UNIT II
ANTIANGINAL DRUGS

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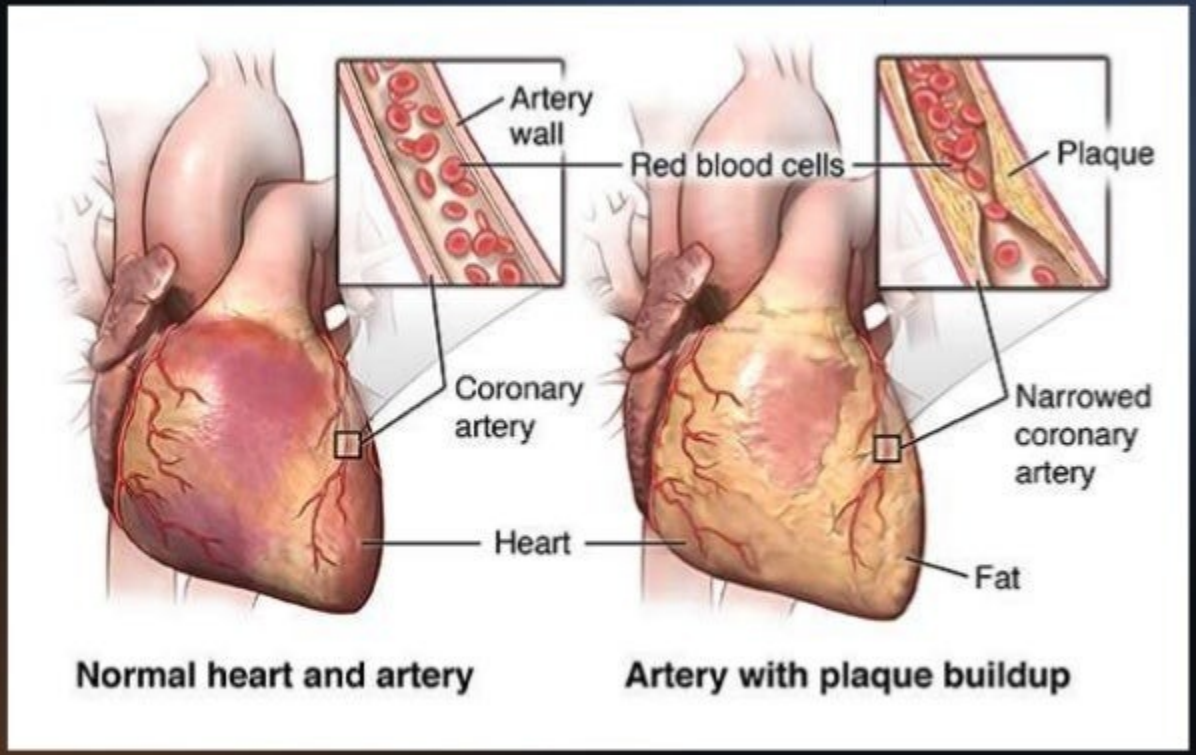
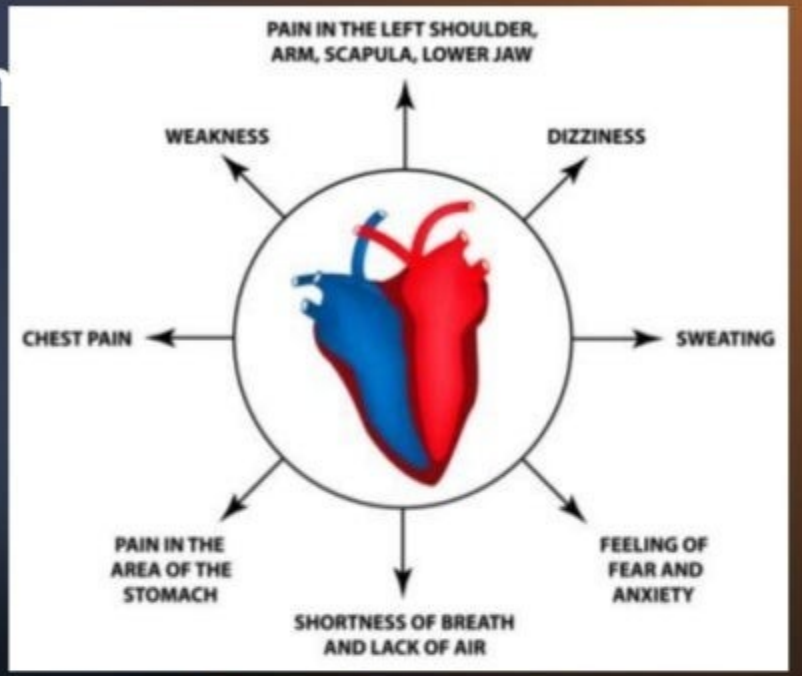
Angina pectoris

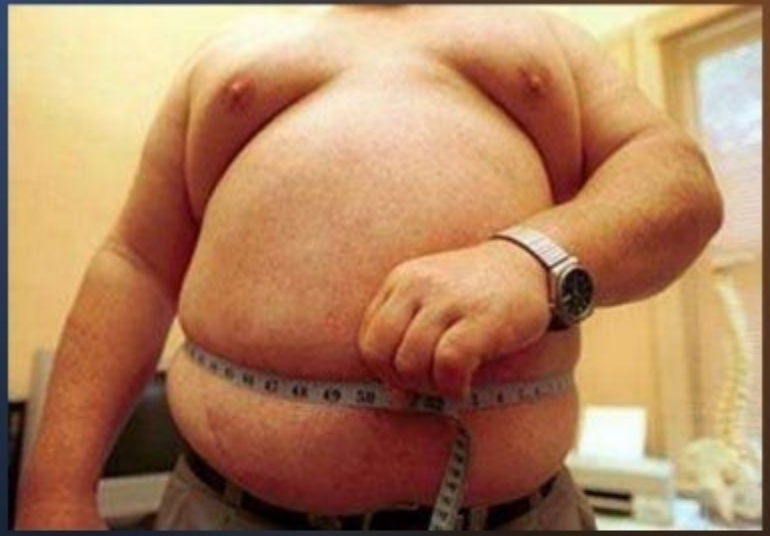
- Angina pectoris is a clinical manifestation that results from coronary atherosclerotic heart disease.
- An acute anginal attack (secondary angina) is thought to occur because of an imbalance between myocardial oxygen supply and demand owing to the inability of coronary blood flow to increase in proportion to increases in myocardial oxygen requirements.
- Angina pectoris (variant, primary angina) may also occur as a result of vasospasm of large epicardial coronary vessels or one of their major branches.
- In addition, angina in certain patients may result from a combination of coronary vasoconstriction, platelet aggregation, plaque rupture, and an increase in myocardial oxygen demand (unstable angina).

Angina pectoris: Causes & Symptom





Risk Factors:



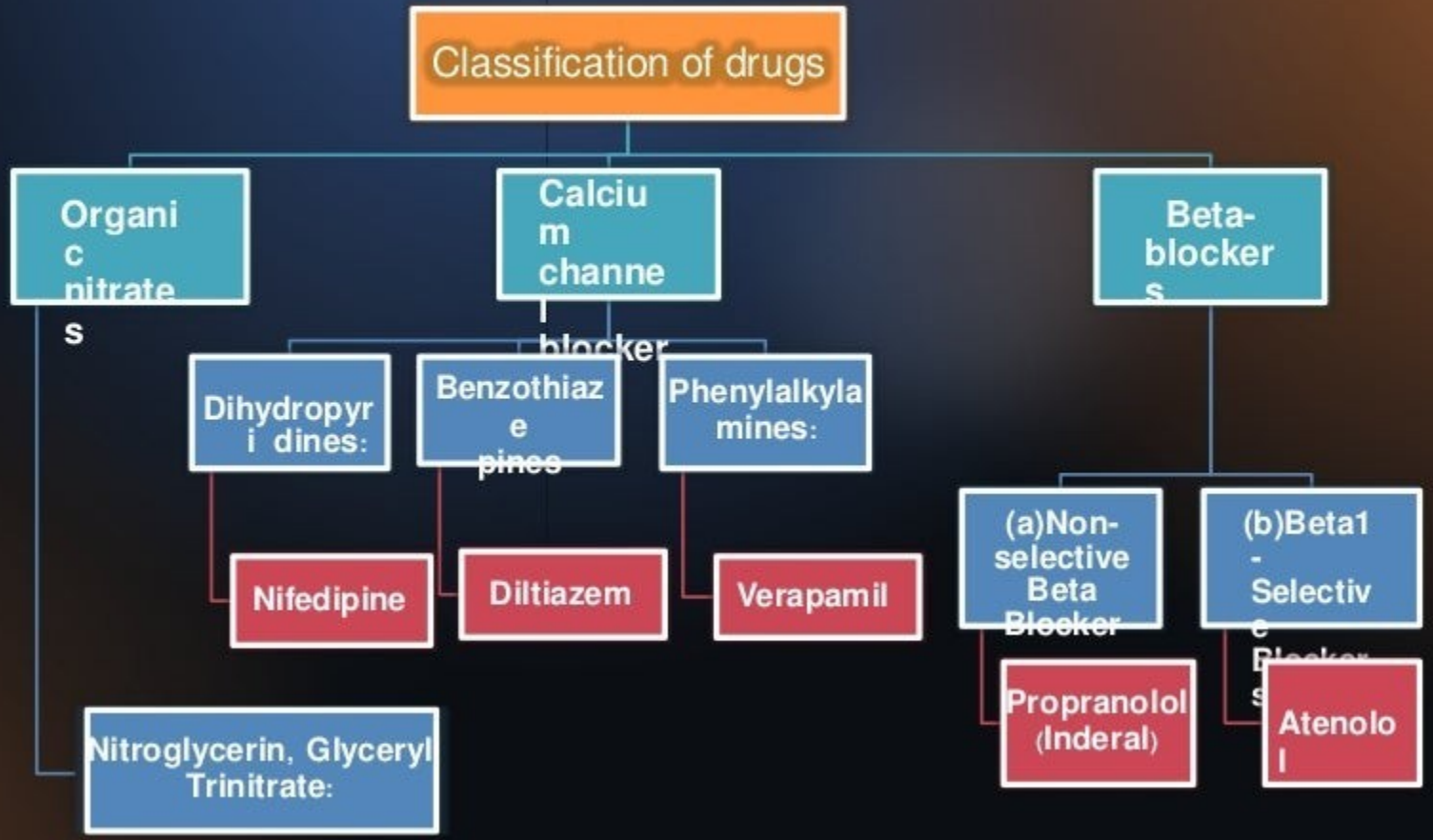

Classification of drugs
Organic nitrates
Calcium channel blocker
Beta-blockers
Dihydropyridines:
Benzothiazepines
Phenylalkylamines:
Nifedipine
Diltiazem
Verapamil
Nitroglycerin, Glyceryl Trinitrate:
(a)Non-selective Beta Blocker
(b)Beta1-Selective Blockers
Propranolol (Inderal)
Atenolol

Table 16.1 Pharmacological Summary of Drugs Used to Treat IHD

Drug Class		Drug Name	Mechanism of Action	Primary Site of Action	Pharmacological Effect	IHD Effect
Organic Nitrates		Nitroglycerin, isosorbide dinitrate, isosorbide mononitrate	NO donor	Arteries, veins, and coronary arteries	Decrease preload and afterload	Decrease workload and increase blood supply
CCBs	Dihydropyridine CCBs	Amlodipine, nifedipine, nicardipine, etc.	L-type Ca^{2+} channel	Arteries and coronary arteries	Decrease afterload	Decrease workload and increase blood supply
	Nondihydropyridine CCBs	Verapamil, diltiazem	L-type Ca^{2+} channel	Arteries, heart and coronary arteries	Decreases heart rate and afterload	Decrease workload and increase blood supply

Table 16.1 Pharmacological Summary of Drugs Used to Treat IHD

β-blockers	Selective β_1-blockers	Metoprolol, atenolol, etc.	Selective β_1-adrenergic receptor antagonist	Heart	Decreases heart rate and myocardial contractile force	Decrease workload
	Nonselective β-blockers	Propranolol, etc.	Nonselective β_1- and β_2-adrenergic receptor antagonist	Heart	Decreases heart rate and myocardial contractile force	Decrease workload
	Mixed α- and β-blockers	Carvedilol labetalol	Nonselective β_1-, β_2-, and α_1-adrenergic receptor antagonist	Heart, arteries, and veins	Decreases heart rate, myocardial contractile force, afterload, and preload	Decrease workload
Late Na^+ channel blocker		Ranolazine	Late Na^+ channel blocker	Heart	Prevents Ca^{2+} overload	Prevents worsening of ischemic effects
I_f channel antagonist		Ivabradine	I_f channel antagonist	Heart	Bradycardia	Decrease workload

Organic Nitrates & Nitrites:

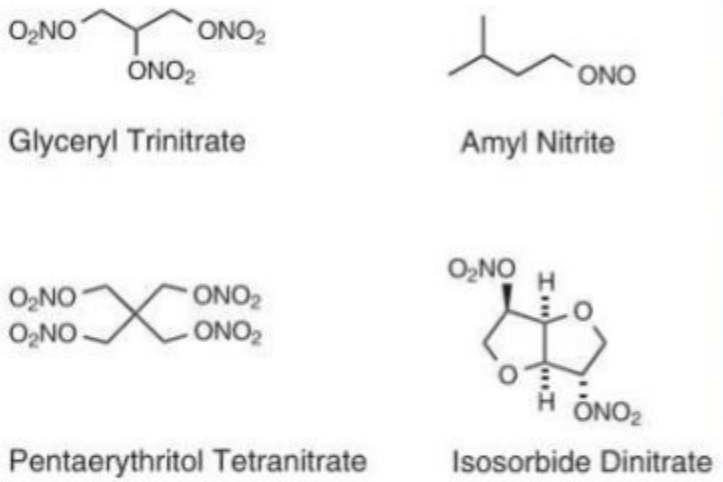


Figure 16.1 Organic nitrates and nitrites.

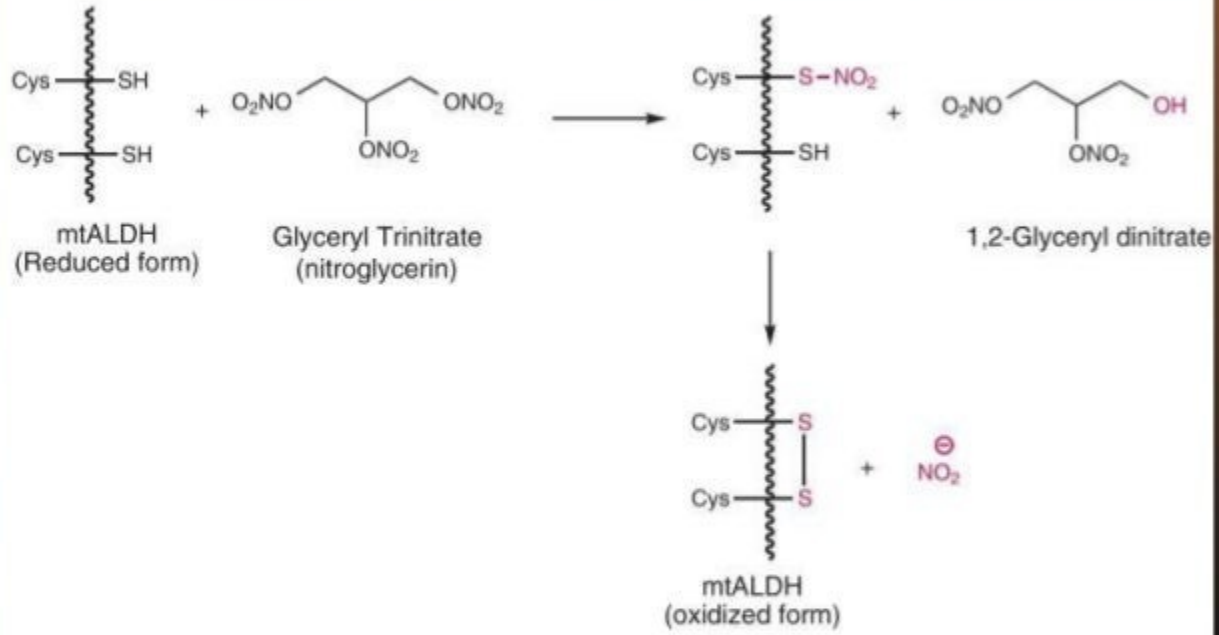
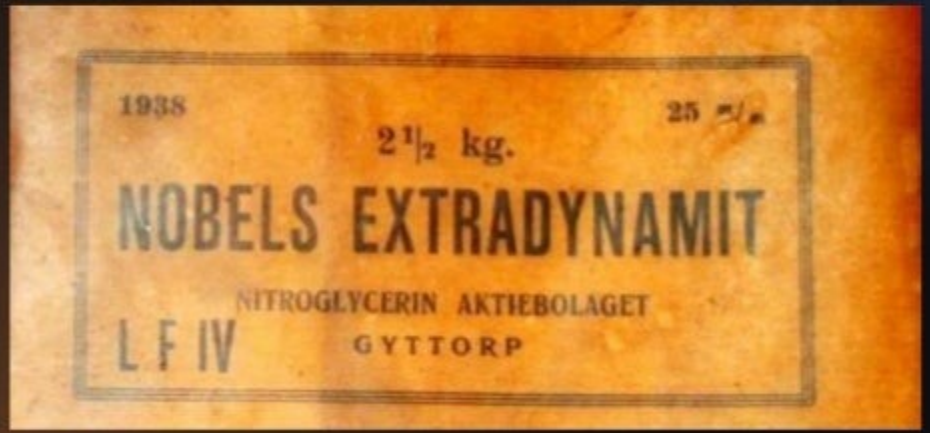


Figure 16.2 Activation of glyceryl trinitrate.

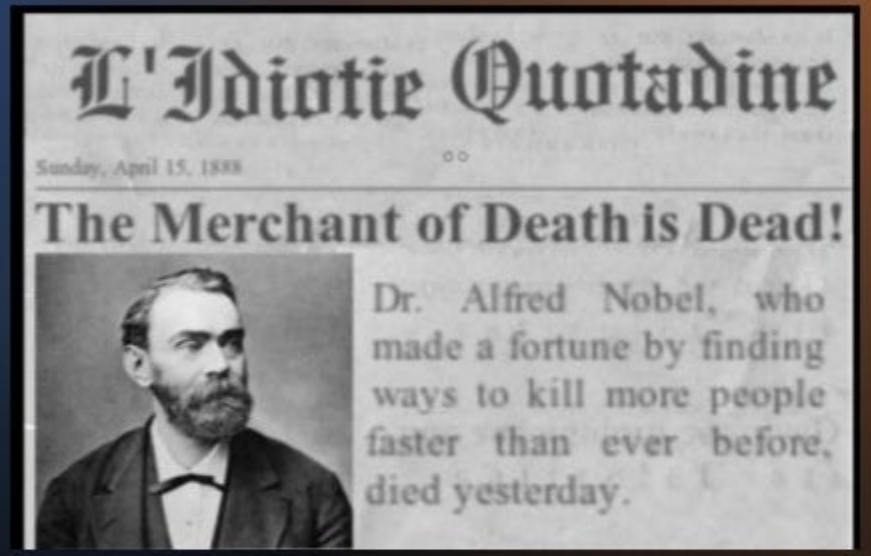
NTG is a prodrug. It is primarily bioactivated in smooth muscles by undergoing complex metabolic reactions and is converted to nitric oxide (NO) or a related compound S-nitrosothiol (SNO) intermediate.


1938
2½ kg.
NOBELS EXTRADYNAMIT
NITROGLYCERIN AKTIEBOLAGET
LF IV
GYTTORP


ALFR.
NOBEL
NAT
MDCCC
XXXIII
OB.
MDCCC
XCVI

History:

- Nitroglycerin (NTG) or glyceryl trinitrate is a synthetic molecule that was discovered by an Italian scientist Ascanio Sobrero in 1846 by reacting glycerol with the classical nitration mixture (nitric and sulfuric acid).
- He not only observed its uncontrolled explosive properties, but when tasted in small quantities, he noted its headache-causing properties.


L'Idiotie Quotadine

Sunday, April 15, 1888

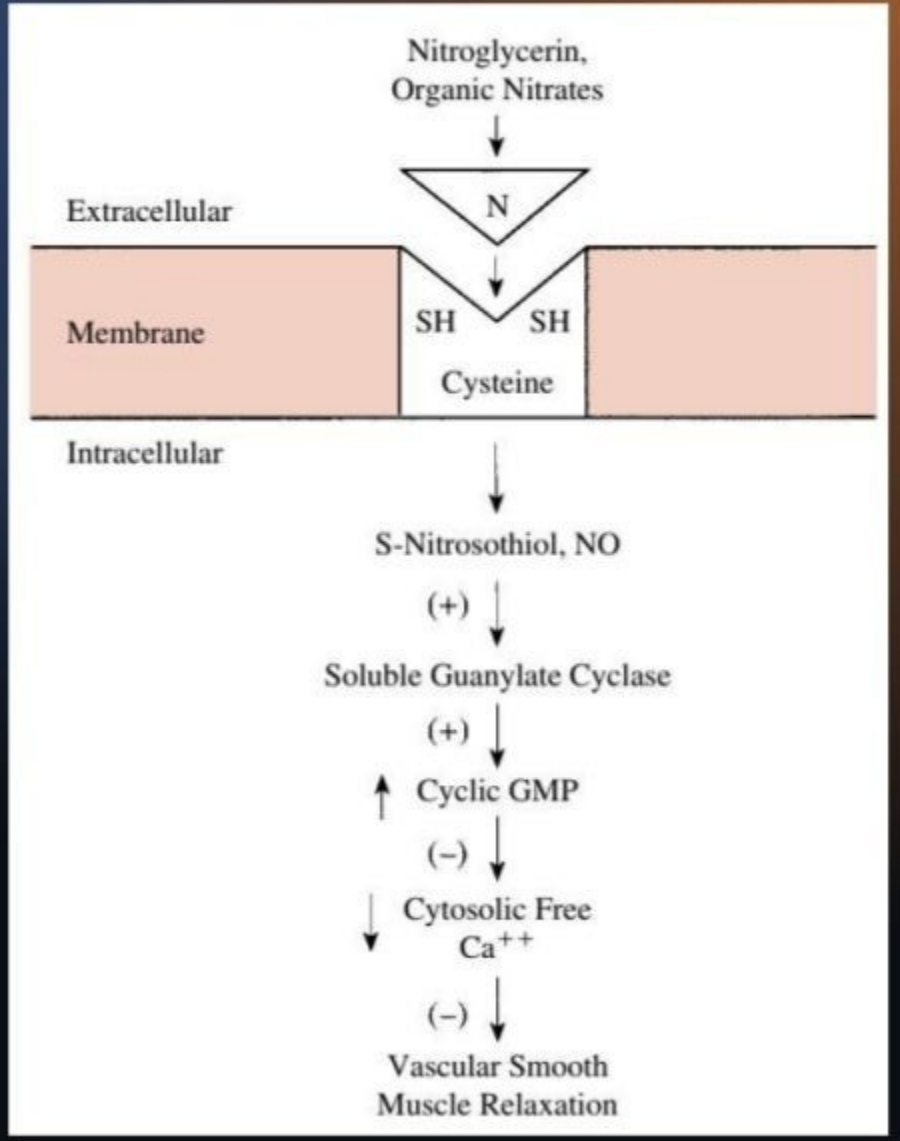
The Merchant of Death is Dead!

Dr. Alfred Nobel, who made a fortune by finding ways to kill more people faster than ever before, died yesterday.

- Subsequently, Alfred Nobel by combining NTG with kieselguhr developed dynamite, which is an explosive under controlled conditions.
- This has led to the success of the Nobel family and eventually much of his wealth was used in the establishment of the renowned Nobel Prize that has been awarded since 1901.

Mechanism of Action:

- The nitrate receptor possesses sulfhydryl groups, which reduce nitrate to inorganic nitrite and nitric oxide (NO).
- The formation of nitrosothiols, and possibly free NO, has been proposed to stimulate intracellular soluble guanylate cyclase, which leads to an increase in intracellular cyclic guanosine monophosphate (GMP) formation.
- The increase in GMP results in vascular smooth muscle relaxation, possibly through inhibition of calcium entry via L-type calcium channels, decreased calcium release from the sarcoplasmic reticulum, or via an increase in calcium extrusion via a sarcolemmal Ca^{2+}-adenosine triphosphatase (ATPase).



Chemistry of Calcium Channel Blockers

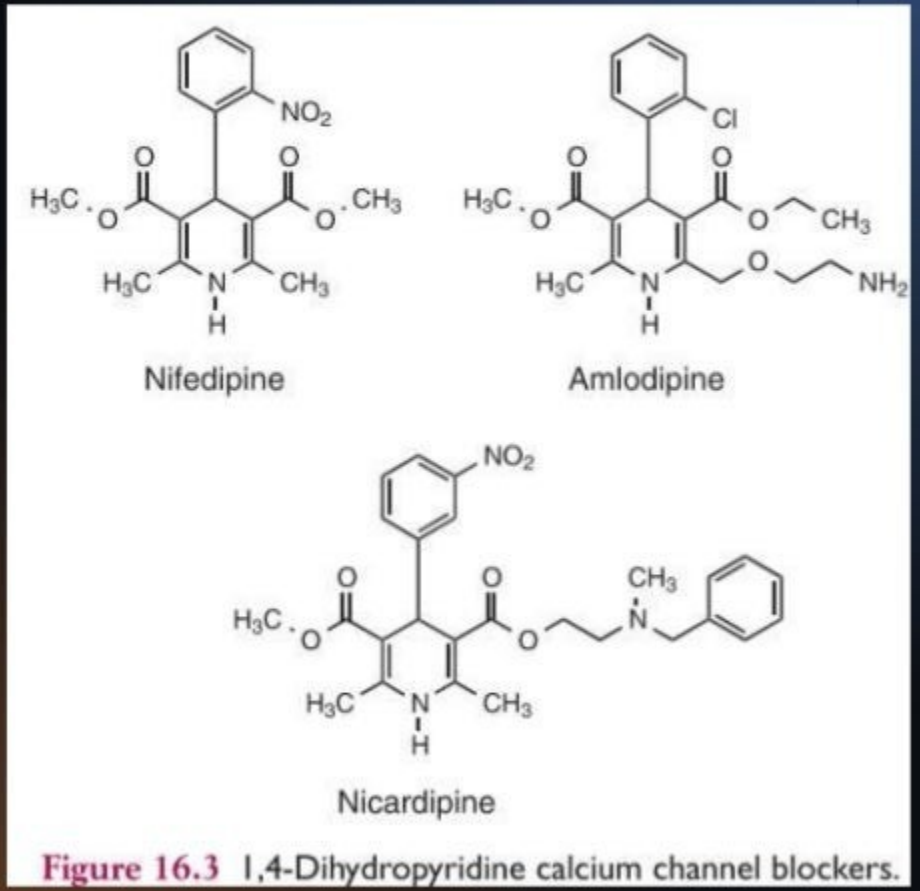


Figure 16.3 1,4-Dihydropyridine calcium channel blockers.

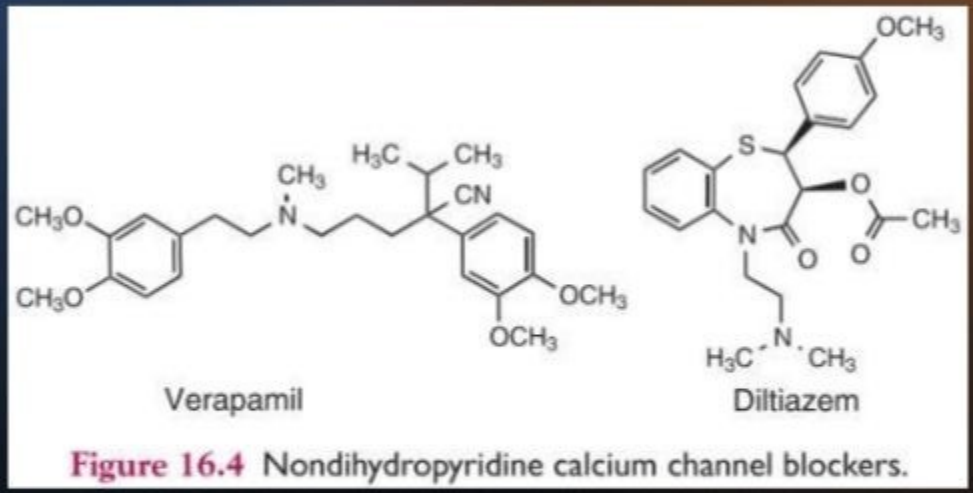


Figure 16.4 Nondihydropyridine calcium channel blockers.

1,4-DIHYDROPYRIDINES:

- Nifedipine is the prototype molecule in the 1,4-DHP class of calcium channel blocker and was discovered in the early 1970s.
- Nifedipine is a symmetrical 1,4-DHP in which both esters (methyl ester) at C-3 and C-5, as well as substitutions at C-2 and C-6 (methyl group), are identical.
- Nifedipine is light sensitive and undergoes decomposition into a pyridine analog and a nitroso pyridine analog.

Nifedipine

- The replacement of the 1,4-DHP ring with other rings leads to compounds with reduced or loss of activity indicating the importance of the ring for optimal activity.
- The 1,4-DHP ring adopts a boat confirmation. The hydrogen attached to the nitrogen in the 1,4 DHP ring forms hydrogen bonding with tyrosine in the receptor.
- Replacement of the hydrogen with other groups and oxidation of the nitrogen is detrimental for its activity.

1,4-DIHYDROPYRIDINES:

- The presence of C-3 and C-5 ester groups on the 1,4-DHP ring is required for optimal activity.
- The C-4 is attached to an ortho and/or meta electron-withdrawing phenyl ring.
- The ortho and/or meta derivatives are considered to be critical for activity because they lock the phenyl ring perpendicular to the 1,4-DHP ring.
- Nifedipine contains an ortho-nitrophenyl group, amlodipine contains an ortho-chlorophenyl group, and nicardipine contains a meta-nitrophenyl group.
- Amlodipine has an amino-ethoxy methyl side chain, and nicardipine has an N-benzyl-N-methylamino side chain, at physiological pH, it exist as ionized forms.

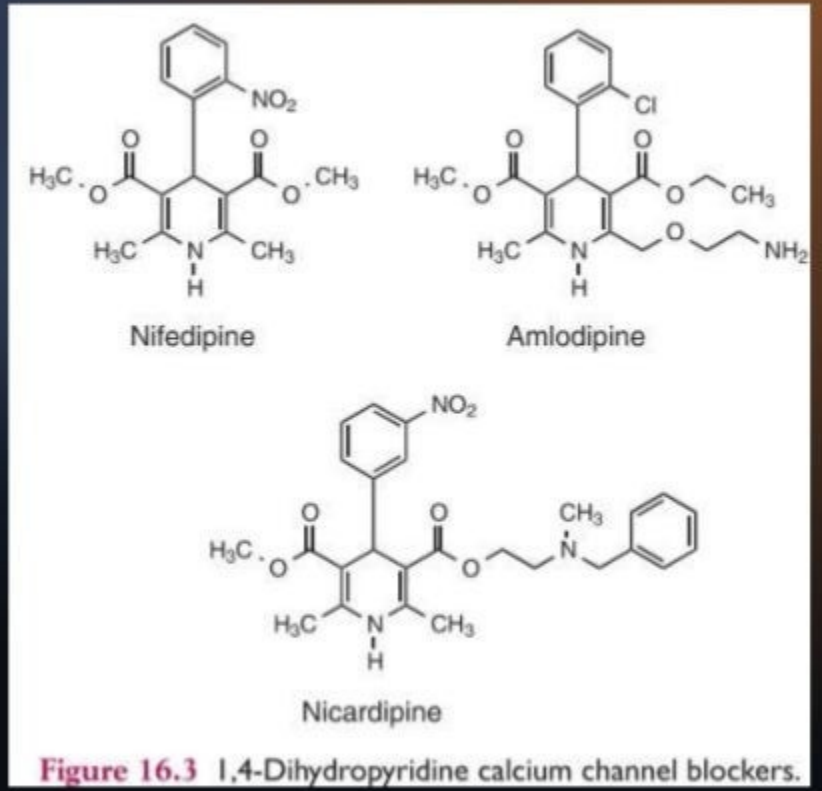


Figure 16.3 1,4-Dihydropyridine calcium channel blockers.

NONDIHYDROPYRIDINES:

- Verapamil contains a basic tertiary nitrogen and is marketed as the hydrochloride salt.
- It contains one chiral center, but it is administered as a racemic mixture of S-enantiomer and R-enantiomer.
- The S(-)-isomer of verapamil is about 10-20 times more potent than the R(+)-isomer as a vasodilator.
- However, the R-isomer is less cardiotoxic than the S-isomer.

- The clinically available diltiazem is a (+)-cis isomer and has two chiral centers 2S, 3S configuration. The (-)-cis enantiomer 2R, 3R does not have vasodilatory properties.
- The Trans diastereomers (ZR, 3S and 2S, 3R) have weak activity. Therefore, stereochemistry has an absolute impact on the pharmacological activity of diltiazem.

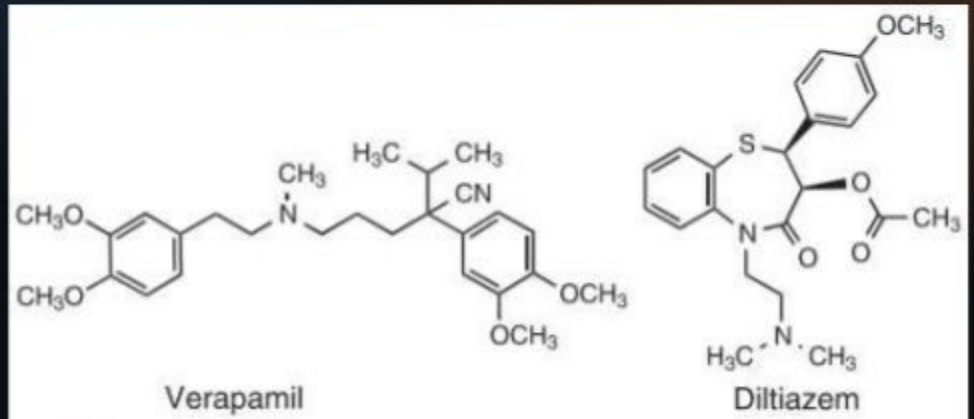
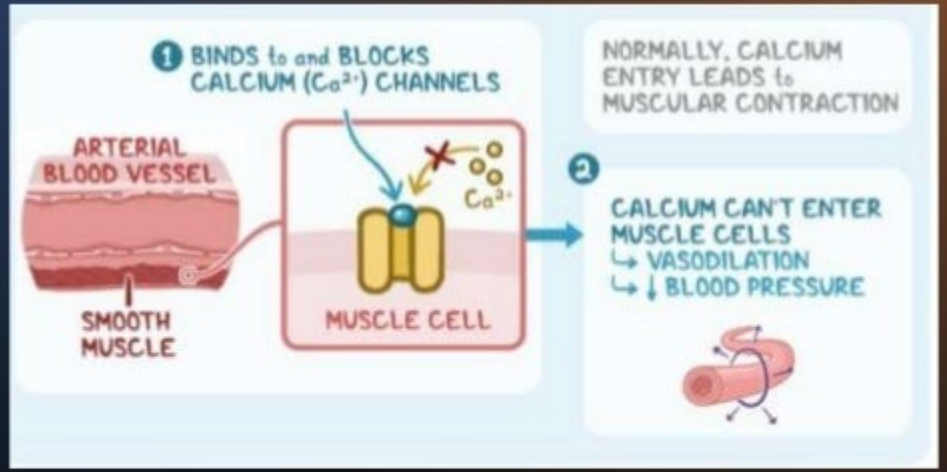
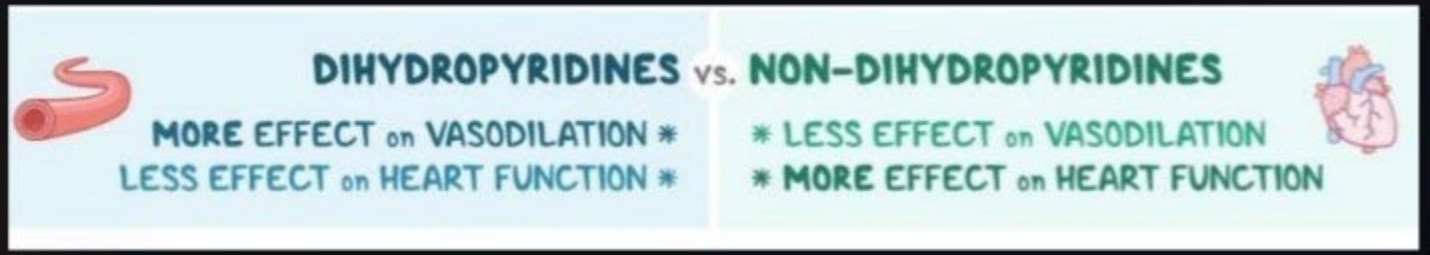


Figure 16.4 Nondihydropyridine calcium channel blockers.

Mechanism of Action: CCBs

- Both dihydropyridines & Non-dihydropyridine analogues have affinity for the L-type Ca^{2+} channels that are present in the arterial smooth muscle, and they block/prevent the influx of Ca^{2+} into the smooth muscle, thereby relaxing vascular smooth muscle.
- Therefore, CCBs decrease afterload and consequently the workload of the heart.
- These drugs are also believed to produce coronary vasodilation which may increase the supply of oxygenated blood or decrease the quivering associated with variant angina.

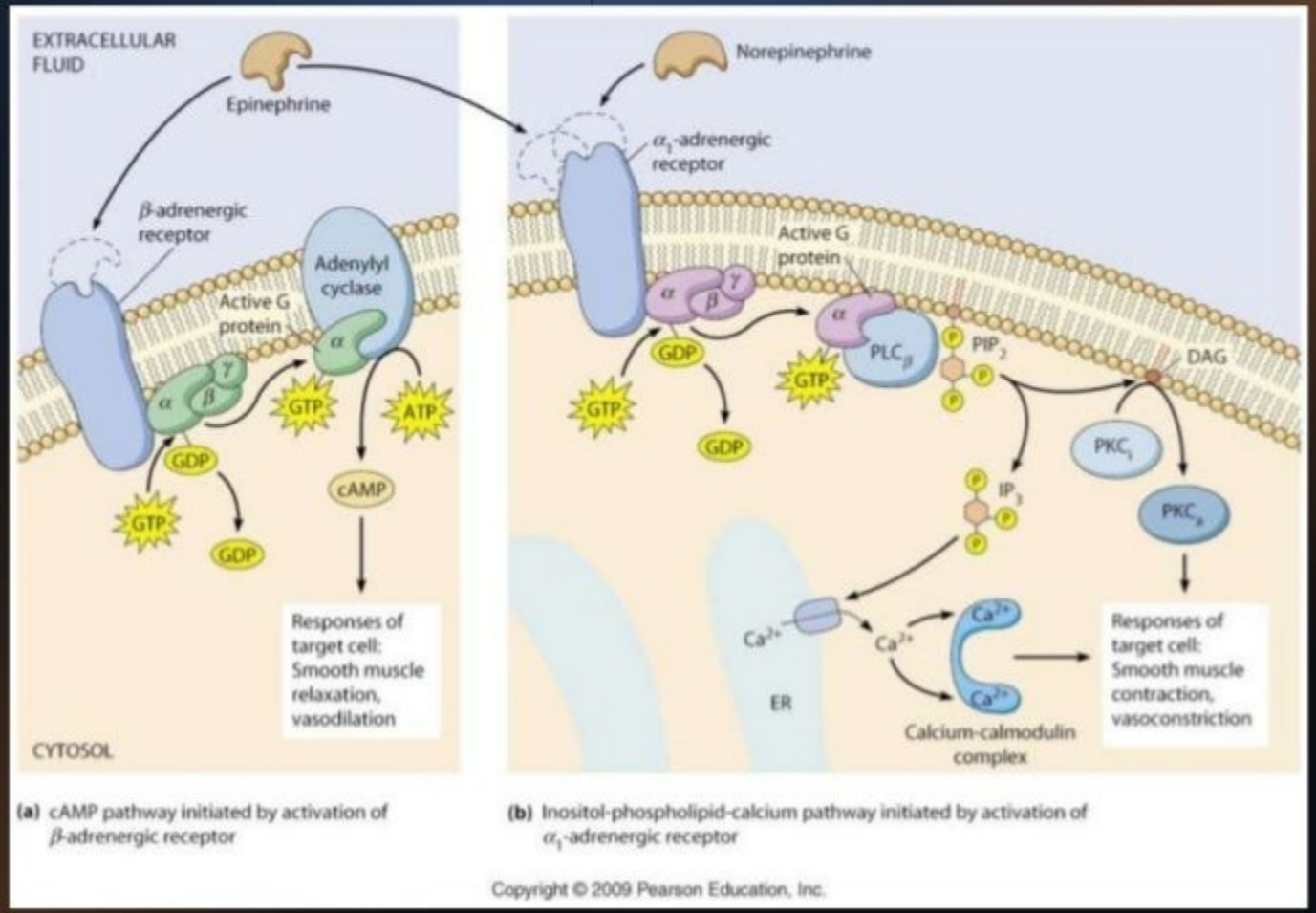




Molecular Mechanism:

- https://www.rcsb.org/3d-view/6JP5?preset=ligandInteraction&sele=C5U
- https://www.rcsb.org/3d-view/6JPA?preset=ligandInteraction&sele=4YH

β-Adrenergic Receptors:



(a) cAMP pathway initiated by activation of β-adrenergic receptor

(b) Inositol-phospholipid-calcium pathway initiated by activation of α_1-adrenergic receptor

Receptor	G protein	Second messenger	Major tissues	Effect
α_1	G_q	IP_3/DAG	Vascular smooth muscle Sphincters[a]	Contraction
α_2	G_i	↓ cAMP	Adrenergic terminals (presynaptic)	↓ NA release
β_1	G_s	↑ cAMP	Cardiac muscle	↑ Force of contraction ↑ Rate
β_2	G_s	↑ cAMP	Airway smooth muscle	Relaxation
			Gut smooth muscle[b]	
			Liver	Gluconeogenesis Glycogenolysis
β_3	G_s	↑ cAMP	Fat cells	Lipolysis
M_1	G_q	IP_3/DAG	Autonomic ganglia	Close K_M channels
M_2	G_i and G_o	↓ cAMP	Cardiac muscle	↓ Rate
		opens K^+ channels	Sphincters[a]	Relaxation
			Gut smooth muscle[b]	Contraction
			Airway smooth muscle	
M_3	G_q	IP_3/DAG	Exocrine glands	↑ Secretion
			Endothelium	NO release

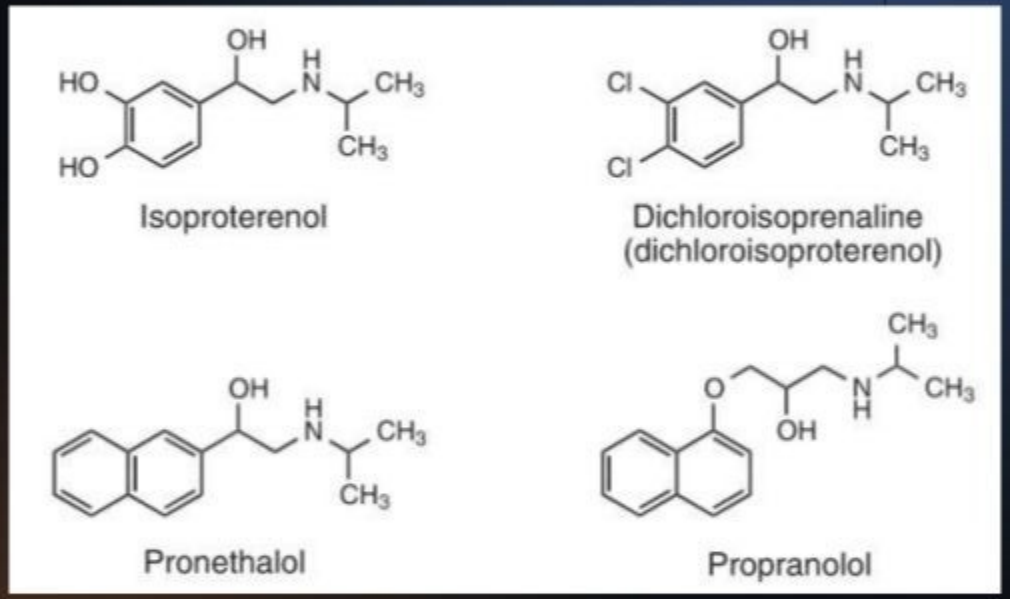
β-Blockers

- β-blockers are one of the oldest and most widely prescribed medications used to treat several types of cardiovascular diseases.
- At normal therapeutic doses, cardio selective β-blockers such as atenolol, metoprolol, bisoprolol, and nebivolol are more selective toward the β_1-adrenergic receptor subtype.
- Other drugs like propranolol antagonize both β_1- and β_2-adrenergic receptors.
- Drugs like carvedilol and labetalol are mixed adrenergic antagonists that not only block β_1- and β_2-receptors but also block α_1-adrenergic receptors.
- In addition, some research suggest that certain β-blockers can produce antioxidant effects, improve NO release, and act as partial agonists at the β2-adrenergic receptors.

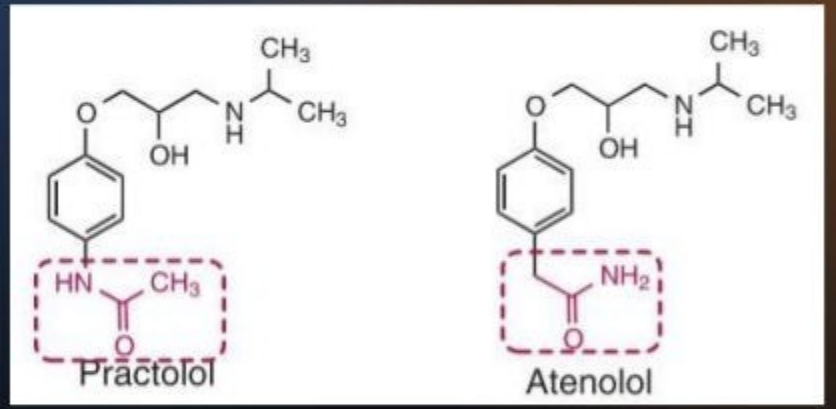
β-Blockers

- β_1-receptors are one of the major receptors expressed in the heart that are involved in its function.
- Because all β-blockers have affinity for the β_1-receptor, this class of drugs inhibit the binding of norepinephrine and epinephrine causing slow heart rate and decreased myocardium contractile force and myocardium rate of relaxation.
- As such, β_1-blockers are utilized in IHD to decrease the workload of the heart.
- β_1-receptors are also present in the juxtaglomerular cells of the kidney and activation of these receptors can produce an increase in renin secretion. Renin is the rate-limiting enzyme involved in the production of angiotensin II, a powerful vasoconstrictor.
- Thus, β-blockers may decrease the secretion of renin, which would decrease plasma levels of angiotensin II and potentially decrease preload and afterload

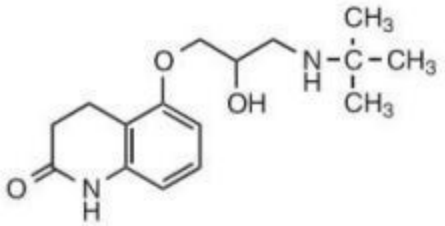
β-Blockers



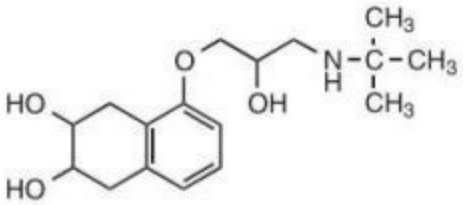
Development of β-adrenergic antagonists



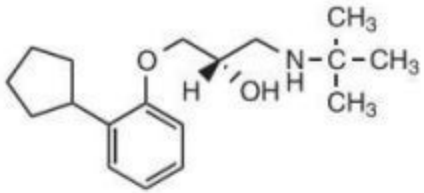
Development of selective β_1 adrenergic antagonists



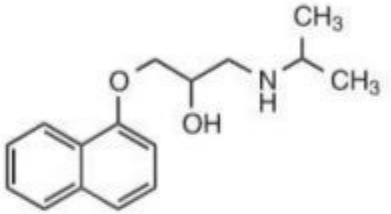
Carteolol



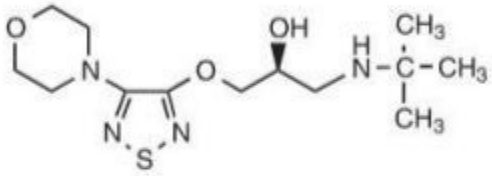
Nadolol



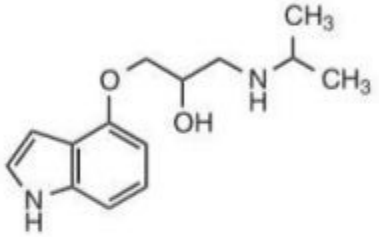
Penbutolol



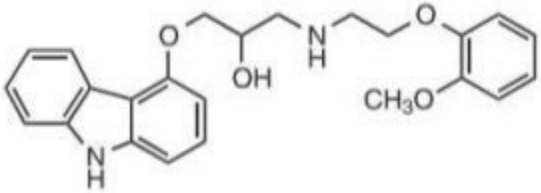
Propranolol



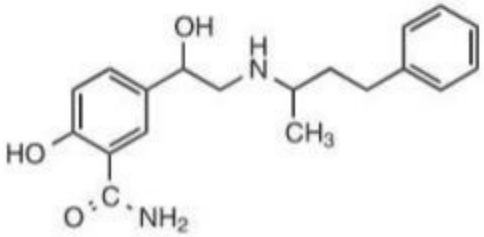
Timolol



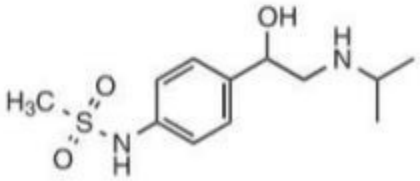
Pindolol



Carvedilol

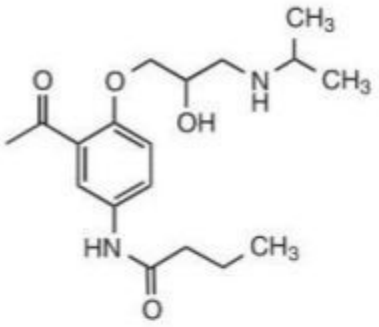


Labetalol

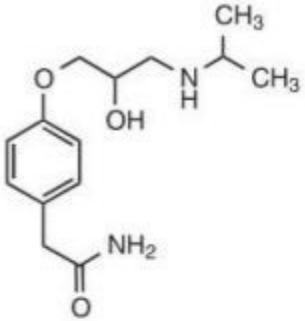


Sotalol

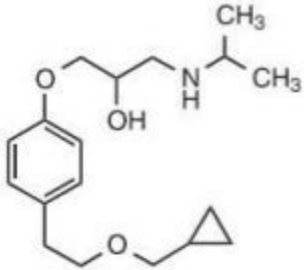
Nonselective β-adrenergic antagonists



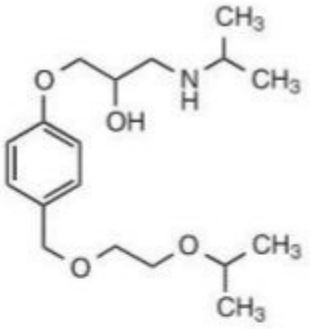
Acebutolol



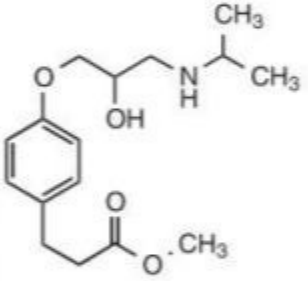
Atenolol



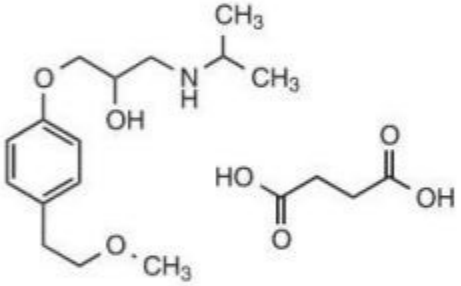
Betaxolol



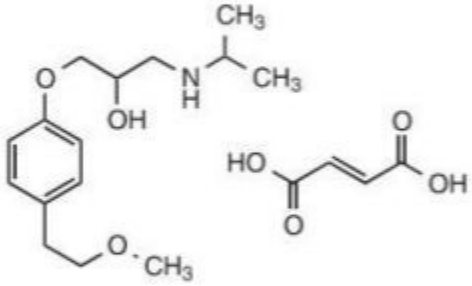
Bisoprolol



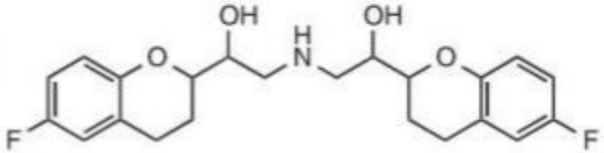
Esmolol



Metoprolol succinate



Metoprolol fumarate



Nebivolol

Selective β_1 adrenergic antagonists

Structural Properties Of β-blockers.

1. At least one aromatic and/or heteroaromatic ring system. They are devoid of catechol functional groups.
2. The aromatic/heteroaromatic ring is in tum attached to an alkyl side chain containing a chiral secondary hydroxyl group and an amine. The amine group is either attached to an isopropyl or a tertiary butyl group with few exceptions.
3. Many of the P-blockers are aryloxypropanolamine derivatives. Exceptions include sotalol, which is an arylethanolamine derivative containing a sulfon, amide group at the para position.
4. Majority of the clinically available selective β_1-blockers are phenyloxypropanolamine derivatives containing substitutions at the para position.
5. Due to the presence of oxymethylene ($-OCH_2$) group in aryloxypropanolamine, the S-enantiomer of aryloxypropanolamine side chain occupy similar space in the P-receptor as the R-enantiomer side chain of arylethanolamine. In general, in p-blockers with one chiral center, the S(-)-enantiomer has better β-receptor binding affinity than the R(+)-enantiomer.
6. Majority of β–blockers are clinically administered as a racemic mixture. Exceptions include timolol which is only available as S(-)-timolol.

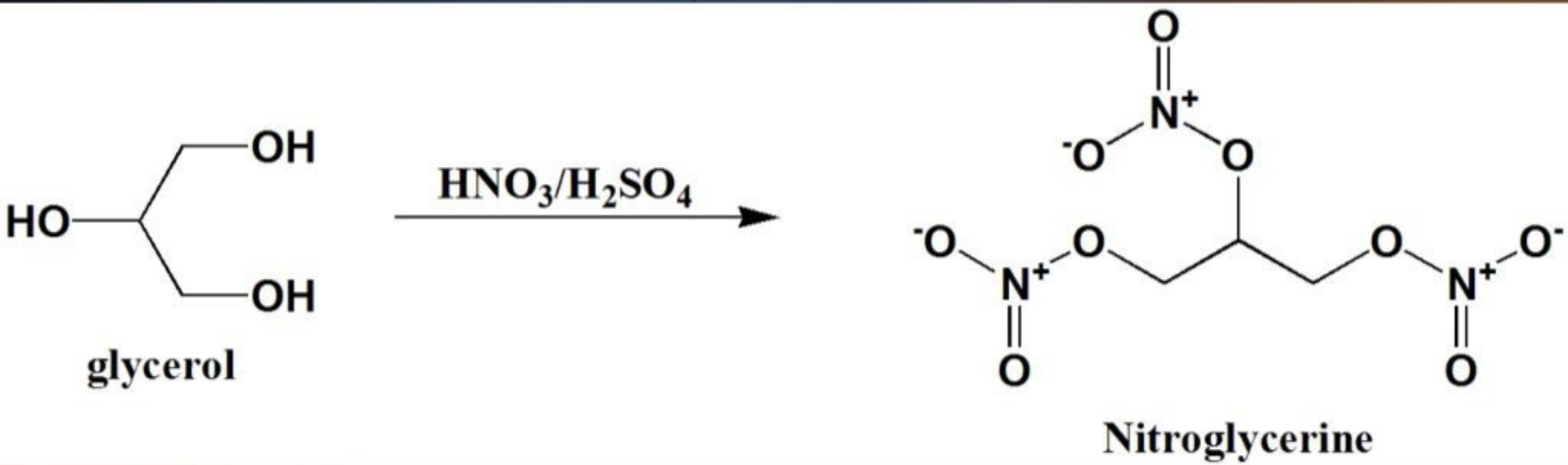
β-Blockers

- β-blockers based on their partition coefficient can be classified into lipophilic and hydrophilic β-blockers.
- This may account for the pharmacokinetic differences between β-blockers.
- For example, a lipophilic β-blocker such as propranolol has a higher partition coefficient (Log = 2.65; cLogP = 2.75) because of the hydrocarbon naphthyl ring system, and as a result, it has a greater ability to penetrate the BBB.
- To the contrary, hydrophilic β-blockers such as atenolol containing a polar acetamide group (LogP = 0.5; clogP = -0.1) are less likely to cross the CNS.
- Lipophilic β-blockers undergo extensive hepatic metabolism leading to shorter half-lives than the hydrophilic β-blockers which are minimally metabolized by the liver.

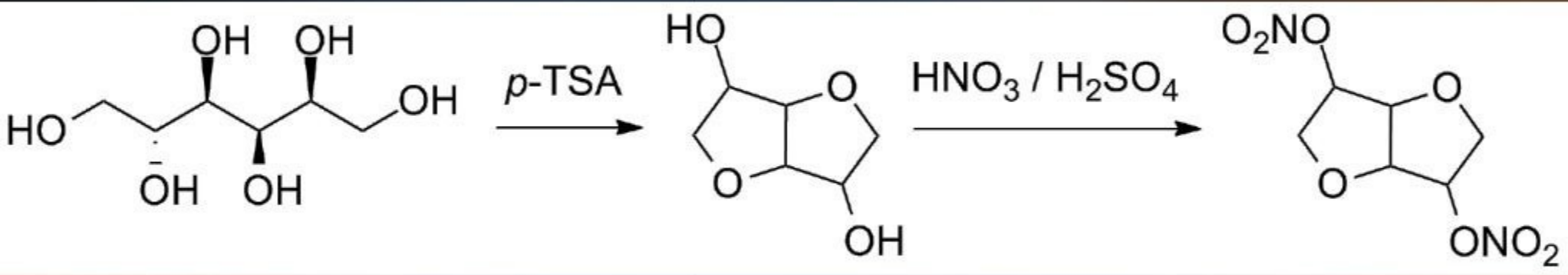
ADVERSE EFFECTS

- Include atrioventricular blockade, bradycardia, hypotension, gastrointestinal disturbances, and pruritic rash.
- Pulmonary side effects such as bronchitis and bronchospasm are associated with all β-blockers. However, cardiovascular selectivity may be achieved with small doses of selective β_1-blockers.
- Nonselective β-blockers are contraindicated in patients with a history of reactive airway disease, e.g., asthma.
- Lipophilic β-blockers have a greater ability to cause CNS disturbances such as insomnia, dreams, hallucinations, and depression.
- Some of the β-blockers may cause a rare oculomucocutaneous reaction. β_2-adrenergic receptors play a significant role in insulin release and gluconeogenesis.
- Nonselective β-blockers are also contraindicated in patients with insulin-dependent (type-1) diabetes.
- Nonselective β-blockers can slow down the recovery of insulin-induced hypoglycemia and block/mask most of these signs of hypoglycemia with the exception of sweating.
- Patients should also avoid sudden discontinuation of β-blockers because of the risk for hypertensive crises caused by the receptor upregulation

Synthesis of Nitroglycerin:



Synthesis of Isosorbide dinitrate



Hexane-1,2,3,4,5,6-hexanol

Isosorbide

UNIT II

DIURETICS

Ms.M.M.Patil

(Assit.Professor)

JES college of pharmacy.Nandurbar

Objectives of today's Lecture

After completion of this lecture you will be able to know

- Diuretics
  - Definition
  - Classification
  - Names of members in classes
  - Mechanism of action
  - Major indications
  - Major side effects and Precautions
  - Major drug interactions
  - MCQs related to Diuretics

Facts of Renal Physiology

- **Kidney-**
  - Weight- 0.5% of Body,
  - Receive 25% of cardiac output (50 times)
- **Kidney functions**
  - **B**alance of electrolytes, Plasma volume, Acid Base
  - **A**ctivation of Vitamin D
  - **S**ynthesis of Erythropoietin, Urokinase
  - **E**xcretion of Urea, Uric acid, Creatinine etc.
- **Transport types**
  - ***Passive***
    - Simple, channel mediated and facilitated diffusion, solvent drag
  - ***Active***
    - Primary and Secondary (Symports and Secondary Counter transport)

Facts related to Renal Physiology

- **Pressure difference** at Bowman's Capsule- 20mm Hg
- **Filter**= Plasma-Proteins
- **Volume** of
  - Filter- 180 liters
  - Urine- 1.5 liters (1%)
- **Kidneys**
  - Renal Blood Flow- 1200ml/min
  - Renal Plasma Flow- 650 ml/min
  - GFR- 120 ml/min
  - Reabsorb – Sodium, Chloride and Bicarbonates >99% While Potassium about 85%

Terminology

Natriuresis- increased sodium excretion
Kaliuresis- Increased Potassium excretion
Diuretics- Drugs which cause a net loss of Na^+ and water in urine. (Exception- Osmotic diuretics (Mannitol) don't cause natriuresis but produce diuresis

Proximal Tubule

- **Leaky**- Freely permeable to water, solutes

- Active absorption of
  - Sodium Chloride,
  - Sodium Bicarbonate
  - Glucose
  - Amino Acids
  - Organic Solutes
    - **Followed by passive absorption of water**

Loop Of Henle

- **Descending limb-**
  - Permeable to water
- **Thick ascending limb –**
  - Impermeable to water but
  - Permeable to sodium by **$Na^+K^+2Cl^-$ Co transport**
  - About **25%** of filtered sodium is absorbed here

Macula Densa and Juxtaglomerular Apparatus

- Contact between Ascending limb with afferent arterioles – by specialized columnar epithelial cells **Macula Densa**
- Macula Densa sense NaCl conc. in filtrate
- Give signal to **J.G. Cells** present in afferent arterioles
- J.G. Cells of afferent arterioles secrete Renin

RAAS in response to low BP, or Low Na

Renin-

- **Angiotensinogen - Angiotensin I**

ACE-

- **Angiotensin II-**
- **Sympathetic, Aldosterone**

Vasoconstriction, Sodium and water retention,

Early Distal Tubule

- Active transport of sodium by **NaCl symport**
- Calcium excretion is regulated (Parathomone and Calcitriol, increase absorption of calcium)

Nephron parts and their functions

SEGMENT	FUNCTION
Glomerulus	Formation of glomerular filtrate
Proximal convoluted tubule (PCT)	Reabsorption of 65% of filtered Na+/K+/ Ca2+, and Mg2+; 85% of $NaHCO_3$, (activity of Carbonic an-hydrase enzyme) and nearly, 100% of glucose and amino acids. Iso-osmotic reabsorption of water., Secretion and reabsorption of organic acids and bases, including uric acid and most diuretics
Thin descending limb of Henle's loop	Passive reabsorption of water
Thick ascending limb of Henle's loop (TAL)	Active reabsorption of 25% of filtered $Na^+/K^+/2Cl^-$; secondary re-absorption of Ca2+ and Mg2+
Distal convoluted tubule (DCT)	Active reabsorption of 4–8% of filtered Na^+ Cl^-; Ca2+ reabsorption under parathyroid hormone control
Cortical collecting tubule (CCT)	Na+ reabsorption (2–5%) coupled to K+ and H+ secretion (under Aldosterone)
Medullary collecting duct	Water reabsorption under Vasopressin control

The relative magnitudes of Na+ reabsorption at sites

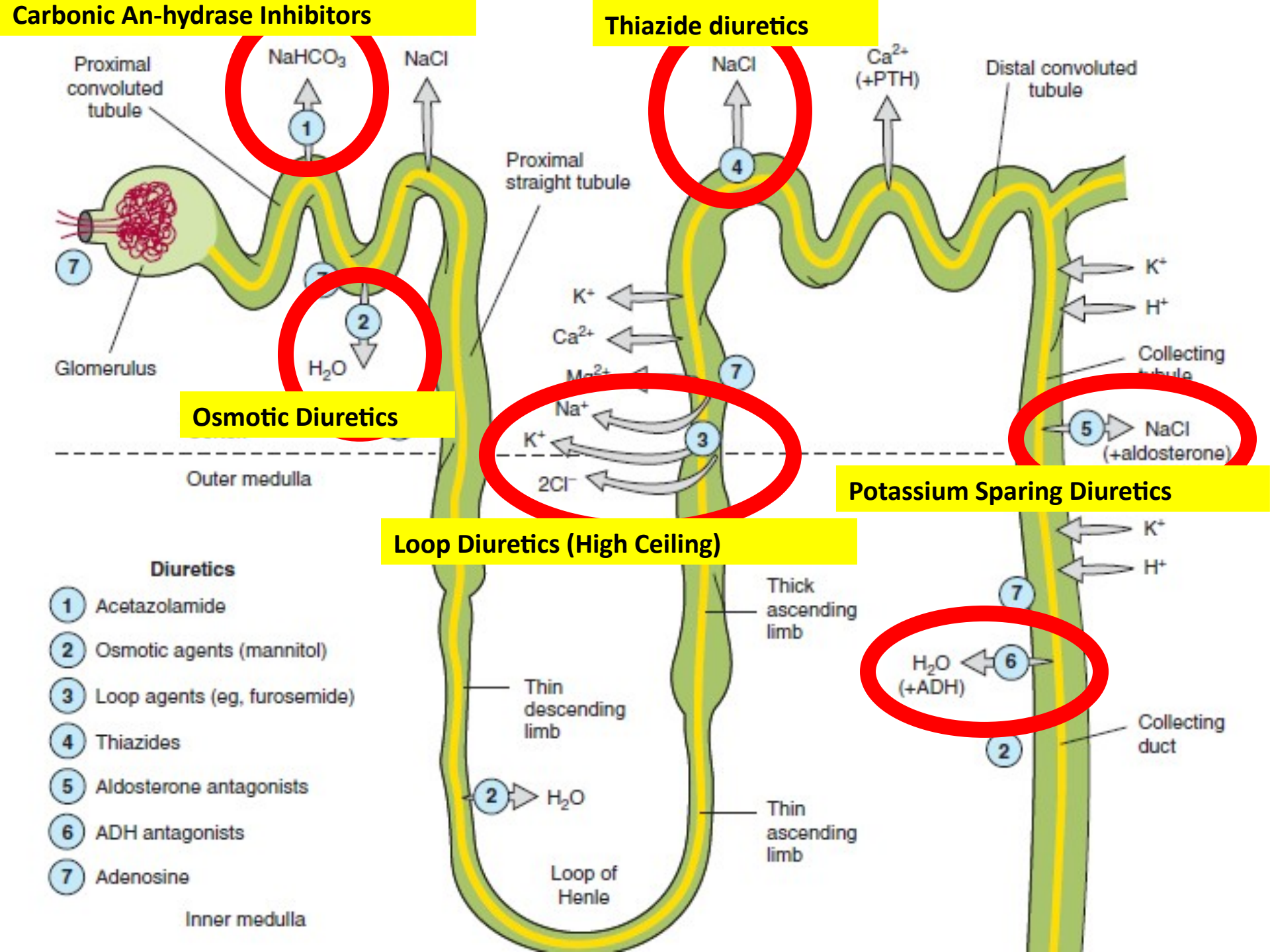
- PT - 65%
- **Asc LH - 25%**
- DT - 9%
- CD - 1%.

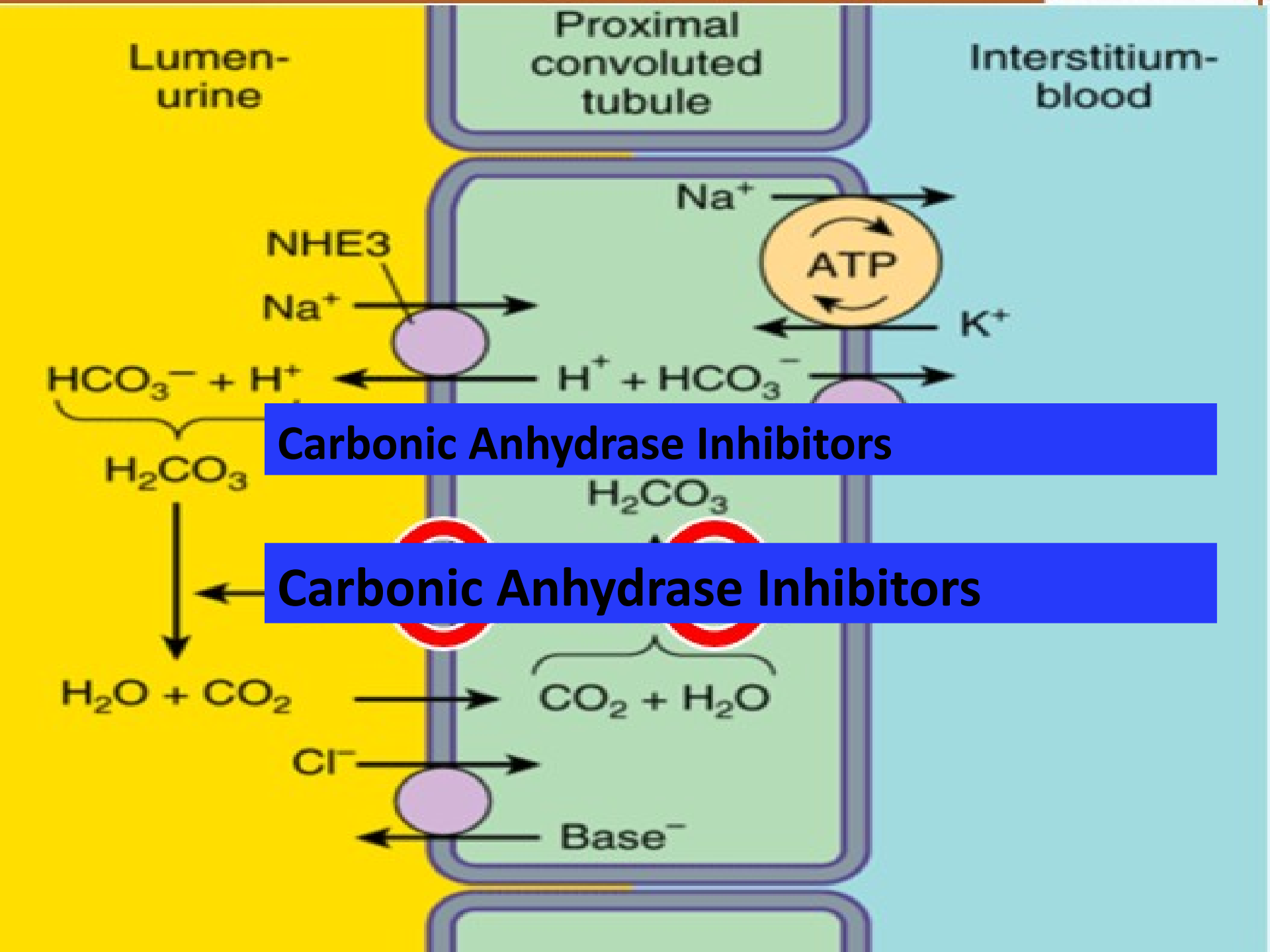
Control of Renal Function

- **Sympathetic-** Increase Na reabsorption, Renin
- **RAAS- Renin in response to Low sodium, Low BP**
- **ADH –** Water reabsorption at collecting duct
- **Atrial Natriuretic Peptide/Factor-** Released when atrial pressure is high and causes solute and water diuresis and reduces blood volume and BP. Inhibits synthesis of Renin, Aldosterone, ADH and overcomes the long term persistent effect of aldosterone **(Opposite of RAAS)**
- **Prostaglandins-** maintain renal circulation

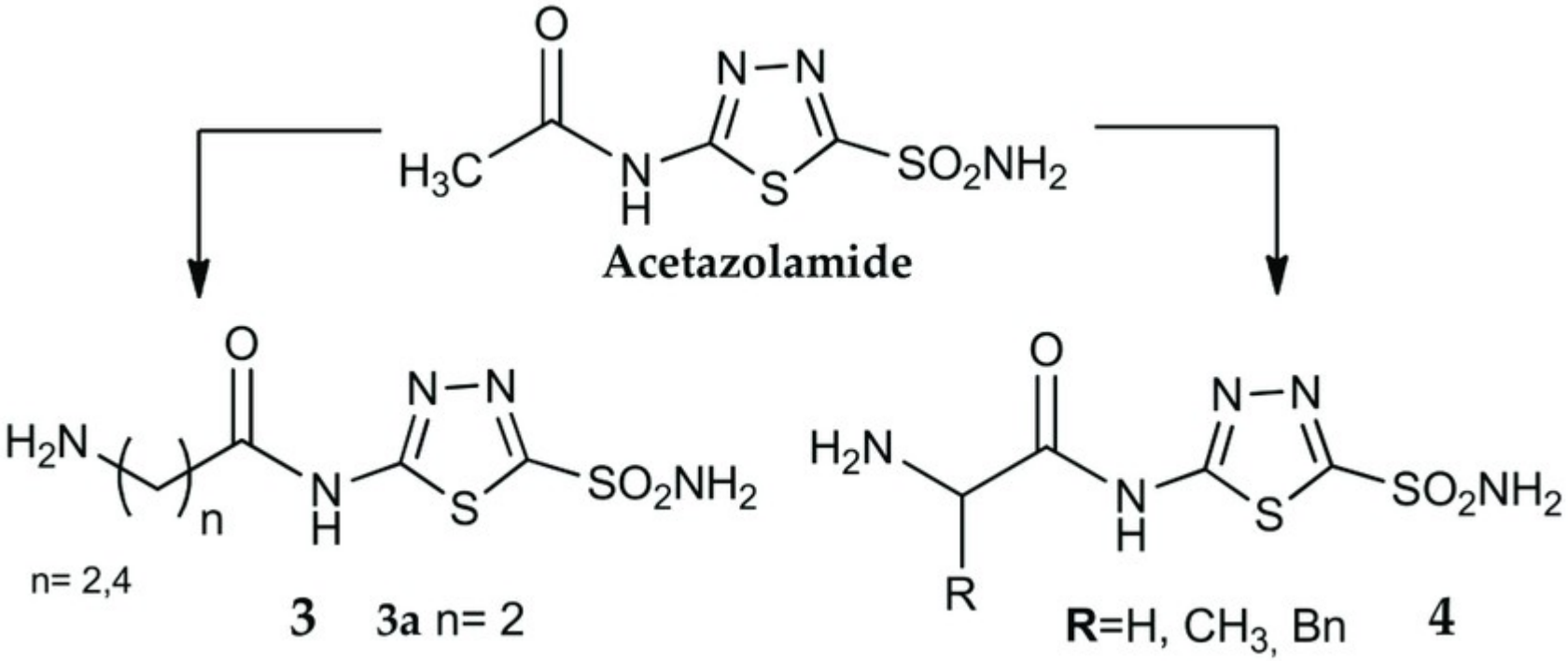
Diuretics

- **Carbonic Anhydrase Inhibitors (Site I)**
  - Brinzolamide, Acetazolamide, Dorzolamide
- **Osmotic Diuretic (Site II)**
  - Glycerine, Urea, Mannitol, Isosorbide
- **Loop Diuretics (Site III)- TALH**
  - Frusemide/ Furosemide, Bumetanide, Torasemide, Ethacrynic acid
- **Thiazide Diuretics (Site IV)**
  - Hydrochlorothiazide, Clopamide, Benzthiazide, Chlorthalidone, Metolazone, Xipamide, Indapamide
- **Potassium Sparing Diuretics (Site V)**
  - **Aldosterone Antagonist**
    - Spironolactone, Canrenone, Eplerone
  - **Direct Acting (Inhibition of renal epithelial Nq+ channel**
    - Triamterene, Amiloride (more potent)


Carbonic An-hydrase Inhibitors
Thiazide diuretics
Proximal convoluted tubule
$NaHCO_3$
NaCl
NaCl
Ca^{2+} (+PTH)
Distal convoluted tubule
Proximal straight tubule
Glomerulus
H_2O
K^+
Ca^{2+}
Mg^{2+}
Na^+
K^+
$2Cl^-$
K^+
H^+
Collecting tubule
NaCl (+aldosterone)
Osmotic Diuretics
Outer medulla
Potassium Sparing Diuretics
Loop Diuretics (High Ceiling)
Diuretics
1 Acetazolamide
2 Osmotic agents (mannitol)
3 Loop agents (eg, furosemide)
4 Thiazides
5 Aldosterone antagonists
6 ADH antagonists
7 Adenosine
Thick ascending limb
Thin descending limb
H_2O
Thin ascending limb
Loop of Henle
H_2O (+ADH)
Collecting duct
Inner medulla


Lumen-
urine
Proximal
convoluted
tubule
Interstitium-
blood
Na+
NHE3
ATP
Na+
K+
HCO3− + H+
H+ + HCO3−
Carbonic Anhydrase Inhibitors
H2CO3
H2CO3
Carbonic Anhydrase Inhibitors
H2O + CO2
CO2 + H2O
Cl−
Base−

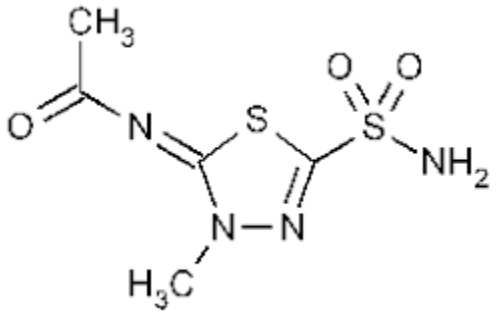
1) Acetazolamide



Acetazolamide

- **Structure Activity Relationship (SAR)**
- 1. **The unsubstituted sulphamoyl group is essential for the activity.**
- 2. **The sulphamoyl group must attached to aromatic ring.**
- 3. S**ubstitution of a methyl group on one of the acetazolamide's ring nitrogens yields**
- **methazolamide which also retain carbonic anhydrase inhibitor activity.**
- **2) Methazolamide**

Methazolamide



IUPAC NAME:N-[5-(amino sulphonyl)3- methyl 1,3,4 thiazol-2-ylidene]acetamide

- **Uses:** 1) as a diuretics
  2) In glaucoma
  3) it also has antineoplastic property.

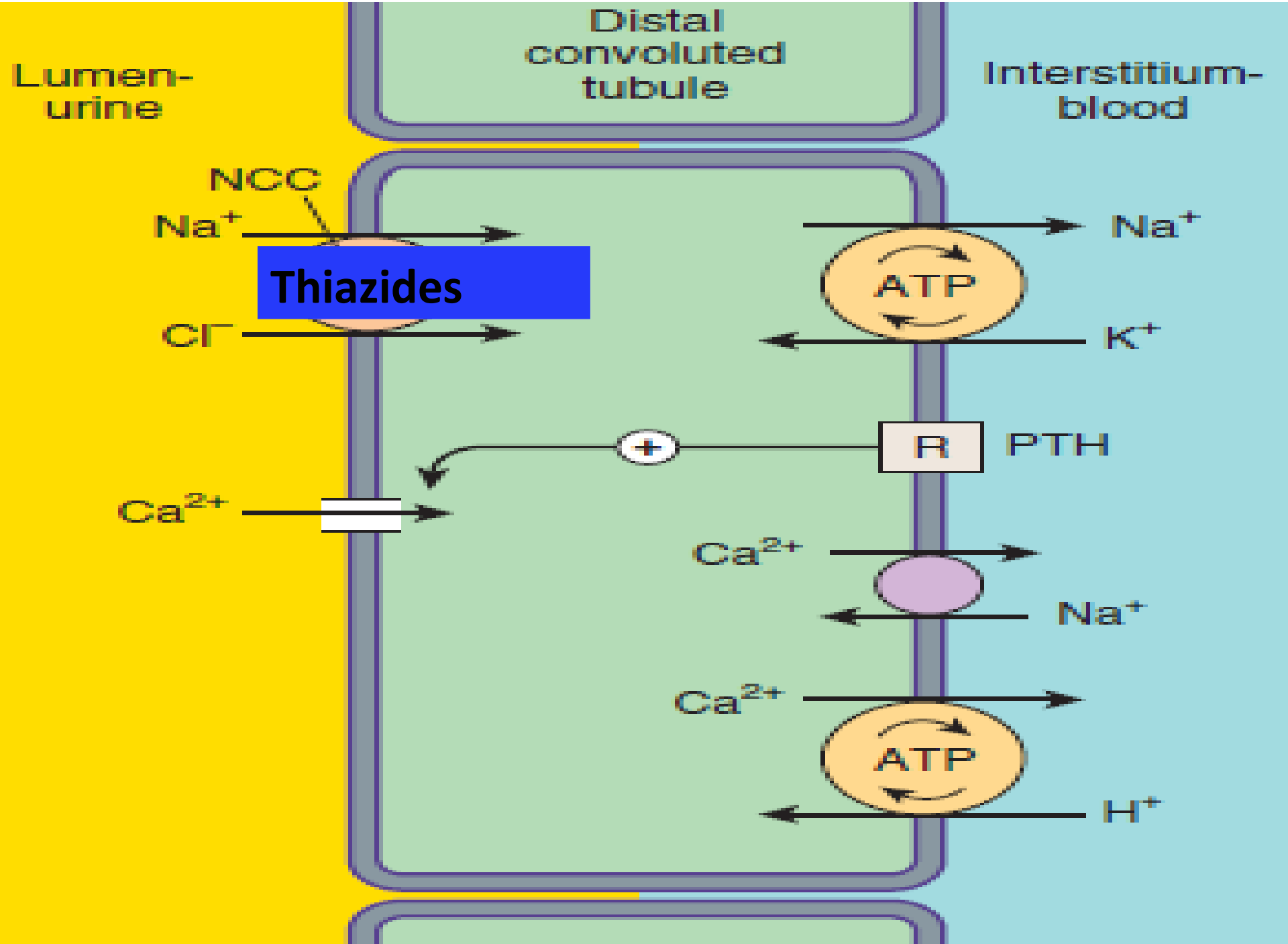
Dichlorphenamide

IUPAC NAME:4,5-dichloro-1,3benzenedisulphonamide.

Uses: In gluacoma

Effective in cases of theapy resistant epilepsy

As a diuretics.


Distal convoluted tubule
Lumen- urine
Interstitium- blood
NCC
Na+
Thiazides
Cl−
ATP
Na+
K+
R
PTH
Ca2+
Ca2+
Na+
Ca2+
ATP
H+

Thiazides

- STRUCTURE ACTIVITY RELATIONSHIP (SAR)

- At position 3 the substitution of alkyl, cycloalkyl, haloalkyl and oralkyl groups give potent diuretic compound. For e.g. Cyclopenthiazide.

- Substitution at position 2 and 3 gives highly potent compound for e.g. Polythiazide.

- Substitution of alkyl group at position 4 gives inactive compound.
- **Substitution at position 6 with c**hlorine, bromine or fluorine give highly active com pound. For e.g. Hydr*o*flumethiazide.

- *A*t position 7 *fr*ee sulphamoyl group (NH,SO,) is essential for diuretic activity.

- **If Methy*l*ation or acylati*o*n is done at position 7, it decreases or completely losse the activity. Further the introduction of benzyı compound i.e. Bendrofluazide.**