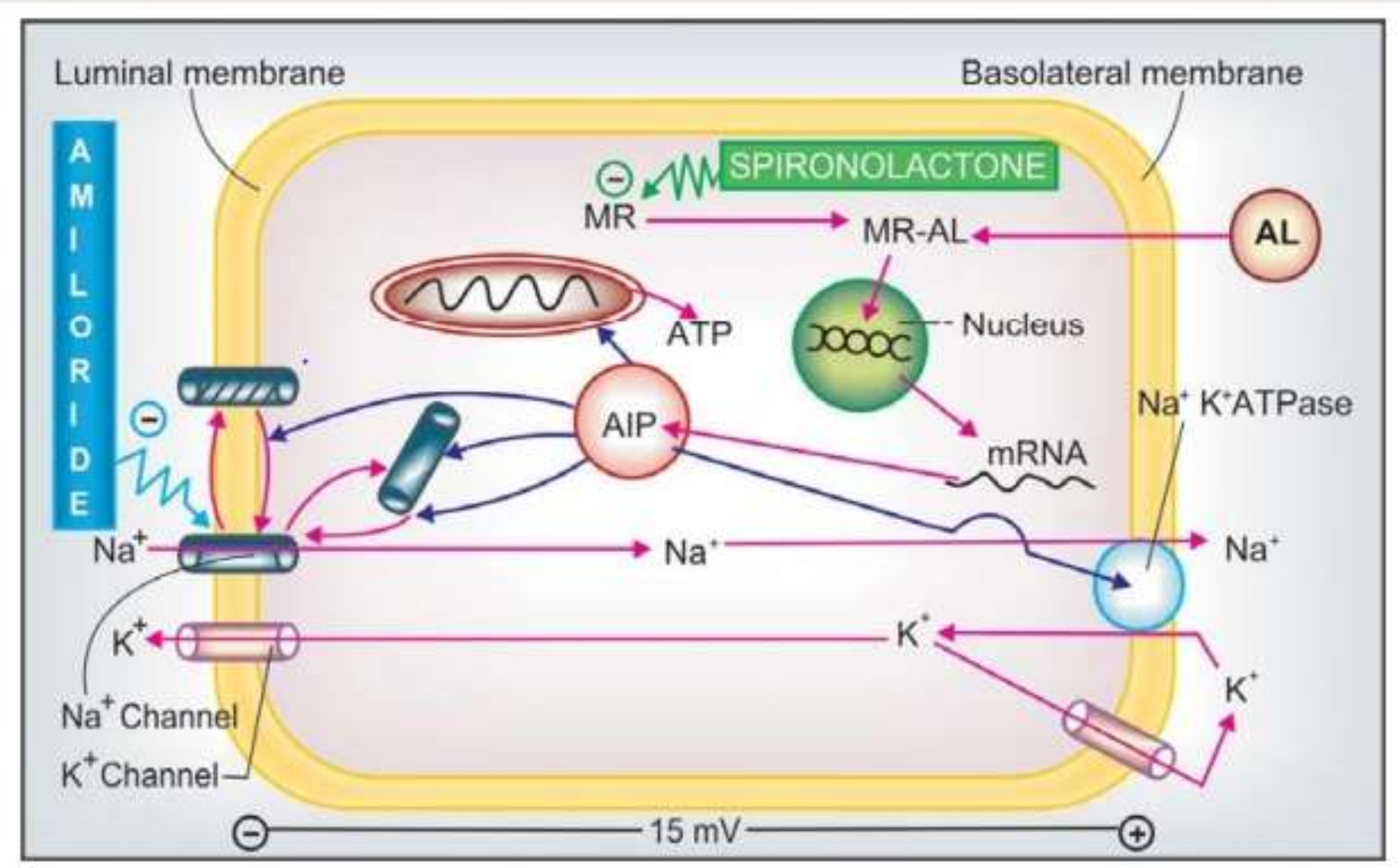
Action On CVS

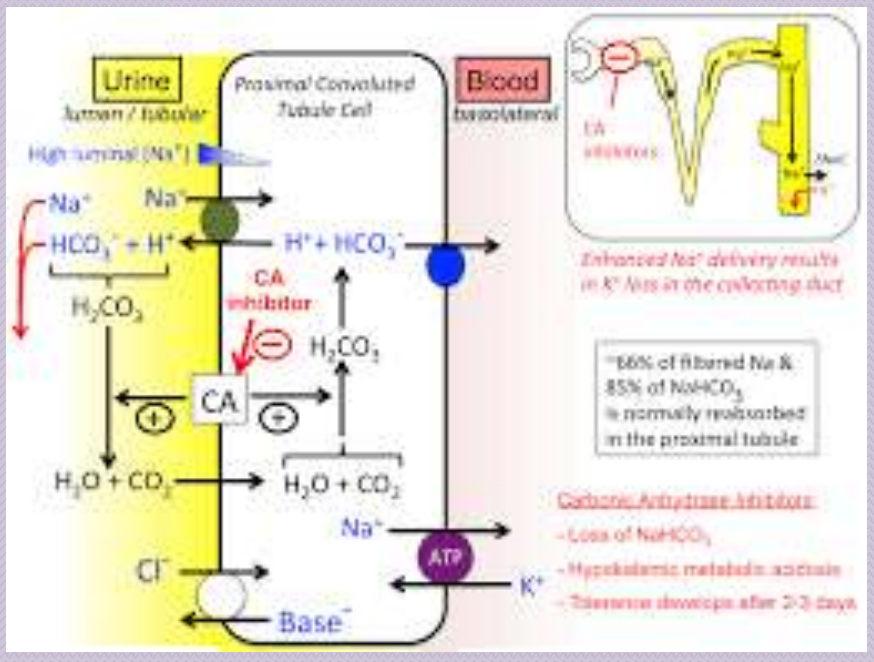


Action on Adrenal Cortex

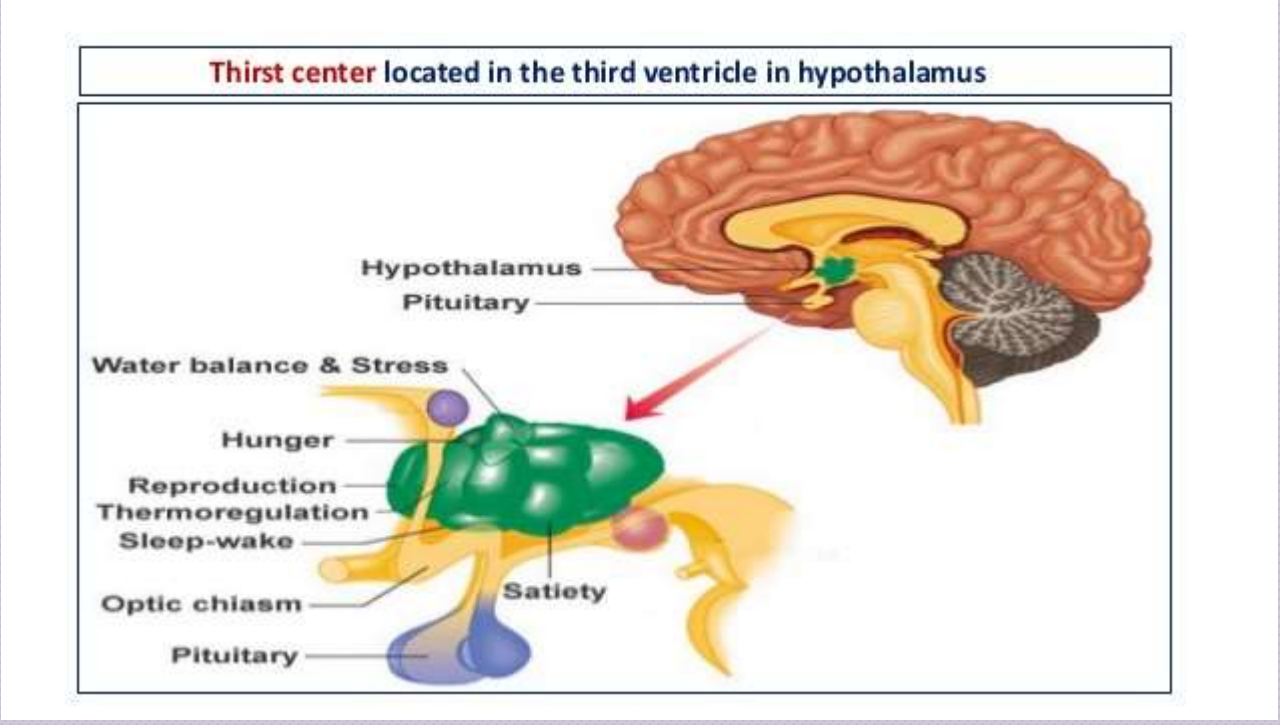


Action On Kidney



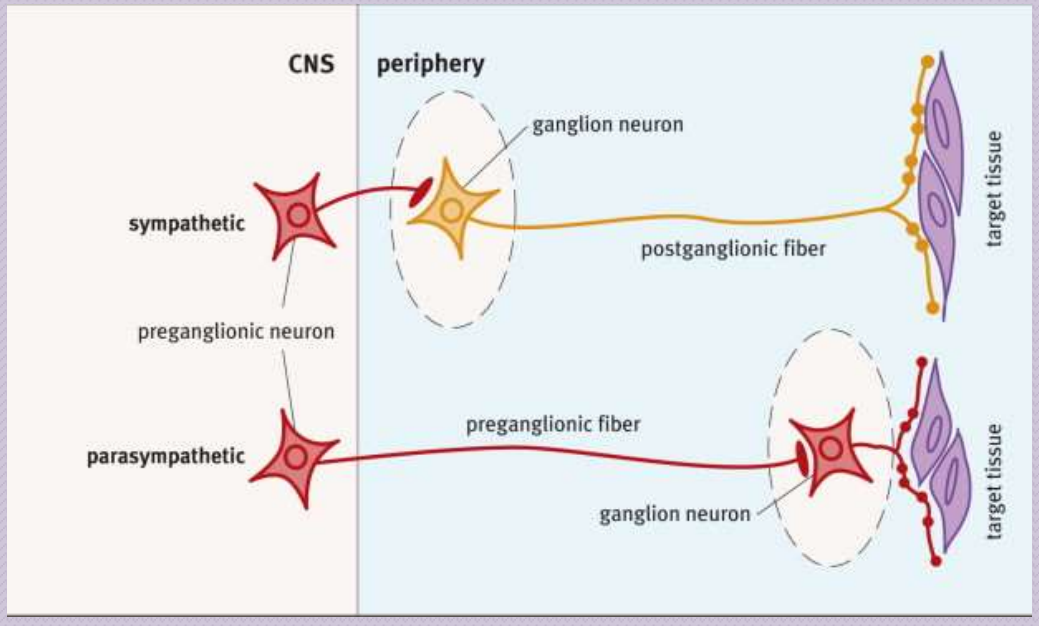

Urine
Lumen / Tubular
Proximal Convoluted Tubule Cell
Blood
basolateral
Na+
Na+
HCO3- + H+
H+ + HCO3-
H2CO3
CA inhibitor
H2CO3
CA
H2O + CO2
H2O + CO2
Na+
ATP
Cl-
K+
Base-
Enhanced Na+ delivery results in K+ loss in the collecting duct
~66% of filtered Na & 85% of NaHCO3 is normally reabsorbed in the proximal tubule
Carbonic Anhydrase Inhibitors
- Loss of NaHCO3
- Hypokalemic metabolic acidosis
- Tolerance develops after 2-3 days

Action On CNS



- Person demanding more and more water
- Blood volumes increases

Peripheral Sympathetic Structures



✓Adrenal Medulla, Autonomic Ganglia, postganlionic fiber

✓Increases output of NA

Thank You

Antiarrhythmic agent

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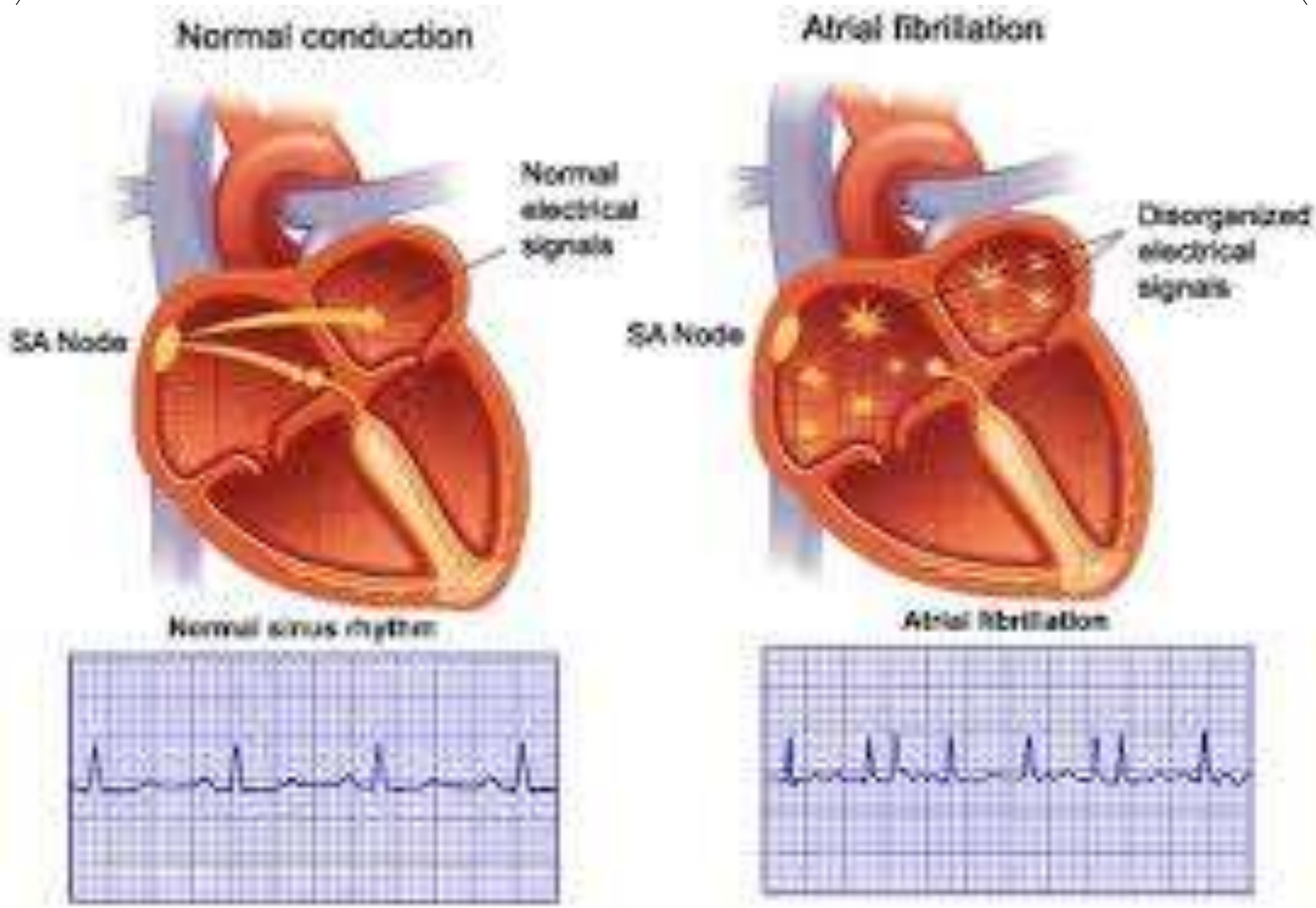

Normal conduction
Normal electrical signals
SA Node
Normal sinus rhythm
Atrial fibrillation
Disorganized electrical signals
SA Node
Atrial fibrillation

Antiarrhythmic agent

Antiarrhythmic agents are a group of pharmaceuticals that are used to suppress abnormal rhythms of the heart (cardiac arrhythmias), such as atrial fibrillation, atrial flutter, ventricular tachycardia, and ventricular fibrillation.

Classification

Class I : Na^+ Chanel Blocker

C lass II : Beta Blockers

Class III : Ca^+ Chanel Blockers

Class IV : Miscellaneous drusg

Some Common Side effect

- Worsening arrhythmias
- Allergic reaction
- Chest pain
- Fainting
- Swelling of the feet or legs
- Blurred vision
- Shortness of breath
- Abnormally fast heartbeat
- Abnormally slow heartbeat
- Dizziness or lightheadedness
- Cough

Other potential side effects.

- Bitter or metallic taste or change in taste
- Loss of appetite
- Increased sensitivity to sunlight
- Diarrhea or constipation

Class I agents interfere with the sodium (Na^+) channel.

A. fast-channel blockers-affect QRS complex

e.g. Quinidine, Procainamide, Disopyramide.

B. Can prolong QRS in overdose/ Little decreased in dv/dt of 0 phase

e.g. Lidocaine, Phenytoin, Mexiletine, Tocainide.

C. Marked deacrease by dv/dt of 0 Phase.

e.g. Encainide, Flecainide, Propafenone, Moricizine.

Class II agents are anti-sympathetic nervous system agents. Most agents in this class are beta blockers.

e.g. carvedilol, Propranolol, Esmolol, Timolol, Metoprolol, Atenolol, Bisoprolol

Class III agents affect potassium (K^+) efflux.

e.g. Amiodarone, Sotalol, Ibutilide, Dofetilide, Dronedarone, E-4031

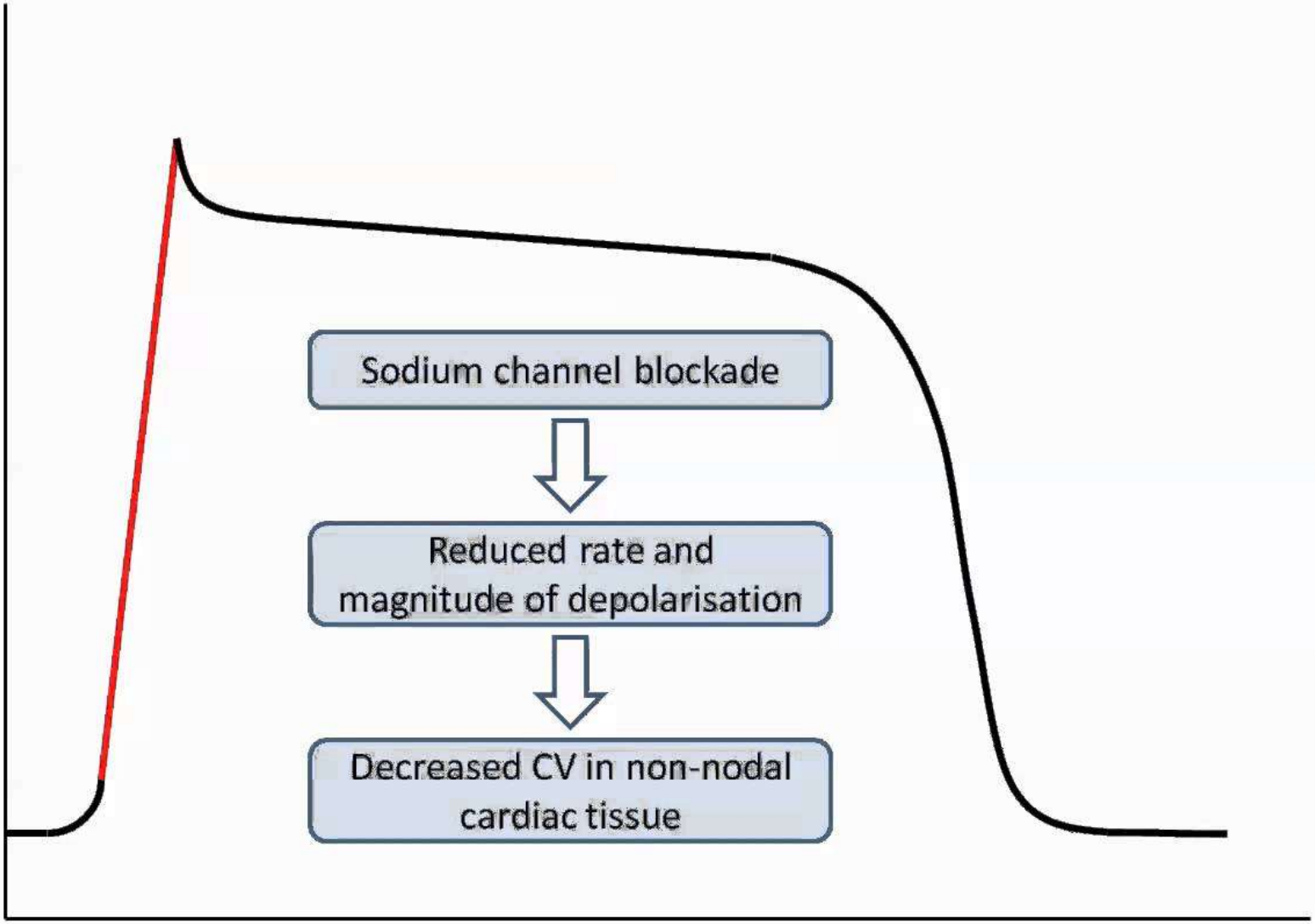
Class IV agents affect calcium channels and the AV node.

e.g. Verapamil, Diltiazem.

Class V agents work by other or unknown mechanisms.

e.g. Adenosine, Digoxin, Magnesium Sulfate.

Class I Antiarrhythmic drugs



VT – Ventricular tachycardia **VF** – Ventricular Fibrillation **SVT** – Supraventricular tachycardia
MI – Myocardial Infarction **WPW** – Wolff-parkinson-white syndrome

Class I agents interfere with the sodium (Na^+) channel.

A. fast-channel blockers-affect QRS complex

Quinidine

Found in Cinchona bark.

Na+ Chanel blockade

Increase P-R and Q-T interval

MOA: It block myocardial Na+ channels reduces automaticity & rate of 0 phase depolarization.

At high conc. it also block the L type Ca+ channels

Other Action

- Fall in B.P. (weak α adrenergic blockade & cardiac depression.)
- Decrease muscle contractility, Uterine contraction, vomiting ,diarrhoea, and neurological effects.
- Levo isomer has antimalerial action,

Drug interaction

Marked fall in B.P. patient receiving vasodilatiors.

Rise in Blood level and toxicity of digoxin due to displacement of tissue binding and inhibition of P-glycprotein meadiated renal and biliary clearence of digoxin.

Risk of torsade de point Increased by hypoklaemia cuased by diuretics.

Synergistic cardiac depression with β Blockers, verapamil.

Quinidine inhibit CY P2D6: prolongs t ½ propafenone

Procainamide

- It is orally active amide derivative of the local anesthetic procain, with cardiac physiological action.

- Slowing of 0 Phase and impulse conductions, prolongation of APD, ERP, QRS, complex and Q-T intervals.

- It is less effective in suppressing ectopic automaticity.

- It causes somewhat less marked depression of contractility and A-V conduction.

- Antivagal action is minimal.

- Not an α blocker causes less fall in B.P. at high doses fall in B.P. due to ganglionic blockade.

Pharmacokinetics

- Bioavailability is about 75%.
- Peak plasma conc. Occurs in 1 Hr.
- Metabolized in liver by acetylation to N-acetyl-procainamed (NAPA) which has no Na^+ channel blocking property.
- More than half of drug is excreted unchanged in urine.
- Plasma $t^{1/2}$ is 3-4 hr.

Adverse effect

- Nausea, vomiting.

- CNS: Weakness, mental confusion, hallucinations are at higher doses.

- Hypersensitivity reactions are rashes, fever, angioedema. Angranulocytosis and aplastic anaemia.

Uses

- Ventricular arrhythmias
- prevention of paroxysmal recurrent atrial fibrillation(triggered by vagal overactivity)
- procainamide in Wolff-Parkinson-White syndrome

Disopyramide

- exerts electrophysiological effects very similar to those of quinidine.

- Disopyramide is used to maintain sinus rhythm in patients with atrial flutter or atrial fibrillation and to prevent recurrence of ventricular tachycardia or ventricular fibrillation.

- The *R*-(-)-enantiomer produces similar Na^+ channel block but does not prolong cardiac action potentials.

- Disopyramide commonly depresses contractility, which can precipitate heart failure , and also can cause *torsades de pointes*.

Pharmacokinetics.

Disopyramide is well absorbed.

Binding to plasma proteins is concentration dependent.

Disopyramide is eliminated by both hepatic metabolism (to a weakly active metabolite) and renal excretion of unchanged drug.

The dose should be reduced in patients with renal dysfunction.

Higher than usual dosages may be required in patients receiving drugs that induce hepatic metabolism, such as phenytoin.

B. Can prolong QRS in overdose/ Little decreased in dv/dt of 0 phase

Lidocaine

Lidocaine decreases automaticity by reducing the slope of phase 4 and altering the threshold for excitability.

Most prominent action is suppression of automaticity.

Lidocaine usually exerts no significant effect on PR or QRS duration; QT is unaltered or slightly shortened

Pharmacokinetics

It is inactive orally due to first pass metabolism in liver.

Action of an i.v. bolus last only 10-20 min because of rapid distribution,

It is hydrolysed, deethylated and conjugated: metabolite are excreted in urine.

Adverse Effect

Dose related neurological effect:

Drowsiness, nausea, paresthesia, blurred vision, disorientation, nystagmus, twitchying and fits.

Only excessive doses causes cardiac depression and h potension.

When a large intravenous dose of lidocaine is administered rapidly, seizures can occur.

Mexiletine

It analogs of lidocaine that have been modified to reduce first-pass hepatic metabolism and permit chronic oral therapy.

Their electrophysiological actions are similar to those of lidocaine.

Tremor and nausea, the major dose-related adverse effects, can be minimized by taking the drugs with food.

Mexiletine is approved for treating ventricular arrhythmias; combinations of mexiletine with quinidine or sotalol may increase efficacy while reducing adverse effects.

Marked deacrease by dv/dt of 0 Phase

Propafenone.

It is an Na^+ channel blocker with a relatively slow time constant for recovery from block.

Its major electrophysiological effect is to slow conduction in fast-response tissues.

Propafenone prolongs PR and QRS durations.

It is used to maintain sinus rhythm in patients with supraventricular tachycardias, including atrial fibrillation; like other Na^+ channel blockers.

It also can be used in ventricular arrhythmias, but with only modest efficacy.

Pharmacokinetics

Propafenone is well absorbed and is eliminated by both hepatic and renal routes.

Undergoes variable first pass metabolism.

CYP2D6 inhibitors like fluoxetine increase its biovailability and plasma conc.

Class II agents are anti-sympathetic nervous system agents. Most agents in this class are beta blockers.

It is likely that most b adrenergic antagonists share antiarrhythmic properties.

In a normal individual propranolol has only mild depressant action on SA node automaticity.

Slow channel responses.

Sotalol prolongs action potential duration throughout the heart and QT interval on the ECG.

It decreases automaticity, slows AV nodal conduction, and prolongs AV refractoriness by blocking both K^+ channels and b adrenergic receptors, but it exerts no effect on conduction velocity in fast-response tissue.

Uses

Decrease myocardial infarction mortality

Prevent recurrence of tachyarrhythmias

Propranolol has sodium channel blocking effects

Class III agents affect potassium (K^+) efflux.

Predominantly block the potassium channels, thereby prolonging depolarization.

These drug may precipitate torsades de ‘pointes due prolongaltion of QT interval.

Some drug like amiodarne possess Na^+ channel blockade, β blockade, K^+ channel blockade and Ca^+ channel blockade action.

Due to this property it has widest anti-arrhythmic spectrum.

It can also cause hypothyroidism by inhibiting peripheral conversion of T_4 and T_3.

Clinical Uses

In Wolff-Parkinson-White syndrome

(sotalol:) ventricular tachycardias and atrial fibrillation

(Ibutilide:) atrial flutter and atrial fibrillation

Class IV agents affect calcium channels and the AV node.

These agent are the blockers of L-type voltage gated calcium channels.

They decreased rate of phase 4 depolarization in SA and AV nodes.

This result in decreased automaticity of SA node and decreased conduction through AV node.

Clinical Uses

Prevent recurrence of paroxysmal supraventricular tachycardia

Reduce ventricular rate in patients with atrial fibrillation

Verapamil is choice of drug for Supraventicular tachycardia (SVT).

Class V agents work by other or unknown mechanisms.

Digoxin, which decreases conduction of electrical impulses through the AV node and increases vagal activity via its central action on the central nervous system, via indirect action, leads to an increase in acetylcholine production, stimulating M3 receptors on AV node leading to an overall decrease in speed of conduction.

Adenosine, used intravenously for terminating supraventricular tachycardias

Magnesium sulfate, an antiarrhythmic drug, but only against very specific arrhythmias which has been used for torsades de pointes.

Work by other or unknown mechanisms (Direct nodal inhibition).

Clinical Uses

Used in supraventricular arrhythmias, especially in Heart Failure with

Atrial Fibrillation, contraindicated in ventricular arrhythmias. Or in the

case of Magnesium Sulfate, used in Torsades de Pointes.

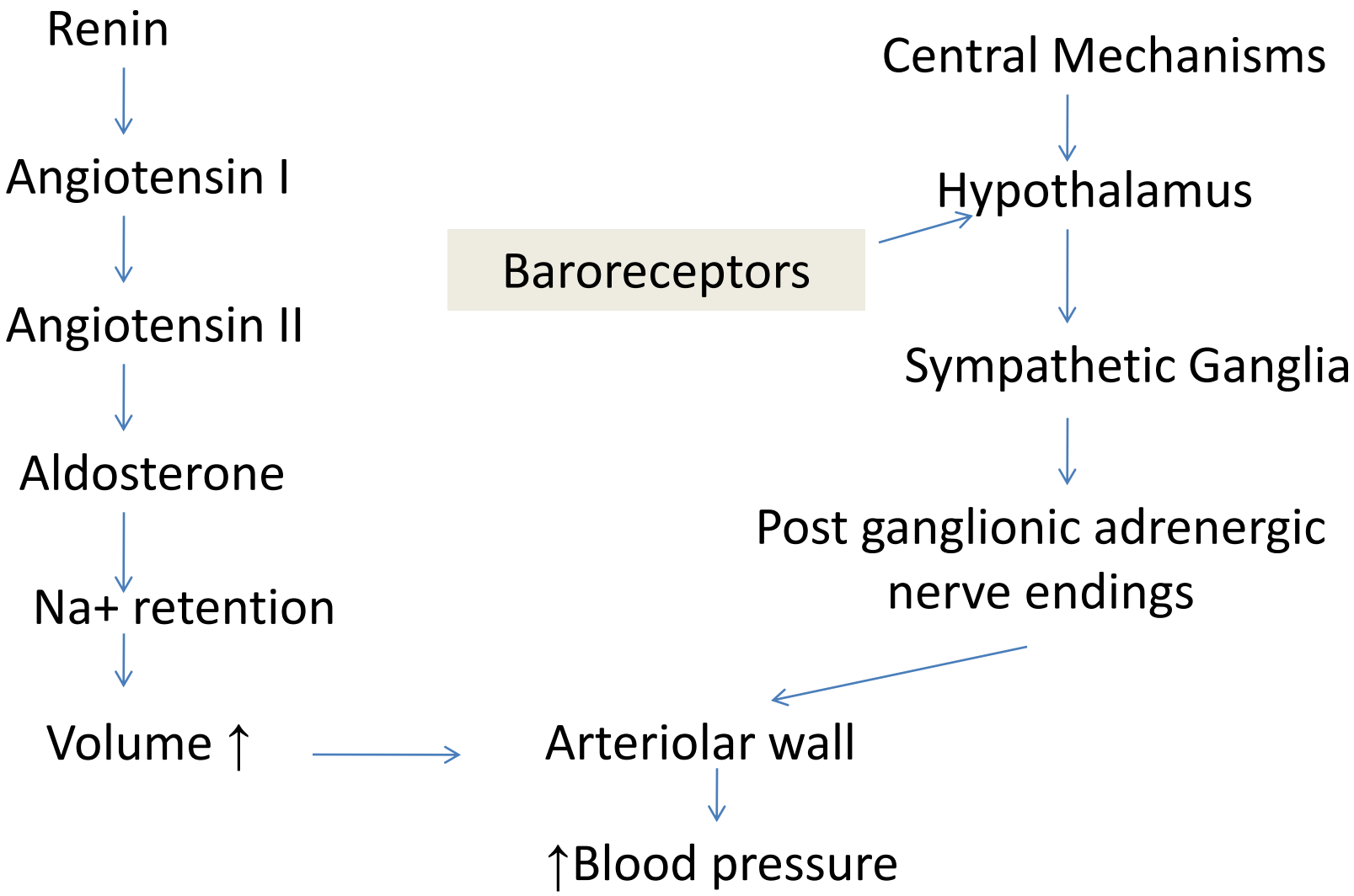
Thank You ?

Antihypertensive drugs

Hypertension

- Most common CVS condition
- Persistant and sustained increased BP has damaging effect on heart, brain, kidney, eye
- Types
  - Primary /essential
    - No specific cause 95% cases
  - Secondary hypertension
    - Due to specific disease or drug 5% cases

Physiology of Hypertension



Classification Of Antihypertensives

1. Angiotensin Converting Enzyme inhibitors
   – Captopril, Enalapril, Lisinopril, Ramipril
2. Angiotensin II receptor Antagonists
   – Losartan
3. Calcium channel blockers
   – Verapamil, Nifedipine, Amlodipine
4. Diuretics
5. Sympatholytics
6. Vasodilators

Classification of antihypertensives

- Diuretics
  - Thiazides: Hydrochlorthiazide, chlorthalidone
  - Loop diuretics: furosemide
  - K sparing diuretics: Spironolactone, Amiloride, Triamterine
- Sympatholytics
  - Centrally acting: clonidine, Methyl dopa
  - Adrenergic receptor blocker:
    - Alpha blocker: Prazozin
    - Beta Blockers: propranolol, atenolol
    - Combined ALPHA + BETA blocker: Labetolol

Classification of antihypertensives

- Vasodilators:
  - Arterial dilators: Hydralazine, minoxidil, diazoxide
  - Arteriovenous dilators: sodium nitroprusside

Angiotensin converting enzyme inhibitors (MOA)

- Inhibit generation of Angiotensin II
- Inhibit degradation of bradykinin which is potent vasodilator
- Dilates both arteries & vein
- Blood flow to vital organs increases
- Decrease aldosterone production indirectly

Pharmacokinetics

- All are prodrugs except captopril & lisinopril
- All are well absorbed orally
- Food reduces absorption of captopril
- DOA of captopril is 8-12 hrs rest others > 24 hrs
- All are excreted through the kidneys

Adverse effects

- Cough
- Angioedema (0.1%)
- Proteinuria
- Taste alterations
- Teratogenic
- Severe hypOtension : first dose phenomenon
- Neutropenia
- Rashes
- Itching
- Loss of appetite, nausea, vomiting, diarrhoea
- Hyperkalemia: in renal insufficiency and with K^+ sparing diuretics

Advantages of ACE inhibitors

- Lack of postural hypotension
- Safe in asthmatics, diabetes
- ↓ incidence of Type 2 DM in high risk cases
- Prevent potassium loss due to diuretics
- Reverse Left ventricular hypertrophy
- No hyperuricemia or derangement of lipids
- No rebound hypertension
- No effect on sexual functions

Uses of ACE inhibitors

- Hypertension: first line drug for all grades of hypertension but specially indicated in
  - Hypertension with diabetes
  - Left ventricular hypertrophy
- Congestive cardiac failure
- Myocardial Infarction
- Diabetic Nephropathy
- Scleroderma renal crisis

Angiotensin receptor blockers(ARBs) (Losartan)

- AT1:
  - Vasoconstriction, aldosterone secretion, release NA
- AT2 receptor:
  - Function is not known
- ARBs: competitively inhibit binding of angiotensin II to AT1 receptor
- Has similar effects like ACE inhibitors
- Uses are similar to ACE inhibitors
- Mainly used in patients who cough with ACE inhibitors

Advantage of Losartan over ACE inhibitors

- There is no increase in bradykinin levels
- So less adverse effects like dry cough & angioedema

Adverse effects

- Headache
- Hypotension
- Hyperkalemia
- Weakness, rashes
- Vomiting
- Teratogenic

Calcium channel blockers

- Nifedipine & Amlodipine preferred
- MOA: decrease PVR without compromising cardiac output (Vasodilation)
- Adverse effects:
  - Headache, flushing, tachycardia, Palpitation
- Sustained release preparations have less side effects
- Beta blockers counteract reflex tachycardia
- Useful in pt with angina, Ashtma, PVD, Migraine, hyperlipidemia, diabetes

Diuretics

Inhibit Na^+-Cl^- Symport in early DCT

↓

Promote Na & water excretion

↓COP & BP

↓Na^+ conc in vascular smooth muscles

↓

↓PVR

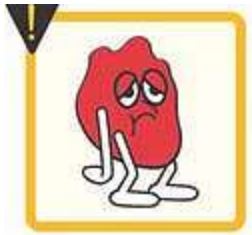
↓

↓BP

Adverse effects of Thiazide diuretics

- Hypokalemia
- Hyperglycemia
- Hyperuricemia
- Hypercalcemia
- Impotence & decreased libido
- Low doses 12.5 mg of hydrochlorthiazide preferred

Sympatholytics

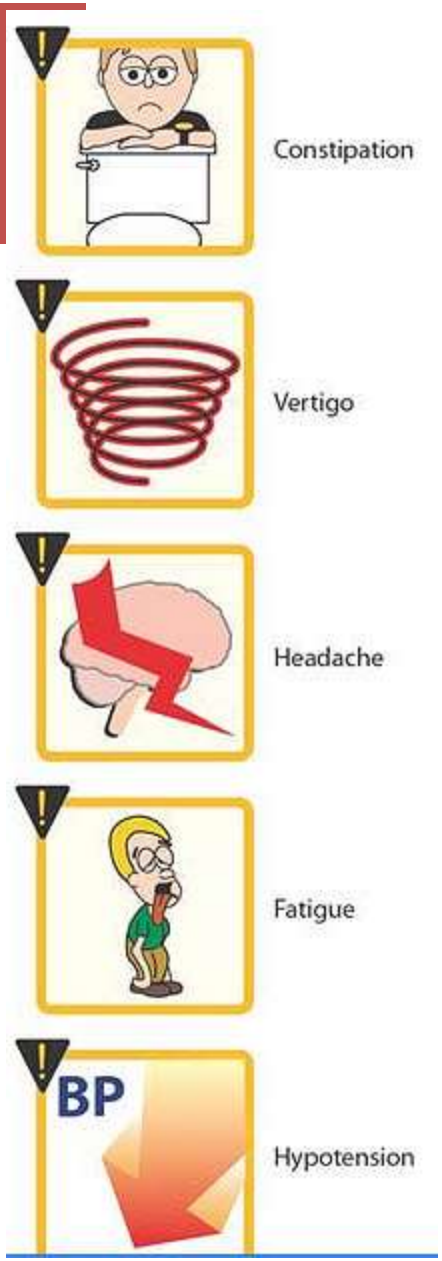


Beta Blockers

- MOA
  - ↓ sympathetic outflow
  - ↓ HR, ↓ Force of contraction and ↓COP
  - ↓ renin release
- Beta blockers mainly useful in
  - Young hypertensives with ↑ renin
  - Associated angina, post MI, Migraine
  - Patients receiving vasodilators to counteract reflex tachycardia

Alpha adrenergic blockers

- Non selective
  - Phenoxybenzamine, phentolamine
- Selective alpha1
  - Prazosin, terazosin



Centrally acting sympatholytics

- Clonidine
  - Highly lipid soluble, crosses blood brain barrier
  - Stimulates α_{2a} receptors in vasomotor centre
  - ↓ sympathetic outflow from VMC leading to ↓HR , ↓ COP & ↓PVR thus ↓ ↓ BP.
  - Adverse effects
    - Dryness of mouth eyes
    - Sedation, bradycardia, impotence
    - Sudden withdrawal = withdrawal symptoms
- Uses:
  - opioid withdrawl, diabetic neuropathy, with anaesthetics

Vasodilators

- Hydralazine
  - Direct arterial dilator
  - Can be given orally
  - Can cause reflex tachycardia, palpitations , Na & water retention
  - Can be countered by giving with diuretic or beta blocker
  - Other S/E: Hypotension, flushing, angina, MI, coronary steal phenomenon, lupus erythematosus

Minoxidil

- K channel opener
- Causes hyperpolarization of vascular smooth muscles , vasodilation and decrease BP
- Used to promote hair growth

Diazoxide

- Treatment of hypertensive emergencies

Antihypertensives to be avoided in pregnancy

- Diuretics
  - Risk of placental wastage, still births
- ACE inhibitors
  - Risk of fetal damage, growth retardation
- Beta blocker
  - LBW, neonatal bradycardia, hypoglycemia

Safe drugs in pregnancy

- Hydralazine
- Alpha methyl dopa
- CCBs
- Prazosin
- Clonidine
- Cardioselective beta blockers

NICE Guidelines for management of Hypertension

	Younger (<55 years) and non-Black	older (>= 55 years) or black
Step 1	A	C
Step 2	A plus C	C plus A
Step 3	A + C + D	A + C +D
Step 4: Resistant Hypertension	A + C + D + consider further diuretic (or alpha- or beta-blocker) **Consider seeking specialist advice**	

*NICE: National Institute of health and Care Excellence

A= ACE INHIBITORS

C= CALCIUM CHANNEL BLOCKERS

D= DIURETICS

Drugs to be avoided in specific conditions

- Asthma
- Peripheral vascular disease
- Diabetes

} β-Blockers

- Hyperlipidemia: Thiazides, β-Blockers
- Gout: thiazides
- Sexually active males: α_1-blockers, diuretics

Hypertensive crisis

- Hypertensive urgencies
  - DBP>120 mm Hg or higher with impending complications
  - DBP needs to be reduced to 100 mm Hg in 24-48 hrs
  - Severe epistaxis
  - Unstable angina
- Hypertensive emergencies
  - Evidence of target organ damage
  - AMI, LVF, Encephalopathy
  - Rapid lowering of BP within 1 hr to 150/100 mm hg

Drugs used in hypertensive crisis

- Sodium nitroprusside
- Nitroglycerine
- Labetolol

IV

- Nifedipine
- Captopril

Sublingual

ANTIANGINAL DRUGS

Angina pectoris – chest pain due to imbalance between the oxygen requirement of the heart and oxygen supplied to it via the coronary vessels.

TYPES OF ANGINA PECTORIS

1. **Classical angina (Stable angina) –**
- due to atherosclerosis of coronary arteries

2. **Variant/ Prinzmetal's angina –**
- due to coronary vasospasm

3. **Unstable angina –**
- progressive occlusion of the coronary artery

- rupture of an atheromatous plaque & platelet aggregation at the ruptured plaque

Antianginal drugs

Classification

1. **Nitrates** – Nitroglycerine (prototype)
   Isosorbide dinitrate
   Isosorbide mononitrate
   Erythrityl tetranitrate

2. **β-blockers** – Propranolol
   Metoprolol
   Atenolol

3. **Calcium channel blockers –**

   Verapamil

   Diltiazem

   Nifedipine, Nimodipine,

   Amlodipine , Felodipine

4. **Potassium channel opener –** Nicorandil

5. **Others –** Aspirin

   Dipyridamole

   Trimetazidine

- To abort or terminate anginal attack:

  Nitroglycerin(sublingually)

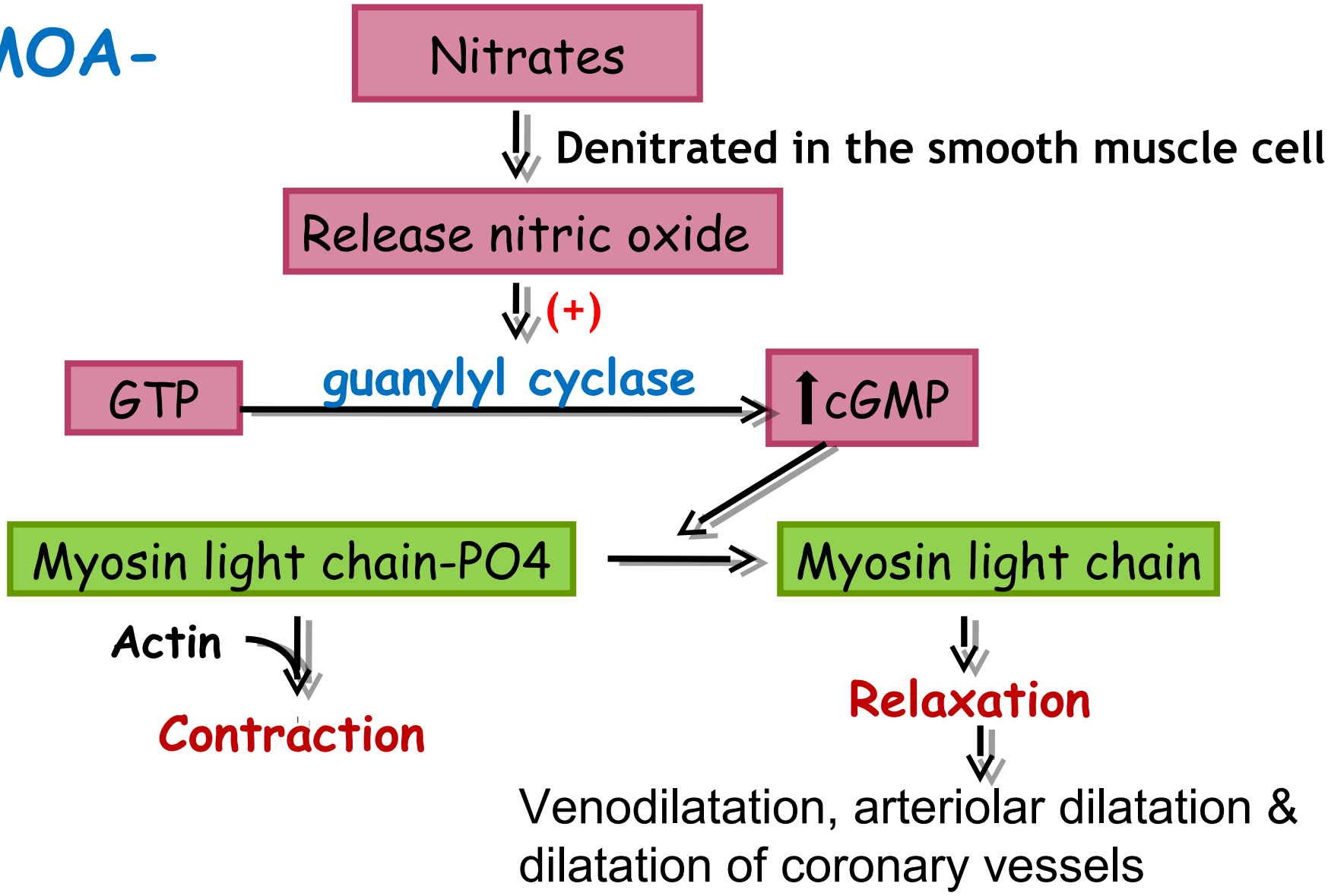
  Isosorbide dinitrate(sublingually)

- For chronic prophylaxsis:

  Nitrates, β-blockers, CCBs, potassium channel openers & others drugs

Nitrates

MOA-



Pharmacological actions

1. Vascular smooth muscles –

- ✓ Preload reduction (prominent action)
- ✓ Afterload reduction
- ✓ Redistribution of coronary blood flow

a) Dilatation of capacitance vessels

Pooling of blood in veins

Decrease venous return to heart

decrease preload

decrease in end diastolic pressure

decrease in O_2 demand

b) Arteriolar dilatation

decrease peripheral resistance

decrease afterload

decrease in cardiac work

c) Relaxation of coronary arteries

↓

redistribution of blood flow to ischaemic areas in angina patients

2. Relaxation of smooth muscles of the bronchi, biliary tract & esophagus

Therapeutic uses

1. Angina pectoris –

- sublingual nitroglycerine – to terminate an acute anginal attack – relieves pain within 3 mins
- oral or transdermal nitroglycerine – chronic prophylaxis
- i.v. nitroglycerine – unstable angina

2. Congestive heart failure & acute left ventricular failure –

- decreases preload & afterload – improves left ventricular function & pulmonary congestion

3. Myocardial infarction –

- i.v. - relieves ischemic pain

4.Cyanide poisoning –

Hemoglobin

↓ i.v. sodium nitrite

Methemoglobin

↓ cyanide

Cyanomethemoglobin

↓ i.v. sodium thiosulfate

Methemoglobin + sodium thiocyanate

(excreted in urine)

Adverse effects

- Flushing of face, throbbing headache
- Postural hypotension & tachycardia
- Palpitation, weakness, dizziness
- Tolerance – 'Monday disease'
- Methaemoglobinemia – high doses

Calcium channel blockers (CCBs)

MOA –

CCB's

⇓

binds to α_1 subunit of L- type Ca^{2+} channels & block their activity

⇓

decrease in transmembrane calcium current

⇓

smooth muscle relaxation, decreased contractility in cardiac muscle, decrease in pacemaker activity & conduction velocity

Verapamil – relatively cardioselective

Nifedipine – relatively vascular smooth muscle selective

Diltiazem – intermediate selectivity

Therapeutic uses

- ✓ Angina pectoris
- ✓ Hypertension
- ✓ **Cardiac arrhythmias** – Verapamil & diltiazem are useful in supraventricular arrhythmias

- ✓ Hypertrophic cardiacmyopathy
- ✓ Raynaud's disease- nifedpine, diltiazem & felodipine decrease the frequency and severity of attacks
- ✓ Prophylaxis of migraine
- ✓ Nifedipine- as uterine relaxant in premature labour

Adverse effects

- **Verapamil & Diltiazem** – nausea, constipation, bradycardia, flushing, headache, edema, hypotension

- **Nifedipine** – postural hypotension, palpitation, reflex tachycardia, edema, flushing, fatigue, dizziness

Thank You

Anti HyperlipidemicDrugs

Presented by

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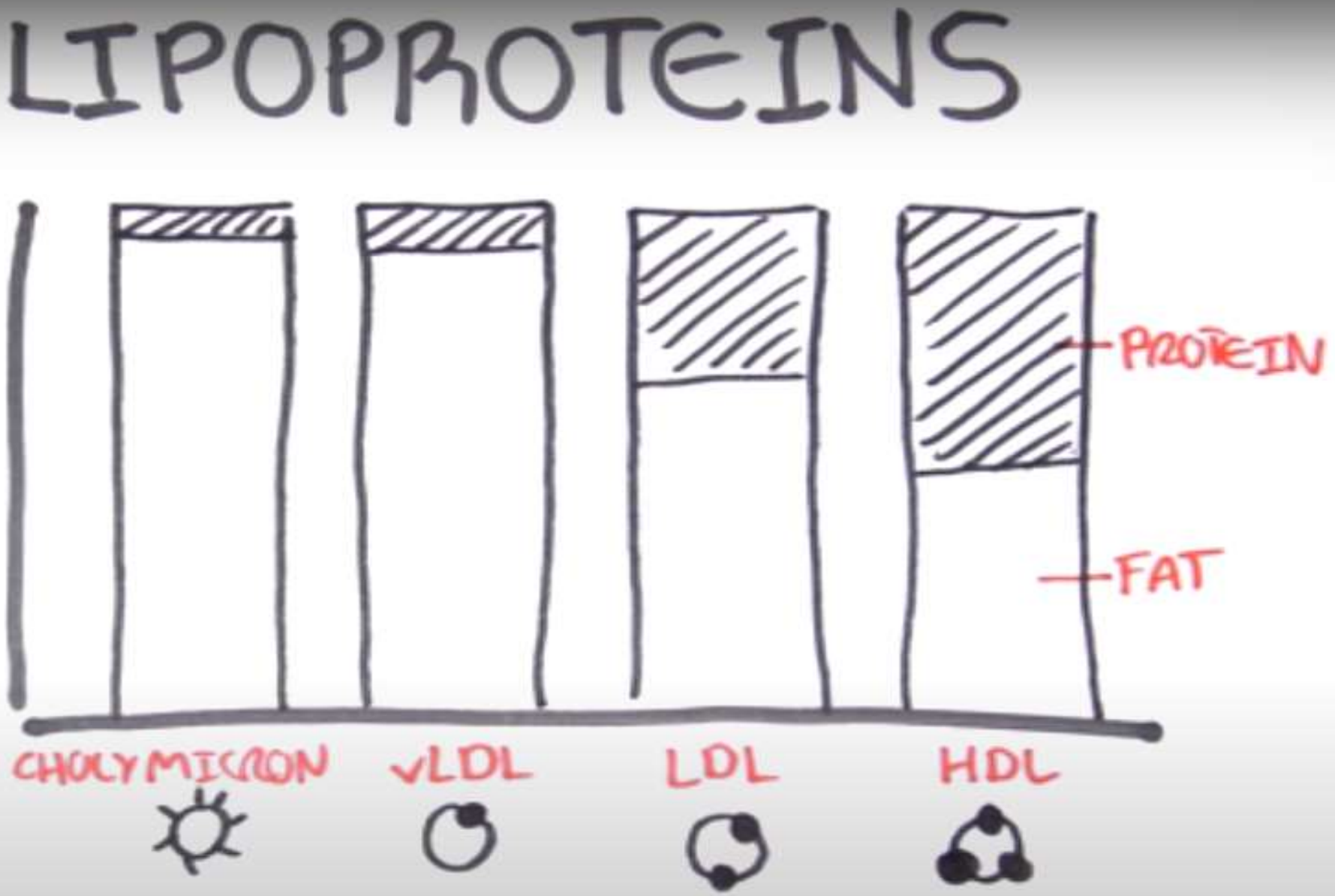
Nandurbar

Content

- Introduction
- Literature Review
- Clinical Survey
- Selection Of Formulation
- Research References
- Details of remaining work plan

Introductions



Chylomicrons

Formed in the intestine and carry triglycerides of dietary origin, unesterified cholesterol, and cholesteryl esters. They transit the thoracic duct to the bloodstream

Low-density lipoprotein (LDL)

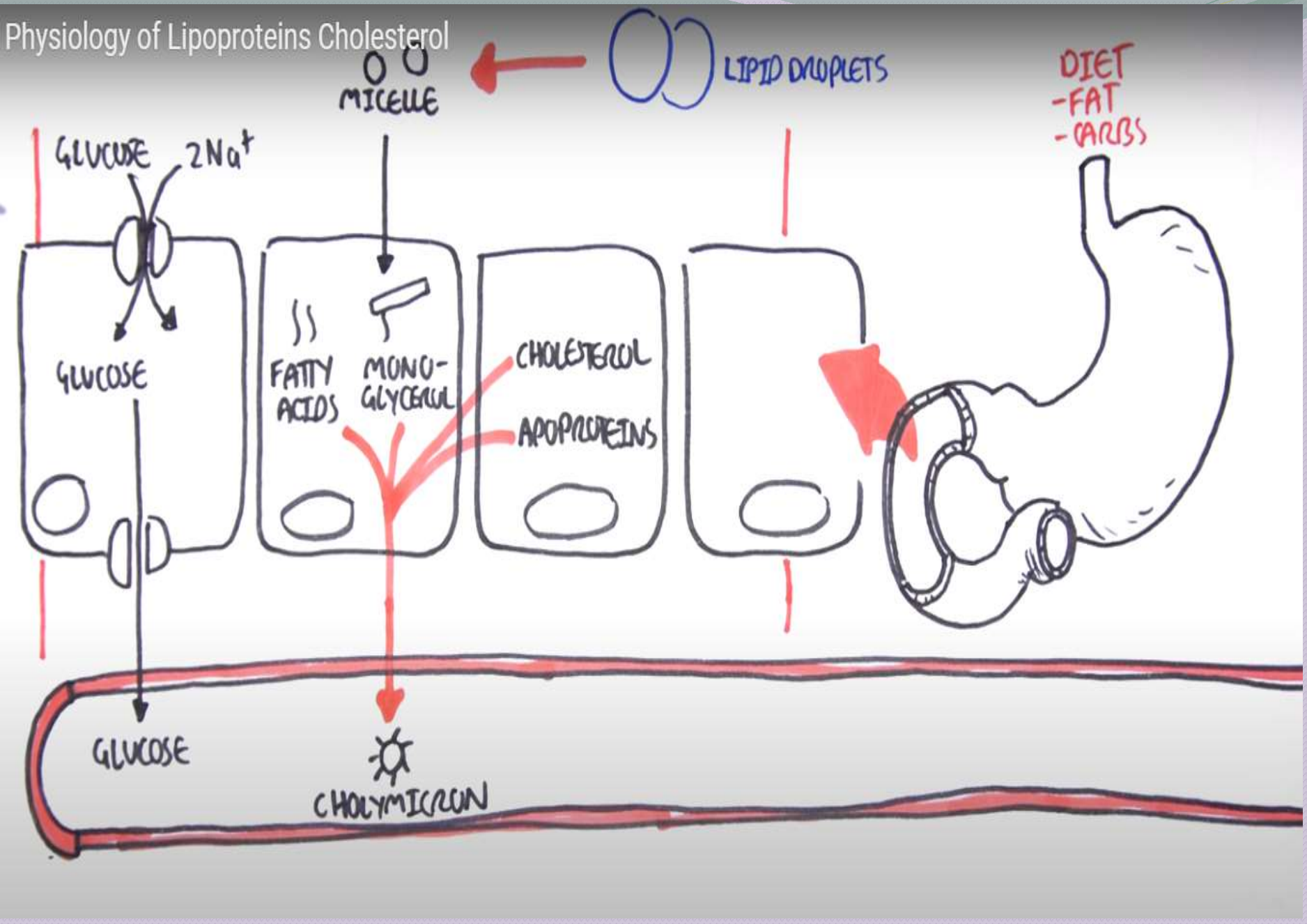
Cholesterol-rich lipoprotein whose regulated uptake by hepatocytes and other cells requires functional LDL receptors; an elevated LDL concentration is associated with atherosclerosis

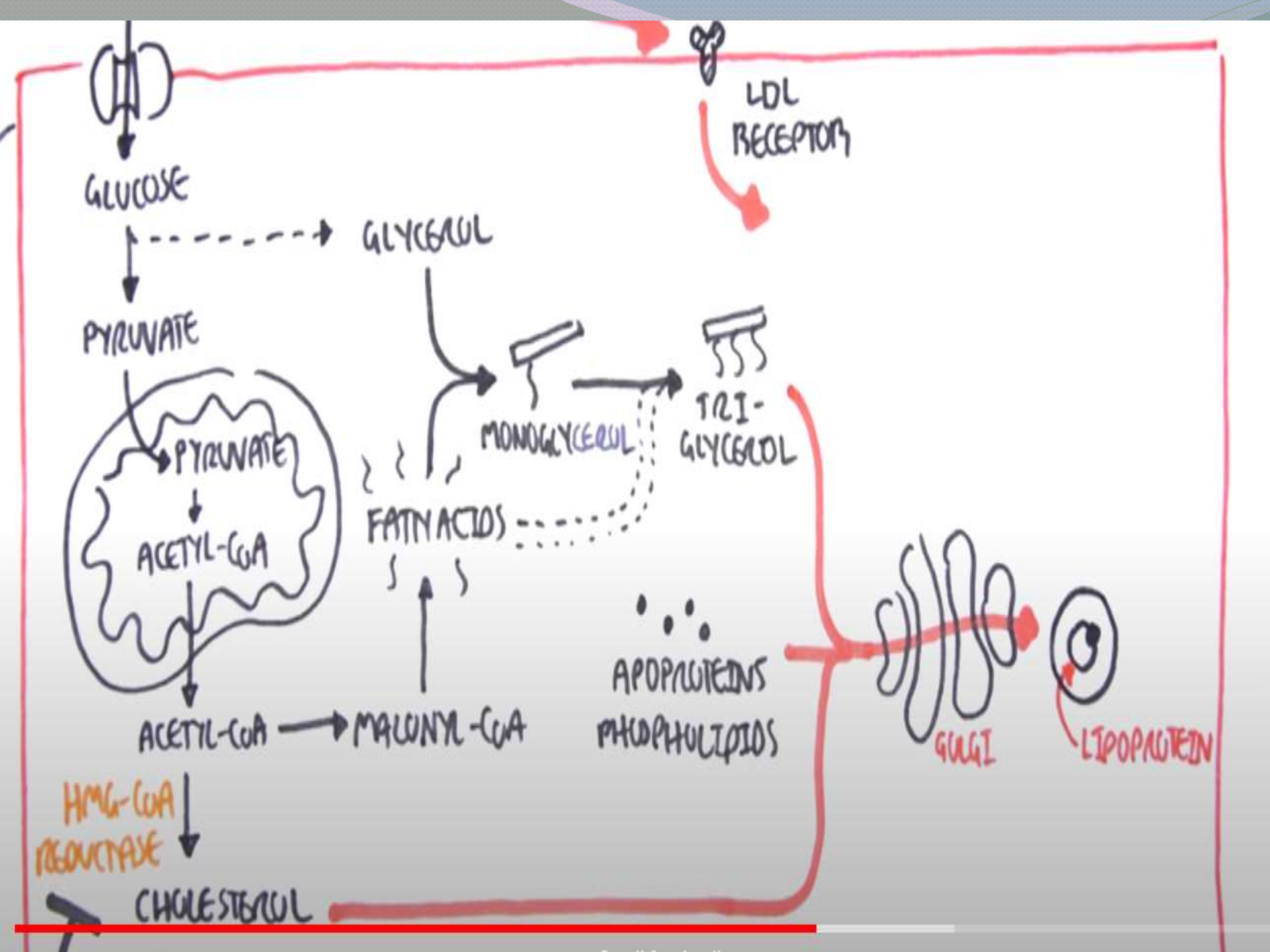
High-density lipoprotein (HDL)

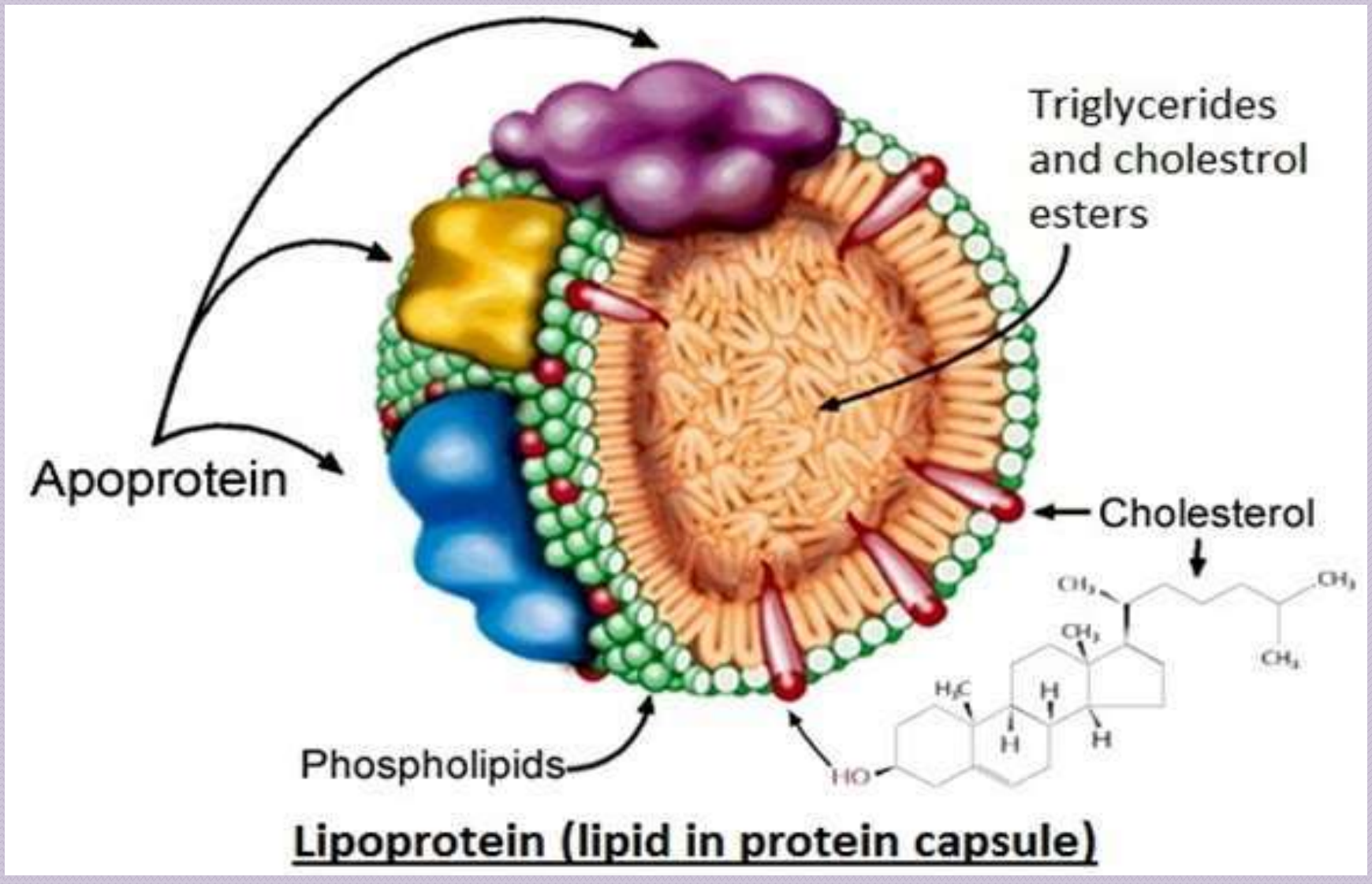
Cholesterol-rich lipoprotein that transports cholesterol from the tissues to the liver; a low concentration is associated with atherosclerosis

Very-low-density lipoprotein (VLDL)

Triglyceride-and cholesterol-rich lipoprotein secreted by the liver that transports triglycerides to the periphery; precursor of LDL


Physiology of Lipoproteins Cholesterol
MICELLE
LIPID DROPLETS
DIET
-FAT
-CARBS
GLUCOSE
2Na+
GLUCOSE
FATTY ACIDS
MONO-GLYCEROL
CHOLESTEROL
APOPROTEINS
GLUCOSE
CHOLYMICRON


LDL
RECEPTOR
GLUCOSE
GLYCEROL
PYRUVATE
PYRUVATE
ACETYL-CoA
MONOGLYCEROL
TRI-
GLYCEROL
FATTY ACIDS
APOPROTEINS
PHOSPHOLIPIDS
ACETYL-CoA
MALONYL-CoA
GOLGI
LIPOPROTEIN
HMG-CoA
REDUCTASE
CHOLESTEROL



Lipoprotein (lipid in protein capsule)

Anti-hyperlipidemicDrugs

1.HMG-CoA Reductase Inhibitors
e.g. Atorvastatin, Fluvastatin, Lovastatin, Pravastatin and Simvastatin.
2.Fibrates
e.g. Fenofibrate, Gemfibrozil and Clofibrate

3.Anion-exchange resins (bile acid sequestrants)

e.g. Colesevelam, Colestipol and Cholestyramine

4.Nicotinic acid
e.g. Niacin.

5.Cholesterol absorption inhibitors
e.g. Ezetimibe.

Other Drugs

e.g. Alpha-tocopherol acetate (vitamin E)
Omega-3

Drugs Therapy

The primary goal of therapy is to:

✓Decrease levels of LDL

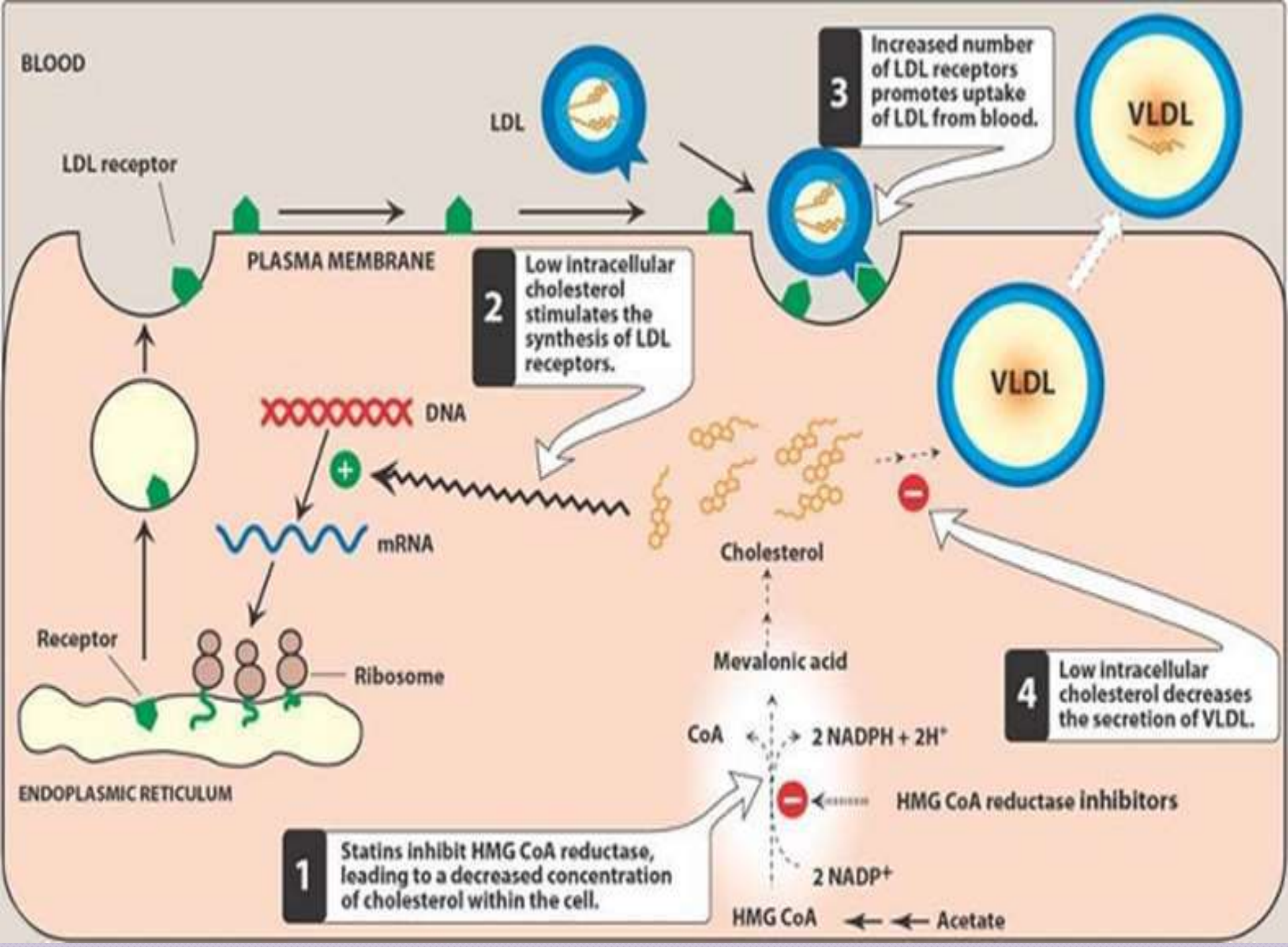
✓Increase in HDL

HMG-CoA Reductase Inhibitors (HMGs or Statins)

- Lovastatin
- Simvastatin
- Pravastatin
- Atorvastatin
- Fluvastatin
- Rosuvastatin

Mechanism of Actionof HMGs or Statins

- Most potent LDL reducers
- They are structural analogs of HMG-CoA
- Competitively inhibit HMG-CoA reductase enzyme
- They block the rate-limiting step in hepatic cholesterol synthesis (conversion of hydroxymethylglutarylcoenzyme A (**HMG-CoA) tomevalonate by HMG-CoA reductase)**
- Low intracellular cholesterol stimulate the synthesis of LDL receptors
- Promote uptake of LDL from the blood
- Low intracellular cholesterol decrease secreation of VLDL to the blood
- They have direct anti-atherosclerotic effects, and have been shown to prevent bone loss.


BLOOD
LDL
3 Increased number of LDL receptors promotes uptake of LDL from blood.
VLDL
LDL receptor
PLASMA MEMBRANE
2 Low intracellular cholesterol stimulates the synthesis of LDL receptors.
VLDL
DNA
mRNA
Cholesterol
Receptor
Ribosome
Mevalonic acid
4 Low intracellular cholesterol decreases the secretion of VLDL.
CoA
2 NADPH + 2H+
ENDOPLASMIC RETICULUM
HMG CoA reductase inhibitors
1 Statins inhibit HMG CoA reductase, leading to a decreased concentration of cholesterol within the cell.
2 NADP+
HMG CoA
Acetate

Therapeutic Uses:

- These drugs are effective in lowering LDL cholesterol levels especially when used in combination with other cholesterol lowering drugs.
- They reduce the risk of coronary events and mortality in patients with ischemic heart disease, and they also reduce the risk of ischemic stroke.

- Rosuvastatin, atorvastatin, and simvastatin have greater maximal efficacy than the other statins while Fluvastatinhas less maximal efficacy
- ↓Triglycerides and ↑HDL cholesterol in patients with triglycerides levels that are higher than 250 mg/dL and with reduced HDL cholesterol levels.

Pharmacokinetics

- Lovastatin and simvastatin are prodrugs that are hydrolyzed in the gastrointestinal tract to the active derivatives
- Pravastatin, Atorvastatin, fluvastatina nd rosuvastatinare active as given
- Absorption varies from 40% to 75% but Fluvastatinc ompletely absorbed.
- ✓ All statins are metabolized in the liver, with some metabolites retaining activity.
- Excretion takes place principally through bile and feces, but some urinary elimination also occurs
- 5–20% is excreted in the urine.
- Plasma Half livesof these drugs range from 1 to 3 hours, atorvastatin (14 hours), pitavastatin(12 hours) and rosuvastatin(19 hours).

➢Because of a circadian rhythm to LDL-receptor synthesis& the cholesterol synthesis also occurs predominantly at night, reductase inhibitors-except atorvastatin and rosuvastatin-should be given in the evening if a single daily dose is used.

Adverse Effect of Statins

✓Transient, and minor abnormality of liver function tests(Mild elevations of serum amino transferases)

✓Increase in creatine kinase (released from skeletal muscle) in 10% of patients

✓Myopathy and rhabdomyolysis (disintegration or dissolution of muscle and elevation of muscle enzymes (creatine kinase, CPK)

NOTE: In patients with renal insufficiency, Plasma creatinekinase levels should be determined regularly.

Drug Interactions:

❖The HMG CoAreductase inhibitors are metabolized by the cytochrome P450 system; drugs or foods (eg, grapefruit juice) that inhibit cytochrome P450 activity increase the risk of hepatotoxicity and myopathy.

❖The HMG CoA reductase inhibitors may also increase warfarin levels. Thus, it is important to evaluate INR

❖Cyclosporine, itraconazole, erythromycin and gemfibrozil or niacin. Plasma creatinekinase levels should be determined regularly in patients taking drugs.

Contraindications

- Pregnancy (teratogenic)
- Nursing mothers.
- Children or teenagers

Thank You