Pharmacology

Lec. 11 College of Dentistry
Dr Maha Mohsin Khalaf University of Baghdad

GENERAL ANAESTHETICS

General anaesthesia refers to drug-induced reversible loss of consciousness and all sensations. The features of GA are:

1. Reversible loss of consciousness.
2. Reversible loss of sensation.
3. Analgesia and amnesia.
4. Muscle relaxation and abolition of reflexes.

There is no single anaesthetic agent that can produce all the above effects. Hence, the anaesthetic protocol includes:

1. Premedication.
2. Induction of anaesthesia (e.g. thiopentone and propofol).
3. Maintenance of anaesthesia (N2O + isoflurane/halothane).
4. Skeletal muscle relaxation.
5. Analgesia—as premedication, during and after the operation.
6. Use of other drugs:

- To reverse neuromuscular blockade.
- To reverse the residual effects of opioids (naloxone) and BZDs (flumazenil).

Minimal alveolar concentration (MAC) is the minimum concentration of an anaesthetic in alveoli required to produce immobility in response to a painful stimulus in 50% patients. It indicates the potency of inhalational general anaesthetics.

Mechanism of action of general anaesthetics

The main site of action of anaesthetics is reticular formation, which normally maintains a state of consciousness. Most anaesthetics depress reticular formation by enhancing the activity of inhibitory transmitters and blocking the activity of excitatory transmitters.

Table 1 Stages of Anaesthesia

I. Stage of Analgesia	II. Stage of Excitement	III. Stage of Surgical Anaesthesia				IV. Stage of Medullary Paralysis
		Plane 1	Plane 2	Plane 3	Plane 4	
• The patient is conscious but drowsy	• Patient loses consciousness • Sympathetic activity is increased; • ↑Heart rate (HR), ↑blood pressure (BP), pupils are dilated; muscle tone is increased; breathing is irregular	• Respiration becomes regular • Muscles relax • Reflexes are gradually lost • Intercostal muscles are paralysed				• Respiration and vasomotor centre are depressed; death occurs within a few minutes

Stage II is the most dangerous period. All these stages (Table 1) are seen mainly with ether because of slow action. Surgical procedures are performed in stage III. The aim of induction is to reach stage III as early as possible followed by maintenance anaesthesia and muscle relaxation.

INDICATION FOR GENERAL ANAESTHESIA IN DENTISTRY

In dental practice, need for general anaesthesia is determined on an individual basis. It is indicated in:

- Acute dentoalveolar abscess and severe pulpitis: It may be difficult to achieve adequate local anaesthesia in these conditions. Management of these conditions may require general anaesthesia.
- Mentally challenged patients: In these patients, conduct of dental procedures safely under local anaesthesia could be difficult.
- Children: In small children where attempts to use local anaesthesia alone or with conscious sedation has been unsuccessful or the child does not cooperate, dental procedures need to be carried out under general anaesthesia.
- Patients allergic to local anaesthetics.
- Extensive dental procedures.

CLASSIFICATION

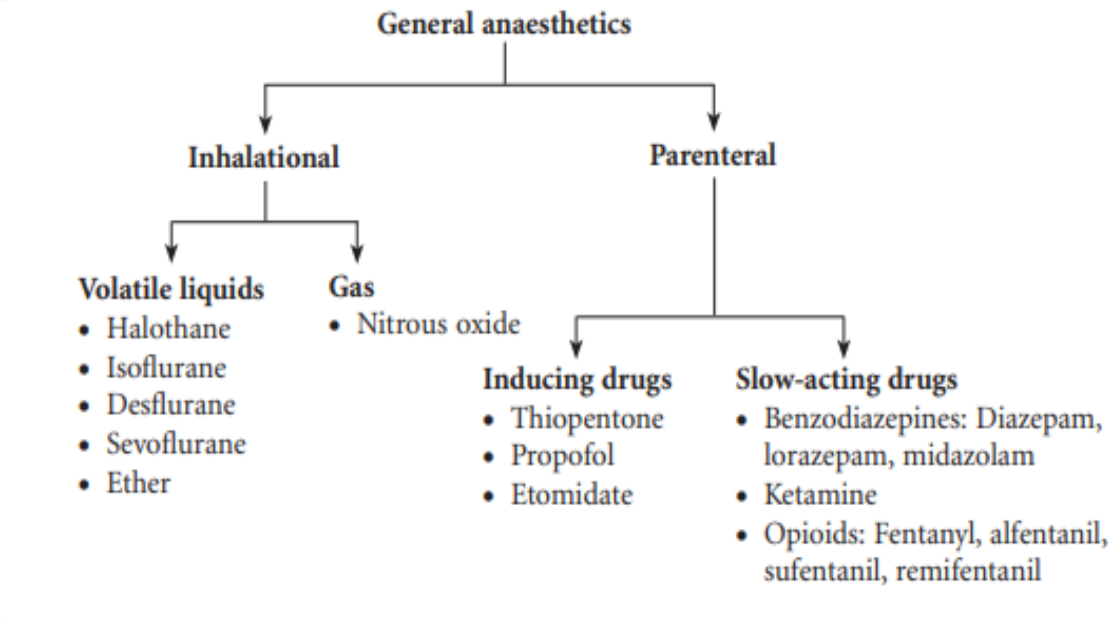


Figure 1: General anaesthetics classification

INHALATION ANAESTHESIA:

Table 7 Comparative Features of Ether, Halothane and Nitrous Oxide

Ether	Halothane	Nitrous Oxide
Volatile liquid	Volatile liquid	Gaseous general anaesthetic
Induction and recovery are slow because of its high solubility in blood	Induction and recovery are faster than ether	Induction and recovery are rapid because of low blood solubility
Irritant, inflammable and highly explosive	Non-irritant and non-inflammable	Non-irritant and non-inflammable
Has wide margin of safety	Margin of safety is not wide	Very wide margin of safety
Potent anaesthetic	Potent anaesthetic	Poor anaesthetic
Excellent analgesia	Poor analgesia	Excellent analgesia
Has curarimimetic effect on skeletal muscles, so the dose of d-tubocurarine (d-TC) required is less	Muscular relaxation is inadequate but potentiates the action of d-TC	Poor skeletal muscle relaxant
Does not sensitize the heart to catecholamines	Sensitizes the myocardium to catecholamines and may precipitate arrhythmias	Has little effect on heart, respiration and BP
Cheap	Expensive	Cheap
Irritant anaesthetic, increases salivary, respiratory secretions—may induce cough and laryngeal spasm. Therefore, pre-anaesthetic atropine is used to overcome these effects	Causes bronchodilatation—preferred in asthmatics	–
Postoperative nausea and vomiting are common	Nausea and vomiting rare	–
No hepatotoxicity	Hepatotoxicity, especially if used repeatedly (halothane hepatitis)	–

Comparative features of halogenated anaesthetics are depicted in Table 3

Table 3 Comparative Features of Halogenated Anaesthetics

Halothane	Isoflurane	Desflurane	Sevoflurane
Volatile liquid	Volatile liquid	Volatile liquid	Volatile liquid
Non-inflammable and non-explosive	Non-inflammable and nonexplosive	Non-inflammable and nonexplosive	Non-inflammable and nonexplosive
Induction and recovery are slow	Induction and recovery are rapid than halothane	Induction and recovery are rapid	Induction and recovery are rapid
Hypotension +	Hypotension +	Hypotension +	Hypotension +
Sensitizes the heart to catecholamines and may cause cardiac arrhythmias	–	–	–
Respiratory depression +	Respiratory depression +	Respiratory depression +	Respiratory depression +
Poor muscle relaxant	Skeletal muscle relaxation +	Skeletal muscle relaxation +	Skeletal muscle relaxation +
Non-irritant to respiratory passages, causes bronchodilatation and is preferred in asthmatics	Causes bronchodilatation; irritates air passages	Causes bronchodilatation; irritates air passages	Does not irritate airways and is a potent bronchodilator
Hepatotoxicity on repeated use	No hepatotoxicity	No hepatotoxicity	No hepatotoxicity
• Not pungent, well tolerated—preferred for induction and maintenance in children	• Commonly used for maintenance anaesthesia • Pungent odour—hence not commonly used for induction • Does not cause seizures • Can be used for neurosurgical procedures • No renal toxicity	• Irritates airways—not used for Induction • Does not cause seizures • No renal toxicity • Can be used in outpatients because of rapid onset of action and rapid recovery	• Nonirritant to airways—can be used for induction • Suitable for induction and maintenance of anaesthesia in children • Can be used even in outpatients because of rapid recovery • Interacts with soda lime—should not be used in closed circuit system

Halogenated anaesthetics: The newer agents like isoflurane, desflurane and sevoflurane are expensive.
+, Present; –, Absent.

- Use of ether is obsolete but is still in use where there are no other facilities available.
- Halothane sensitizes the myocardium to the arrhythmogenic effects of catecholamines.
- Speed of induction and recovery depends on the solubility of the anaesthetic agent in blood and fat.
- Anaesthetics with low blood solubility produce rapid induction and recovery (e.g. N2O and desflurane).
- Anaesthetics with high solubility in blood produce slow induction and recovery (e.g. ether).

PARENTERAL GENERAL ANAESTHETICS:

INDUCING DRUGS:

Thiopentone Sodium: It is an ultra-short-acting barbiturate. It is a commonly used i.v. anaesthetic for induction of anaesthesia. It is highly lipid soluble, hence has a rapid onset and short duration (5–8 min) of action. It is highly alkaline (pH 10.5–11), hence highly irritant. It should be prepared as a fresh solution before injection. It is injected as 2.5% solution. After a single i.v. dose, it rapidly enters the highly perfused

organs like brain, liver, heart, etc. and produces anaesthesia. As blood level of the drug falls rapidly, it diffuses out of the central nervous system into the blood and then to the less-perfused organs like skeletal muscle and adipose tissue. This redistribution results in termination of drug action. Repeated doses will result in accumulation and delayed recovery.

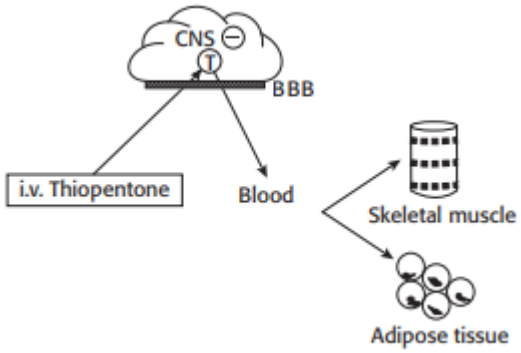


Figure 2 Redistribution of thiopentone: CNS, central nervous system; BBB, blood–brain barrier; T, thiopentone; Θ inhibition.

Uses 1. Thiopentone sodium is used for induction of anaesthesia. 2. It is occasionally used as anticonvulsant in cases not controlled by other drugs.

Advantages of thiopentone 1. Rapid induction of anaesthesia and rapid recovery. 2. Does not sensitize the myocardium to circulating catecholamines.

Disadvantages/adverse effects of thiopentone 1. Depresses the respiratory centre. 2. Depresses the vasomotor centre and myocardium. 3. Poor analgesic. 4. Poor muscle relaxant. 5. Causes laryngospasm 6. Accidental intra-arterial injection causes vasospasm and gangrene of the arm. 7. It can precipitate acute intermittent porphyria, hence contraindicated in susceptible individuals (absolute contraindication).

Propofol

It is available as 1% emulsion for intravenous administration. Propofol is a commonly used, popular, rapidly acting anaesthetic.

1. Induction of anaesthesia and recovery are rapid. Residual symptoms are less.

2. Most suitable for out-patient surgical procedures

3. No irritation of air passages.

4. Postoperative nausea and vomiting are rare.

5. Causes respiratory depression and fall in BP.

6. Pain on injection occurs—can be reduced with lignocaine

7. Intravenous propofol is useful for the induction of anaesthesia in adults. Controlled i.v infusion of propofol can be used for the maintenance of anaesthesia for short procedures.

8. Frequently used to sedate patients in intensive care unit (ICU) who are intubated.

SLOW-ACTING DRUGS

Ketamine It produces ‘dissociative anaesthesia’, which is characterized by sedation, amnesia, marked analgesia, unresponsiveness to commands and dissociation from the surroundings. It acts by blocking N-

methyl-Daspartate (NMDA) type of glutamate receptors. It is commonly given by i.v. route; other routes are i.m., oral and rectal. Ketamine is the only i.v. anaesthetic that has analgesic effect and causes sympathetic stimulation. Heart rate, BP, cardiac output and skeletal muscle tone are usually increased; causes bronchodilatation—suitable for use in asthmatics. It is used in patients with hypovolaemia.

Uses

1. For operations on the head, neck and face.

2. In children for minor surgical and diagnostic procedures.

3. For dressing burn wounds.

4. Combined with diazepam, it has been used in angiographies and cardiac catheterization.

Adverse effects and contraindications

1. Increases BP and heart rate, hence, contraindicated in patients with hypertension and ischaemic heart disease.

2. Increases intracranial pressure.

3. Causes emergence delirium and hallucinations.

Benzodiazepines

Benzodiazepines are slow-acting parenteral anaesthetics. They include diazepam, lorazepam and midazolam. Use of large doses delays recovery and prolongs amnesia. They have poor analgesic effect; do not cause postoperative nausea and vomiting. The effects of BZDs can be reversed by flumazenil. They are useful for angiography, endoscopies, fracture reduction, etc.

Opioid Analgesics They include fentanyl, alfentanil, sufentanil, remifentanil and pethidine. They are potent analgesics and can be used along with anaesthetics—to decrease the requirement of anaesthetic.

Complications of general anaesthesia

- Hypoxia
- Nausea, vomiting
- Dislocation of temporomandibular joint
- Persisting sedation
- Cardiac arrhythmias, especially with halothane
- Subcutaneous emphysema of face can occur rarely
- Hyperthermia

Preanaesthetic Medication

It is the use of drugs before the administration of anaesthetics to make anaesthesia more pleasant and safe.

Objectives/aims of premedication

1. To reduce anxiety and apprehension: Benzodiazepines like diazepam, lorazepam or midazolam are preferred because of their sedative, amnesic, calming, anxiolytic effects and wide margin of safety. They reduce anxiety by acting on limbic system.

2. To prevent vagal bradycardia and reduce salivary secretions caused by anaesthetics: Antimuscarinic agents such as atropine or glycopyrrolate may be used to reduce salivary and bronchial

secretions. They are used to prevent vagal bradycardia and hypotension. They also prevent laryngospasm by reducing respiratory secretions. Glycopyrrolate is preferred because it rarely causes CNS effects.

3. To relieve pre- and postoperative pain: Opioid analgesics such as morphine, pethidine or fentanyl may be used to relieve pain. NSAIDs like diclofenac can also be used.

4. For antiemetic effect: Metoclopramide, domperidone or ondansetron may be used to control vomiting.
5. To prevent acid secretion and stress ulcer: H2-Blocker such as ranitidine or proton-pump inhibitor like omeprazole may be used to reduce gastric acid secretion especially before prolonged surgery.

6. To hasten gastric emptying before emergency surgery: Metoclopramide or domperidone may be used. They are prokinetic drugs—increase the tone of lower oesophageal sphincter and accelerate gastric emptying, thus prevent aspiration pneumonia.

Conscious Sedation

Conscious sedation is a level of CNS depression where a patient does not lose consciousness but is able to communicate and cooperate during the procedure/treatment.

Indications

- Uncooperative patients.
- Anxious patients.
- Emotionally compromised patients.

Conscious sedation should be avoided in:

- Chronic obstructive pulmonary disease.
- Pregnancy.
- Prolonged surgery.
- Psychoses.

Drugs used

1. Benzodiazepines

– Diazepam is the most commonly used drug for conscious sedation. Small doses (1–2 mg) of diazepam is administered intravenously slowly. It can also be administered orally.

– Midazolam is a short-acting benzodiazepine given intravenously.

– Temazepam is given orally. It is safe and has better patient compliance.

2. Nitrous oxide + Oxygen: Nitrous oxide is given by inhalational route along with 100% oxygen.
3. Chloral hydrate (orally), propofol (i.v. infusion), fentanyl (i.v.), etc. can also be used for conscious sedation.

LOCAL ANAESTHETICS

Local anaesthetics (LAs) are the drugs that, when applied topically or injected locally, block nerve conduction and cause reversible loss of all sensation in the part supplied by the nerve. The order of blockade of nerve function proceeds in the following manner—pain, temperature, touch, pressure and finally skeletal muscle power.

Local anaesthetics are weak bases. They consist of three parts:

(i) hydrophilic amino group,

(ii) lipophilic aromatic group and
(iii) intermediate ester or amide linkage.

Classification of local anaesthetics

1. According to clinical use

a. Surface anaesthetics Cocaine, lignocaine, tetracaine, benzocaine, oxethazaine, benoxinate, butylaminobenzoate, dyclonine.

b. Injectable anaesthetics

i. Short acting with low potency: Procaine, chloroprocaine.

ii. Intermediate acting with intermediate potency: Lignocaine, mepivacaine, prilocaine.

iii. Long acting with high potency: Tetracaine, bupivacaine, dibucaine, ropivacaine.

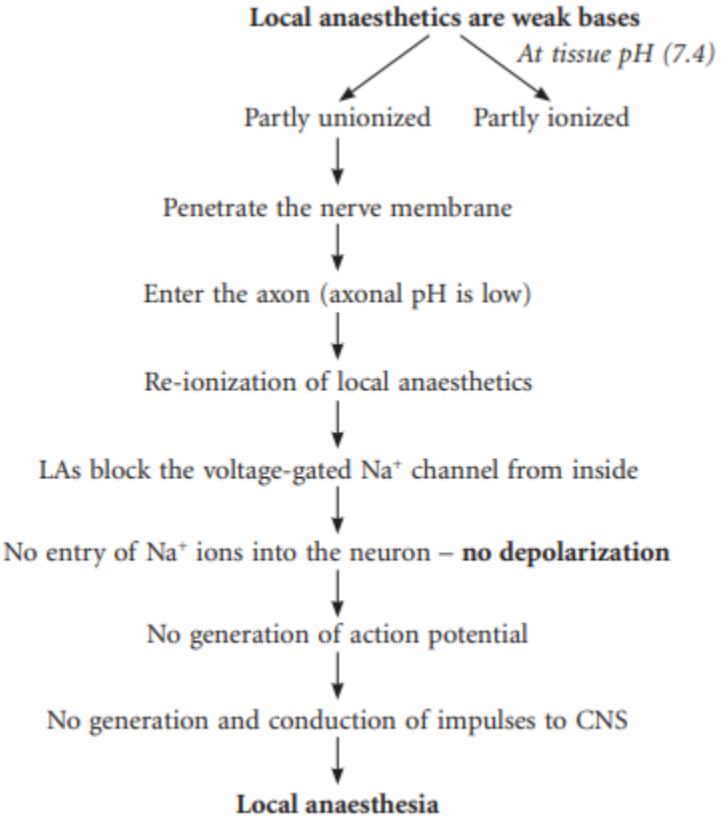
2. According to structure

a. Esters: Cocaine, procaine, chloroprocaine, benzocaine, tetracaine.

b. Amides: Lignocaine, mepivacaine, bupivacaine, prilocaine, articaine, ropivacaine.

Mechanism of action

Main site of action of local anaesthetics is the cell membrane. The LAs in 'unionized' form easily penetrate the nerve sheath and the axon membrane. Within the axoplasm, the molecules become 'ionized' and block the voltage-gated Na+ channels.



- Action of local anaesthetic is pH dependent and the penetrability of LA is increased at alkaline pH (i.e. when the unionized form is more). Penetrability is very poor at acidic pH. In infected tissues, pH is low, which causes ionization of the drug. This reduces the penetration of LA through the cell membrane, thus decreases the effectiveness of LAs. Therefore, LAs are less effective in inflamed and infected areas.
- Diameter of nerve fibres: LAs block small fibres first followed by larger fibres.
- Myelinated fibres are blocked earlier than nonmyelinated nerve of the same diameter.
- Sensory fibres are blocked earlier than motor fibres because of their high firing rate and longer duration of action potential.
- Fibres in the centre are blocked later than ones located in the circumference of the nerve bundle.
- Degree of plasma protein binding: Higher the plasma protein binding, longer the duration of action of the drug, e.g. procaine is poorly bound to plasma proteins, hence has a short duration of action; whereas bupivacaine is highly bound and has a longer duration of action.
- Rate of diffusion from the site of administration: It depends on the initial concentration gradient of the drug. Higher the concentration, rapid is the onset of action.
- Lipid solubility: Higher the lipid solubility more is the potency of the drug, e.g. lignocaine is more potent than procaine as it is more lipid soluble.
- Presence of vasoconstrictor: Prolongs the duration of local anaesthetics. The commonly used vasoconstrictor with local anaesthetics is adrenaline. Others are phenylephrine, felypressin, etc.

Combination of vasoconstrictor with local anaesthetic

The commonly used vasoconstrictor with a local anaesthetic is adrenaline. Addition of a vasoconstrictor (e.g. adrenaline) to the LA has the following advantages:

1. Slow absorption from the local site, which results in prolonged duration of action of local anaesthesia.
2. Decreased bleeding in the surgical field.
3. Slow absorption of LA reduces its systemic toxicity.

Disadvantages and contraindications of combining vasoconstrictor with LA:

1. Intense vasospasm and ischaemia in tissues with end arteries may cause gangrene of the part (e.g. fingers, toes, ear lobule, tip of the nose, etc.). Hence, use of vasoconstrictors is contraindicated in these sites.

2. Absorption of adrenaline can cause systemic toxicity—tachycardia, palpitation, rise of BP and precipitation of angina or cardiac arrhythmias. Hence, combined preparation (LA with adrenaline) should be avoided in patients with hypertension, congestive cardiac failure (CCF), arrhythmias, ischaemic heart disease and uncontrolled hyperthyroidism.

3. May delay wound healing by reducing the blood flow to the affected area.

Felypressin: It is a synthetic analogue of vasopressin. It can also be used with local anaesthetic to prolong the duration of action. It may be safely used with a local anaesthetic in patients with hyperthyroidism, cardiovascular diseases and those receiving monoamine oxidase (MAO) inhibitors or tricyclic antidepressants. It is contraindicated in pregnant patients because of its oxytocic (uterine stimulant) action on the uterus.

Pharmacological actions

1. Nervous system

a. Peripheral nerves: The order of nerve fibres affected is autonomic fibres, pain, temperature, touch, pressure and motor fibres.

b. CNS: Most of the LAs cross the blood–brain barrier (BBB)—initially they cause CNS stimulation and then depression in higher doses. They cause excitement, tremor, twitching, restlessness and convulsions. Large doses can cause respiratory depression, coma and death.

2. Cardiovascular system

a. Heart: LAs, by blocking Na+ channels, decrease abnormal pacemaker activity, contractility, conductivity, excitability, heart rate, cardiac output and increase effective refractory period.

- At higher concentrations, the intravenous administration of LAs may precipitate cardiac arrhythmias.
- Bupivacaine is more cardiotoxic than other LAs—may cause cardiovascular collapse and death. Lignocaine decreases automaticity and is useful in ventricular arrhythmias.

b. Blood vessels: Local anaesthetics produce hypotension due to vasodilatation and myocardial depression.

Pharmacokinetics

Most of the ester-linked LAs are rapidly metabolized by plasma cholinesterase whereas amide-linked drugs are metabolized mainly in liver. LAs (procaine, lignocaine, etc.) are not effective orally because of high first-pass metabolism. In liver diseases, the metabolism of lignocaine may be impaired; hence dose must be reduced accordingly.

Adverse effects

1. Central Nervous System (CNS): LAs initially cause CNS stimulation followed by depression. They are restlessness, tremor, headache, drowsiness, confusion and convulsions followed by respiratory depression, coma and death.

2. CVS: Bradycardia, hypotension, cardiac arrhythmias, rarely cardiovascular collapse and death. Bupivacaine is highly cardiotoxic.

3. Allergic reactions: These are skin rashes, itching, erythema, urticaria, wheezing, bronchospasm and rarely anaphylactic reaction. The incidence of allergic reactions is more with ester-linked LAs than with amide-linked LAs.

4. Mucosal irritation (cocaine) and methaemoglobinaemia (prilocaine) may be seen.

5. Methylparaben, a preservative in LA solutions, may cause allergic reaction

Some Important Local Anaesthetics (Table 4)

Table 4 Properties of Local Anaesthetics

Drug	Group	Duration of Action (min)	Potency	Onset	Tissue Penetrability	Other Points
Procaine	Ester	15–30 (short)	Low	Slow	Poor	No surface anaesthesia
Chloroprocaine	Ester	15–30 (short)	Low	Rapid	–	–
Tetracaine	Ester	120–240 (long)	High	Very slow	Moderate	• Widely used in spinal and corneal anaesthesia • High systemic toxicity because of slow metabolism
Cocaine	Ester	–	–	Intermediate	Good	• Inhibits the reuptake of NA in both central and peripheral nerves • Causes tachycardia, rise of BP, mydriasis and euphoria • Rarely used, only as topical anaesthetic for upper respiratory tract
Lignocaine	Amide	30–60 (intermediate)	Intermediate	Rapid	Good	• Most widely used local anaesthetic; also used in ventricular arrhythmias. • Used topically for aphthous ulcers and oral mucositis.
Mepivacaine	Amide	45–90 (intermediate)	Intermediate	Intermediate	–	• No surface anaesthesia
Bupivacaine	Amide	120–240 (long)	High	Intermediate	Moderate	• Highly cardiotoxic, widely used for spinal, epidural, infiltration and nerve block—because of the long duration of action
Ropivacaine	Amide	120–360 (long)	Intermediate	Intermediate	Moderate	• Similar to bupivacaine, less cardiotoxic
Prilocaine	Amide	Intermediate	–	Intermediate	Moderate	• Widely used, can cause methaemoglobinaemia
Dibucaine	Amide	180–600 (long)	High	Slow	Good	• Useful as topical anaesthetic for anal mucous membrane
Articaine	Amide	60	–	Rapid	–	• Used in dentistry for infiltration and nerve block anaesthesia; can cause methaemoglobinaemia, paraesthesia, neuropathy

Eutectic Mixture [EMLA—Eutectic Mixture of Local Anaesthetics: Lignocaine (2.5%) and Prilocaine (2.5%)] The melting point of the mixture is less than that of either compound alone. It can penetrate intact skin. EMLA has to be applied 1 h before the procedure and is used for dermal anaesthesia during venesection and skin graft procedures. It should not be used on mucous membranes or abraded skin. It is contraindicated in patients with methaemoglobinaemia and infants.

Benoxinate It is a surface anaesthetic; useful for corneal anaesthesia.

Benzocaine and butylaminobenzoate Surface anaesthetics; cause minimal systemic toxicity; available as ointment and lozenges; used for haemorrhoids, anal fissure and sore throat.

Oxethazaine It is a topical anaesthetic and is used to anaesthetize gastric mucosa. It produces symptomatic relief in gastritis. It is available in combination with antacids.

Dyclonine It is used topically to relieve pain of radiation/chemotherapy induced oral mucositis

Table 5 Comparative Features of Esters and Amides

Ester Type of Local Anaesthetic, e.g. Procaine	Amide Type of Local Anaesthetic, e.g. Lignocaine
Short acting	Intermediate acting
Has poor tissue penetrability, hence no surface anaesthetic effect	Has good tissue penetrability
Has slow onset of action	Has rapid onset of action
Is metabolized by plasma cholinesterase	Is metabolized by hepatic microsomal enzymes
Allergic reactions are common with esters	Allergic reactions are rare
Useful for infiltration and nerve block anaesthesia; at present, it is rarely used	Widely used for all types of anaesthesia—spinal, epidural, i.v. regional block, nerve block, infiltration and surface anaesthesia

Respiratory System
Third stage

ا.م.د. رحاب فيصل احمد

دكتوراه طب الفم

Respiratory System :

- Asthma, chronic obstructive pulmonary disease (COPD), and allergic rhinitis are commonly respiratory disorders. Each of these conditions may be associated with a troublesome cough, which may be the only presenting complain.
- **Asthma** is a chronic disease characterized by hyperresponsive airways and episodes of acute bronchoconstriction causing shortness of breath, it is characterized by reversible airways obstruction and bronchial hyper reactivity.
- **COPD** is characterized by incompletely reversible airways obstruction and mucus hypersecretion; it is predominantly a disease of the smaller airways.

Nevertheless, distinguishing the two can be difficult in some patients.

- **Allergic rhinitis** characterized by itchy, watery eyes, runny nose, and a nonproductive cough that can significantly decrease quality of life.
- Drugs used to treat respiratory conditions can be delivered topically to the nasal mucosa, inhaled into the lungs, or given orally or parenterally for systemic absorption.
- Local delivery methods, such as nasal sprays or inhalers, are preferred to target affected tissues while minimizing systemic side effects

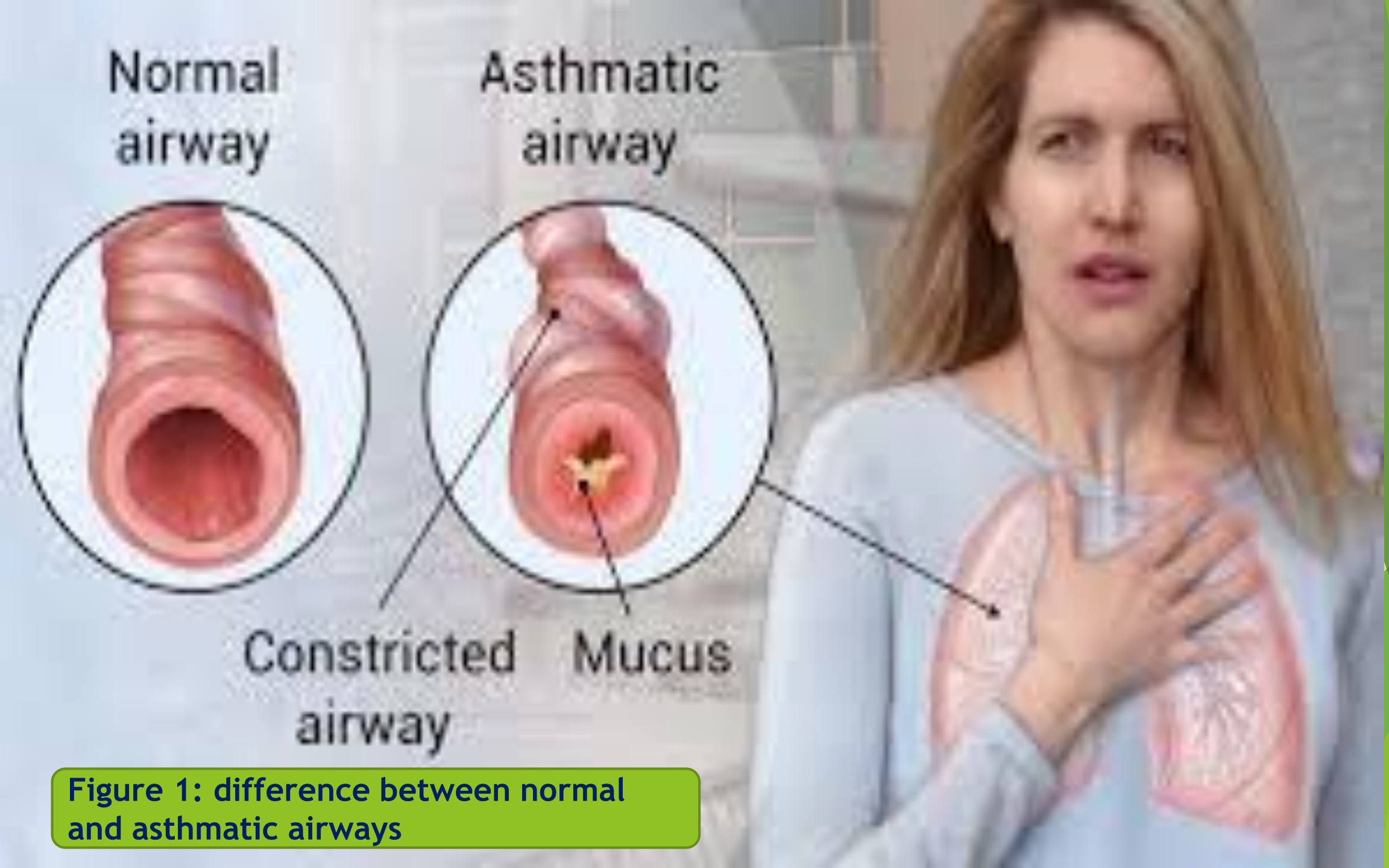
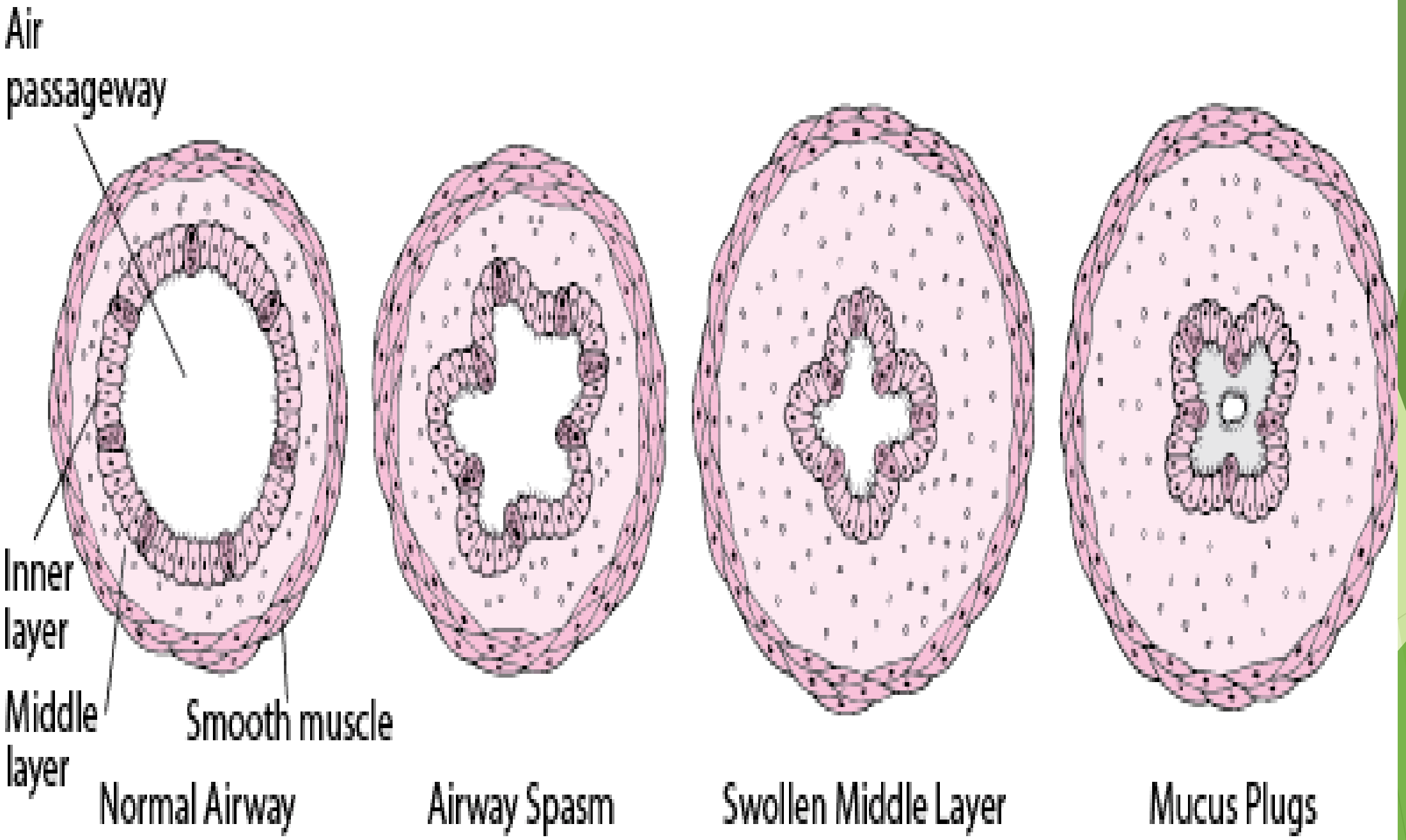


Figure 1: difference between normal and asthmatic airways


Air passageway
Inner layer
Middle layer
Smooth muscle
Normal Airway
Airway Spasm
Swollen Middle Layer
Mucus Plugs

The bronchi become hyperreactive as a result of a persistent inflammatory process in response to a number of stimuli that include biological agents, e.g. allergens, viruses, and environmental chemicals such as ozone and glutaraldehyde.

Some mediators such as histamine are preformed and their release causes an immediate bronchial reaction.

- **Preferred drugs used to treat asthma:**
- **β2 -Adrenergic agonists :** Inhaled β2 -adrenergic agonists directly relax airway smooth muscle, They are used for the quick relief of asthma symptoms, as well as adjunctive therapy for long-term control of the disease.

- 1. Short-acting β2 agonists(SABAs) albuterol and levalbuterol: (Quick relief)- onset of action (5 to 30 minutes) and provide relief for 4 to 6 hours.
- 2. Long-term control: Salmeterol and formoterol, have a long duration of action, providing bronchodilation for at least 12 hours.
- Neither salmeterol nor formoterol should be used for quick relief of an acute asthma attack.

- **NOTE**: β2 agonists have **no anti-inflammatory effects**, and they should **never be used for patients with persistent asthma**.
- Direct acting β2 -selective agonist include albuterol and levalbuterol: (significant bronchodilation)
- **Adverse effects**, such as tachycardia, hyperglycemia, hypokalemia, and hypomagnesemia, are minimized with inhaled delivery versus systemic administration. These agents can cause β2 -mediated skeletal muscle tremors.
- Inhaled corticosteroids remain the long-term controllers of choice in asthma, and LABAs are considered to be useful adjunctive therapy for attaining asthma control.
- **Adverse effects** : long-acting β2 agonists (LABAs) are similar to quick-relief β2 agonists.

Corticosteroids

- Inhaled corticosteroids ICS are the drugs of choice for long-term control in patients with any degree of persistent asthma.
- Corticosteroids inhibit the release of arachidonic acid through phospholipase A2 inhibition, thereby producing direct anti-inflammatory properties in the airways.
- No other medications are as effective as ICS in the long-term control of asthma in children and adults.
- To be effective in controlling inflammation, glucocorticoids must be used regularly. Severe persistent asthma may require the addition of a short course of oral glucocorticoid treatment.

Corticosteroids

- 1. Actions on lung:
- ICS do not directly affect the airway smooth muscle. Instead, ICS therapy directly targets underlying airway inflammation by decreasing the inflammatory cascade (eosinophils, macrophages, and T lymphocytes), reversing mucosal edema, decreasing the permeability of capillaries, and inhibiting the release of leukotrienes.
- After several months of regular use, ICS reduce the hyper responsiveness of the airway smooth muscle to a variety of Broncho constrictor stimuli, such as allergens, irritants, cold air, and exercise.

2. Routes of administration

a. Inhalation.

B. Oral –systemic.

a. Inhalation: The development of ICS has markedly reduced the need for systemic corticosteroid treatment to achieve asthma control. However, as with all inhaled medications, appropriate inhalation technique is critical to the success of therapy.

b. Oral/systemic: Patients with a severe exacerbation of asthma (status asthmaticus) may require intravenous methylprednisolone or oral prednisone to reduce airway inflammation.

- **3. Adverse effects**: Oral or parenteral glucocorticoids have a variety of potentially serious side effects, whereas ICS, particularly if used with a spacer, have few systemic effects.
- ICS deposition on the oral and laryngeal mucosa can cause adverse effects, such as oropharyngeal candidiasis (due to local immune suppression) and hoarseness.
- Patients should be instructed to rinse the mouth in a “swish-and-spit” method with water following use of the inhaler to decrease the chance of these adverse events

Alternative drugs: These drugs are useful for treatment of asthma in patients who are poorly controlled by conventional therapy or experience adverse effects secondary to corticosteroid treatment..

- These drugs should be **used in conjunction** with ICS therapy for most patients, **not as monotherapy**
- A. Leukotriene modifiers
- B. Cromolyn
- C. Cholinergic antagonists
- D. Theophylline
- Omalizumab

Alternative drugs

- **Leukotriene modifiers**:- Leukotrienes (LT) B4 and the cysteinyl leukotrienes, LTC4, LTD4, and LTE4, are products of the 5-lipoxygenase pathway of arachidonic acid metabolism and part of the inflammatory cascade. **5-Lipoxygenase is found in cells of myeloid origin,** such as mast cells, basophils, eosinophils, and neutrophils.
- **B. Cromolyn** is a prophylactic anti-inflammatory agent that **inhibits mast cell degranulation and release of histamine**. It is an alternative therapy for mild persistent asthma. However, it is not useful in managing an acute asthma attack, because it is not a bronchodilator. Due to its short duration of action, this agent requires dosing three or four times daily, Adverse effects are minor and include cough, irritation, and unpleasant taste.
- **C.Cholinergic antagonists**: The anticholinergic agents block vagally mediated contraction of airway smooth muscle and mucus secretion.
- Adverse effects such as xerostomia and bitter taste are related to local anticholinergic effects

- **D. Theophylline** is a bronchodilator that relieves **airflow obstruction** in **chronic asthma** and decreases its symptoms. It may also possess anti-inflammatory activity,
- Theophylline competitively inhibits type III and type IV phosphodiesterase enzyme (PDE), this enzyme responsibles for breaking down cyclic AMP in smooth muscle cells, possibly resulting in bronchodilation.

- **CHRONIC OBSTRUCTIVE PULMONARY DISEASE**
- COPD is a chronic, irreversible obstruction of airflow that is usually progressive. **Symptoms include cough, excess mucus production, chest tightness, breathlessness, difficulty sleeping, and fatigue**.
- Although symptoms are similar to asthma, the characteristic irreversible airflow obstruction of COPD is one of the most significant differences between the diseases.
- Smoking is the greatest risk factor for COPD.
- Drug therapy for COPD is aimed at relief of symptoms and prevention of disease progression.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

- **A. Bronchodilators** Inhaled bronchodilators, including the β2 -adrenergic agonists and anticholinergic agents (ipratropium and tiotropium). These drugs increase airflow, alleviate symptoms, and decrease exacerbation rates. Combination of both an anticholinergic and a β2 agonist may be helpful in patients who have inadequate response to a single inhaled bronchodilators.
- **B. Corticosteroids** The addition of an ICS to a long-acting bronchodilator may improve symptoms, lung function and quality of life in COPD patients. However, **the use of an ICS is associated with an increased risk of pneumonia, and therefore, use should be restricted to these patients.**
- Although often used for acute exacerbations, oral corticosteroids are not recommended for long-term treatment.
- **C. Other agents: Roflumilast** is an oral phosphodiesterase-4 inhibitor used to reduce exacerbations in patients with severe chronic bronchitis. Although its activity is not well defined in COPD, it is theorized to reduce inflammation by increasing levels of intracellular cAMP in lung cells

DRUGS USED TO TREAT ALLERGIC RHINITIS

- **Rhinitis** is an inflammation of the mucous membranes of the nose and is characterized by **sneezing, itchy nose/eyes, watery rhinorrhea, nasal congestion, and sometimes, a nonproductive cough.**

- An attack may be precipitated by **inhalation of an allergen (such as dust, pollen, or animal dander)**. The foreign material interacts with mast cells coated with IgE generated in response to a previous allergen exposure.
- The mast cells release mediators, such as histamine, leukotrienes, and chemotactic factors that promote bronchiolar spasm and mucosal thickening from edema and cellular infiltration.

- **Antihistamines and/or intranasal corticosteroids are preferred therapies for allergic rhinitis.**

- A. Antihistamines (H1 -receptor blockers) :
- Antihistamines are useful for the management of symptoms of allergic rhinitis caused by histamine release **(sneezing, watery rhinorrhea, itchy eyes/nose)**. However, they are more effective for prevention of symptoms rather than treatment. Two types:
- **First generation antihistamines** (diphenhydramine and chlorpheniramine) are usually not preferred due to adverse effects, such as sedation, performance impairment, and other anticholinergic effects.
- **Second generation antihistamines** (fexofenadine, loratadine, desloratadine, cetirizine, and intranasal azelastine) are generally better tolerated.
- Combinations of antihistamines with decongestants are effective when congestion is a feature of rhinitis.

- B.Corticosteroids Intranasal corticosteroids, such as **beclomethasone, ciclesonide, mometasone, and triamcinolone**, are the most effective medications for treatment of allergic rhinitis. Systemic absorption is minimal, and side effects of intranasal corticosteroid treatment are localized.
- These include nasal irritation:

1.Nose bleed,

2. sore throat, and, rarely, candidiasis.

- To avoid systemic absorption, patients should be instructed not to inhale deeply while administering these drugs because the target tissue is the nose, not the lungs or the throat.
- For patients with chronic rhinitis, improvement may not be seen until 1 to 2 weeks after starting therapy.

- C. α-Adrenergic agonists:
- 1. Short-acting α-adrenergic agonists (“nasal decongestants”),

such as phenylephrine, constrict dilated arterioles in the nasal mucosa and reduce airway resistance.

2. Longer-acting oxymetazoline is also available. When administered as an aerosol, **these drugs have a rapid onset of action and show few systemic effects**.

Unfortunately, the α-adrenergic agonist intranasal formulations should be used no longer than 3 days due to the risk of rebound nasal congestion (rhinitis medicamentosa**). For this reason, the α-adrenergic agents have no place in the long-term treatment of allergic rhinitis.

** rhinitis medicamentosa: inflammation of nasal mucosa

The physiological functions of histamine

- ▫ Body epithelia (the gut, the respiratory tract and in the skin), where it is released in response to invasion by foreign substances.
- ▫ Glands (gastric, intestinal, lachrymal, salivary), where it mediates part of the normal secretory process
- ▫ Mast cells near blood vessels, where it plays a role in regulating the microcirculation.
- ▫ Histamine functions as a neurotransmitter in the brain.
- ▫ It also occurs as a component of venoms and in secretions from insect stings.

Actions of Histamine: acts as a local hormone (autacoid) similarly to serotonin or prostaglandins, i.e. **it functions within the immediate vicinity of its site of release.**

With gastric secretion, for example, stimulation of receptors on the histamine containing cell causes release of histamine, which in turn acts on receptors on parietal cells with then secrete hydrogen ion.

- **Histamine receptors: Histamine binds to H1, H2 and H3 receptors, all of which are G-protein coupled.**
- **The H1 receptor is largely responsible for mediating its pro-inflammatory effects, including the vasomotor changes, increased vascular permeability and upregulation of adhesion molecules on vascular endothelium, i.e. it mediates the oedema and vascular effects of histamine.**
- **H2 receptors mediate release of gastric acid.**
- **H3 receptors are expressed in a wide range of tissues including brain and nerve endings, and function as feedback inhibitors for histamine and other neurotransmitters.**
- **More recently identified is the H4 receptor, which is involved in leucocyte chemotaxis.**

Thus, histamine antagonists are classified as:

- histamine H1-receptor antagonists
- histamine H2-receptor antagonists: **cimetidine, famotidine, nizatidine, ranitidin**

- Histamine H1-receptor antagonists. The selectivity implied by the term 'antihistamine‘ is unsatisfactory because the older first-generation antagonists show considerable blocking activity against muscarinic receptors, and often serotonin and α-adrenergic receptors as well.
- These features are a disadvantage when H1 antihistamines are used specifically to antagonize the effects of histamine, e.g. for allergies. Hence the appearance of second-generation H1 antagonists that are more selective for H1 receptors and largely free of anti-muscarinic and sedative effects has been an important advance.
- The older first generation H1 antihistamines cause **drowsiness and patients should be warned of this**, e.g. about driving or operating machinery, and about additive effects with alcohol.
- The newer second-generation H1 antihistamines penetrate the blood-brain barrier less readily and are largely devoid of such central effects.

Uses:- The H1 antihistamines are used for symptomatic relief of allergies such as hay fever and urticaria.

- Non-sedative newer second-generation drugs:
- These newer drugs are relatively selective for H1 receptors, enter the brain less readily than do the earlier antihistamines, and lack the unwanted antimuscarinic effects. **(acetylcholine receptors that are important in parasympathetic nervous system**)
- Differences lie principally in their duration of action. Cetirizine (t½ 7 h), loratadine (t½ 15 h) and terfenadine (t½ 20 h) are effective taken once daily and are suitable for general use.
- Acrivastine (t½ 2 h) is so short acting that it is best reserved for intermittent therapy, e.g. when breakthrough symptoms occur in a patient using topical therapy for hay fever.
- Other non-sedating antihistamines are desloratadine, fexofenadine, levocetirizine and mizolastine.

- Adverse effects :
- The second-generation antihistamines **are well tolerated but a noteworthy effect occurs with terfenadine.** This drug can cause ventricular tachycardia and probably explains the sudden deaths reported during early use of terfenadine. The event is prone to occur with high dose or when metabolism of terfenadine is inhibited, and inhibiting drugs include erythromycin, ketoconazole and even grapefruit juice.
- Fexofenadine, the active metabolite of terfenadine, appears to be safer regarding the effect on the heart.
- **Sedative first-generation agent:**
- **Chlorphenamine (t½ 20 h)** is effective when urticaria is prominent, and its sedative effect is then useful.
- Diphenhydramine (t½ 32 h) is strongly sedative and has antimuscarinic effects; it is also used in parkinsonism and motion sickness.
- Promethazine (t½ 12 h) is so strongly sedative that it is used as an hypnotic in adults and children.
- Adverse effects Apart from sedation, these include: dizziness, fatigue, insomnia, nervousness, tremors and antimuscarinic effects, e.g. dry mouth, blurred vision and gastrointestinal disturbance.
- Dermatitis and agranulocytosis can occur. Severe poisoning due to overdose results in coma and sometimes in convulsions.

DRUGS USED TO TREAT COUGH

- **Coughing** is an important defense mechanism of the respiratory system to irritants and is a common reason for patients to seek medical care.
- A troublesome cough may represent **several etiologies, such as**:
- **common cold, sinusitis, and/or an underlying chronic respiratory disease.**
- In some cases, **cough may be an effective defense reflex against an underlying bacterial infection and should not be suppressed.**
- Before treating cough, identification of its cause is important to ensure that antitussive treatment is appropriate.
- **Drugs are used:**
- A. Opioids
- B. Benzonatate.

- A. Opioids: 1. Codeine, an opioid, **decreases the sensitivity of cough centers in the central nervous system to peripheral stimuli and decreases mucosal secretion.**
- These therapeutic effects occur at doses lower than those required for analgesia.
- **side effects**, such as: constipation, dysphoria, and fatigue, still occur.
- 2. **Dextromethorphan** is a synthetic derivative of morphine that has no analgesic effects in antitussive doses. In low doses, it has a low addictive profile. However, since it may cause dysphoria at high doses.
- **Dextromethorphan has a significantly safer side effect profile than codeine and is equally effective for cough suppression.**
- **Guaifenesin, an expectorant, is available as a single-ingredient formulation and is also a common ingredient in combination products with codeine or dextromethorphan.**

B. Benzonatate Unlike the opioids, suppresses the cough reflex through peripheral action. It anesthetizes the stretch receptors located in the respiratory passages, lungs, and pleura.

Side effects include:

dizziness, numbness of the tongue, mouth, and throat.

These localized side effects may be particularly problematic if the capsules are broken or chewed and the medication comes in direct contact with the oral mucosa

HISTAMINE AND ANTIHISTAMINE:

Histamine is a naturally occurring amine that is found in most tissues in an inactive bound form, and pharmacologically active free histamine, released in response to stimuli such as physical trauma or immunoglobulin (IgE) is an important component of the acute inflammatory response.

Corticosteroids:

- The adrenal gland consists of the cortex and the medulla. The medulla secretes catecholamines, whereas the cortex, secretes two types of corticosteroids **(glucocorticoids and mineralocorticoids) and the adrenal androgens**.
- The adrenal cortex has three zones, and each zone synthesizes a different type of steroid hormone.
- ***The outer zona glomerulosa*** produces mineralocorticoids (for example, aldosterone) that are responsible for regulating salt and water metabolism. Production of aldosterone is regulated primarily by the renin–angiotensin system.
- ***The middle zona fasciculata*** synthesizes glucocorticoids (for example, cortisol) that are involved with metabolism and response to stress.
- ***The inner zona reticularis*** secretes adrenal androgens.

- A. Glucocorticoids
- Cortisol is the principal human glucocorticoid. Normally, its production is diurnal, **with a peak early in the morning followed by a decline** and then a secondary, smaller peak in the late afternoon. Factors such as stress and levels of the circulating steroid influence secretion.
- B. Mineralocorticoids
- **Mineralocorticoid**s help to **control fluid status and concentration of electrolytes, especially sodium and potassium**.
- **Aldosterone** acts on distal tubules and collecting ducts in the kidney, **causing reabsorption of sodium, bicarbonate, and water**. Conversely, aldosterone **decreases reabsorption of potassium, which, with H+, is then lost in the urine**.

- Enhancement of sodium reabsorption by aldosterone also occurs in gastrointestinal mucosa and in sweat and salivary glands.

Therapeutic uses of the corticosteroid:

- **Endocrinal uses:**
- 1. **Acute adrenal insufficiency**: It is a medical emergency. It is treated with i.v. hydrocortisone and i.v. normal saline with 5% glucose to correct fluid and electrolyte imbalance.
- **Precipitating causes such as trauma, infection or haemorrhage should be treated.**
- **2. Chronic adrenal insufficiency**: Treated with oral hydrocortisone (two-third of the daily dose is given in the morning and one-third in the evening) along with adequate salt and water.
- **Non-endocrinal uses**
- Corticosteroids are one of the most important groups of drugs used clinically in a variety of diseases. Because of their dramatic symptomatic relief, they are often misused. Non-endocrinal diseases require supra-physiological doses of steroid, which inevitably carries risk.
- The beneficial effects of glucocorticoids are mainly due to their **anti-inflammatory and immunosuppressant effects.**

- 1. In dentistry: Topical or systemic glucocorticoids are used in: a. Recurrent aphthous stomatitis b. Chronic ulcerative stomatitis c. Oral pemphigoid d. Erythema multiforme e. Temporomandibular joint pain: Intraarticular triamcinolone is used.
- 2. Rheumatoid arthritis: They produce an immediate and dramatic symptomatic relief in rheumatoid arthritis; but they do not halt the progression of the disease. Intra-articular injection is preferred only if one or two joints are involved.
- 3. Osteoarthritis: rarely used.
- 4. Rheumatic fever: They produce more rapid symptomatic relief than aspirin. **Prednisolone is given along with aspirin and should be continued until the erythrocyte sedimentation rate (ESR)** comes to normal and then the steroid is tapered off gradually.
- 5. Allergic diseases: The manifestations of allergic diseases, such as hay fever, reactions to drugs, urticaria, contact dermatitis, angioneurotic oedema and anaphylaxis, can be suppressed by glucocorticoids; but they have a slow onset of action. Hence, severe reactions such as anaphylaxis and angioneurotic oedema require immediate therapy with adrenaline. In hay fever, serum sickness and mild allergic reactions, antihistamines are the preferred drugs.

- 6. Bronchial asthma: They have anti-inflammatory and anti-allergic effects; hence they reduce mucosal oedema and bronchial hyperirritability.
- **In acute severe asthma**, i.v. hydrocortisone is given along with nebulized β2 - agonist and ipratropium bromide. **If a chronic asthmatic needs steroid**, **it is better to give inhalational preparations** like beclomethasone, budesonide or fluticasone because they cause minimal systemic adverse effects.

- 7. Collagen diseases: Collagen diseases such as polymyositis, polyarteritis nodosa, etc. can be controlled with large doses of glucocorticoids. Steroids with negligible salt and water retaining property is preferred.
- 8. Renal disease: Glucocorticoids are the first-line drugs in nephrotic syndrome.
- 9. Ocular diseases: They are frequently used to suppress inflammation in the eye; thus they prevent damage to vision. Agents may be administered topically, sub-conjunctivally, systemically or by retrobulbar 13 injection, depending upon the condition.
- **Steroids are contraindicated in herpes simplex keratitis and ocular injuries.**

- 10. Skin diseases: They dramatically relieve itching, pain, and inflammation in allergic and other dermatoses. To minimize systemic effects, topical steroids are preferred.
- Systemic steroid therapy is needed in severe conditions like exfoliative dermatitis, dermatomyositis, pemphigus, etc. Psoriasis, keloids and hypertrophic scar are sometimes treated by intralesional injection of steroids.
- 11. Haematological disorders: Autoimmune haemolytic anaemias usually respond to glucocorticoids. Because of their lympholytic action, glucocorticoids are used to treat certain malignancies, leukaemia, lymphomas, Hodgkin's disease, multiple myeloma, etc., usually in combination with antineoplastic drugs.
- 12. Cerebral oedema
- 13. Intestinal diseases
- 14. Shock
- 15. Organ transplantation
- 16. Hypercalcaemi

Thank you

Pharmacokinetics and Pharmacodynamics of Drugs

By

Dr. Samir AL_Shujairy

The word pharmacology is made up of two words (greek): pharmacon = drug and logos = study.

Pharmacology: it is the science that deals with the study of various drugs, their usages, doses, indications, side effects and its interactions.

- **It is study the actions of drugs on the living system.**

- **It includes physical and chemical properties, biochemical and physiological effects, mechanism of action, therapeutic uses and adverse effects of drugs.**

Drug: **is a substance used in the diagnosis, prevention or treatment of disease.**

Drug: (WHO): is any substance or product that used or intended to be used to modify or explore physiological systems or pathological states for the benefit of recipient.

Dose: The amount of a drug necessary to elicit the desired therapeutic effect or response in the patient.

- **terms (dose) and (dosage).**
- **Dose: the quantity of medication to be administered at one time.**

Adverse Drug Reaction: A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function.

Pharmacokinetics: **is the study of the absorption, distribution, metabolism and excretion of drugs, i.e what the body does to the drug.**

In Greek – kinesis means movement.

Chemotherapy: **Effect of drugs upon microorganisms and parasites which living and multiplying in a living organism.**

Pharmacognosy: **study the sources of drug and the physical and chemical properties of drug of vegetable and animal origin**

Sources of Drugs

1. **Natural Sources**

- **Plants:**
  - **Alkaloids:** eg. Morphine, Atropine
  - **Glycosides**: eg. Digoxin, Digitoxin.
- **Animals**: Insulin, Heparin.
- **Minerals**: Iron, Magnesium sulphate.
- **Microorganisms:** Penicillins, Streptomycin.

2. Semisynthetic: Hydromorphone, Hydrocodone.

3. Synthetic: Aspirin, paracetamol.

4. genetic engineering: Human insulin, Human growth hormone and Hepatitis B Vaccine.

Two types of pharmacology

1. Experimental pharmacology: it is done in the laboratory on experimental animals such as rodents and non-rodents animals.

2. Clinical pharmacology: it is the study of drugs effects in human being.

Drug Nomenclature (Naming of drugs)

The three basic types of drug names are

- **The Chemical name:** technical description of the actual molecule e.g. **Chemical name for aspirin is acetyl salicylic acid.**
- **Generic name:** Generic names are less complicated and easier to remember than chemical names.
- **Brand name (trade name):** is assigned by the company marketing the drug. The name is usually selected to be **short and easy** to remember.

Classification of Drugs

Chemical classification:-

- **Generic name**

Some examples of Chemical, Generic, Brand Names

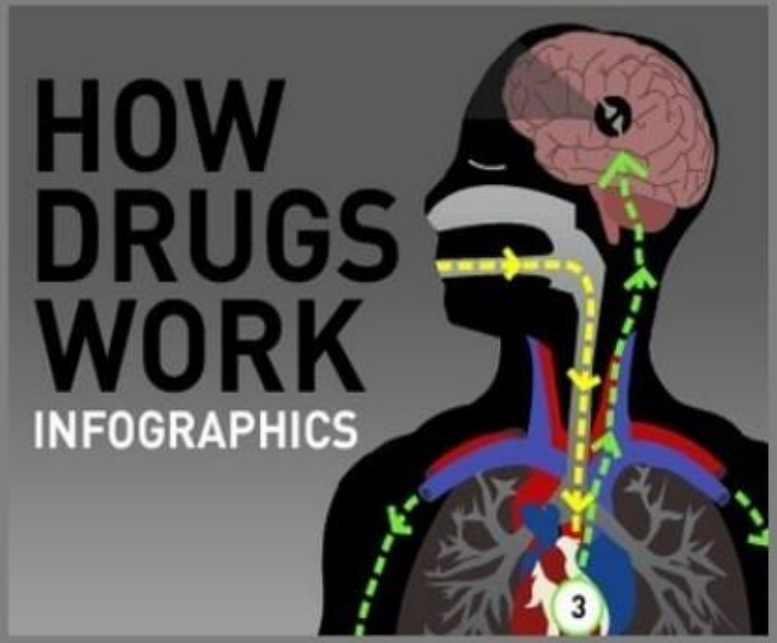
Chemical Name	Generic Name/ Non- Proprietary Name	Brand Name/ Proprietary Name
Acetyl Salicylic Acid	Aspirin	Disprin
Acetaminophen	Paracetamol	Crosin, Calpol, Metacin
Aminobenzyl Penicillin	Ampicillin	Roscillin

Classification of Drugs

Chemical classification:-

Pharmacokinetics

Absorption
Distribution
Metabolism
Excretion
Bioavailability



Pharmacokinetics

The study of mechanisms and factors associated with the absorption, distribution, metabolism, and excretion of drugs.

PK: is the movement of the drugs into, within and out of the body.

The four pharmacokinetics process are divided in to

- **Absorption**
- **Distribution**
- **Metabolism**
- **Excretion**

Absorption: **is the transfer of a drug from its site of administration to the blood stream.**

All these processes involve passage of the drug molecules across various barriers like the intestinal epithelium, cell membrane & so on to reach the site of action.

Mechanisms of drug absorption

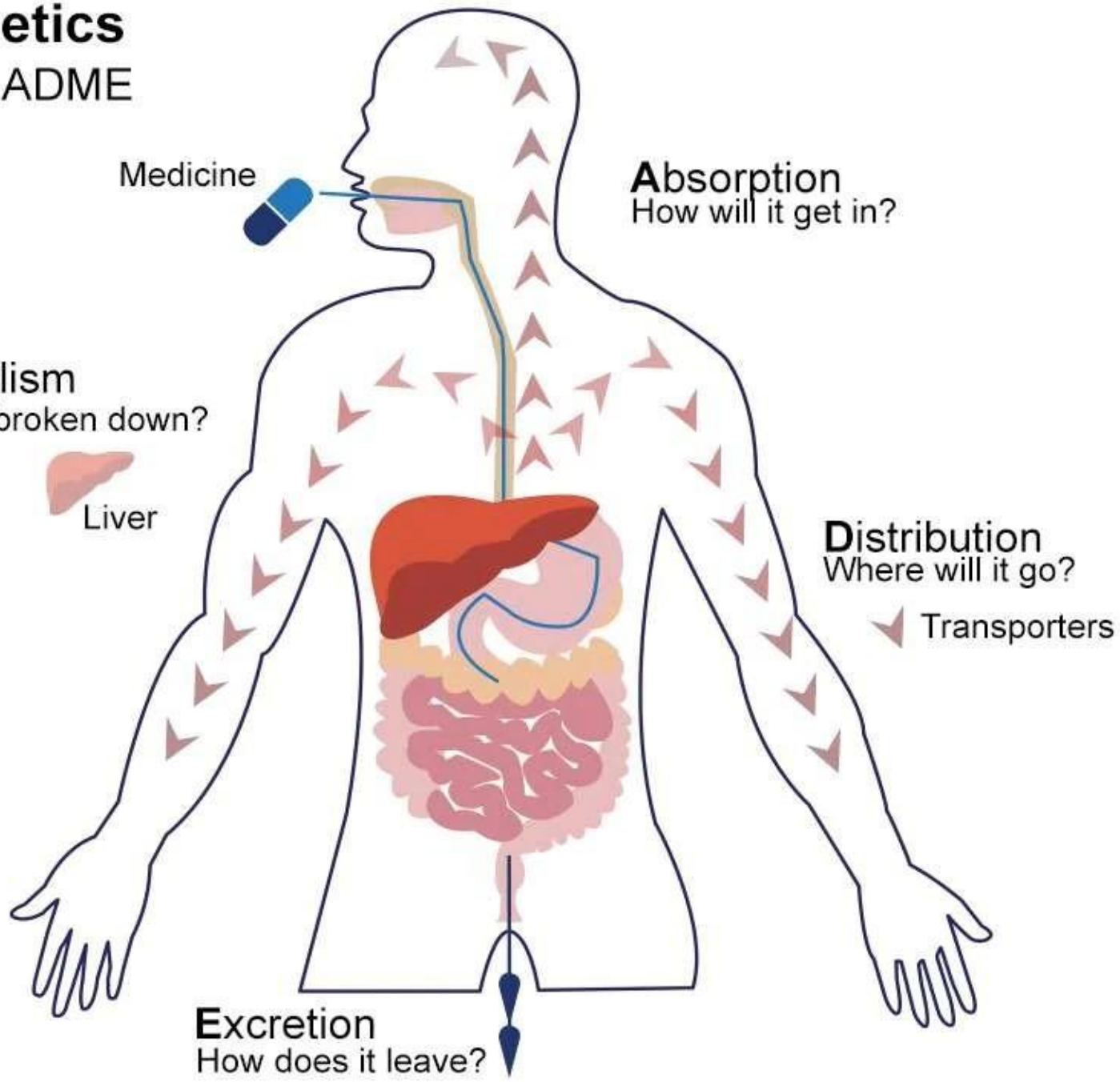
1. **Simple diffusion = passive diffusion.**
2. **Active transport.**
3. **Facilitated diffusion.**
4. **Pinocytosis (Endocytosis).**

The rate and efficiency of absorption depend on the route of administration.

- **For IV. Injection absorption is complete**, the total dose of drug reaches the systemic circulation.
- **But other route partial absorption and lower bioavailability For example, the oral route** requires that a drug dissolve in the GI tract and penetrate the epithelial cell of the intestinal mucosa
- **disease states or the presence of food may affect.**

Pharmacokinetics

The principles of ADME



EUPATI
European Patients' Academy on Therapeutic Innovation
www.eupati.eu

Pharmacokinetics

- **Absorption**

1. Simple diffusion/Passive diffusion.

This mechanism does not utilize energy. With the help of concentration gradient across a membrane separating two body compartments where the drug moves from region of high concentration to one of lower concentration.

- **water soluble drug (ionized or polar) is readily absorbed via aqueous channels or pores in cell membrane.**

- **Lipid soluble drug (non-ionized or non polar) is readily absorbed via cell membrane itself.**

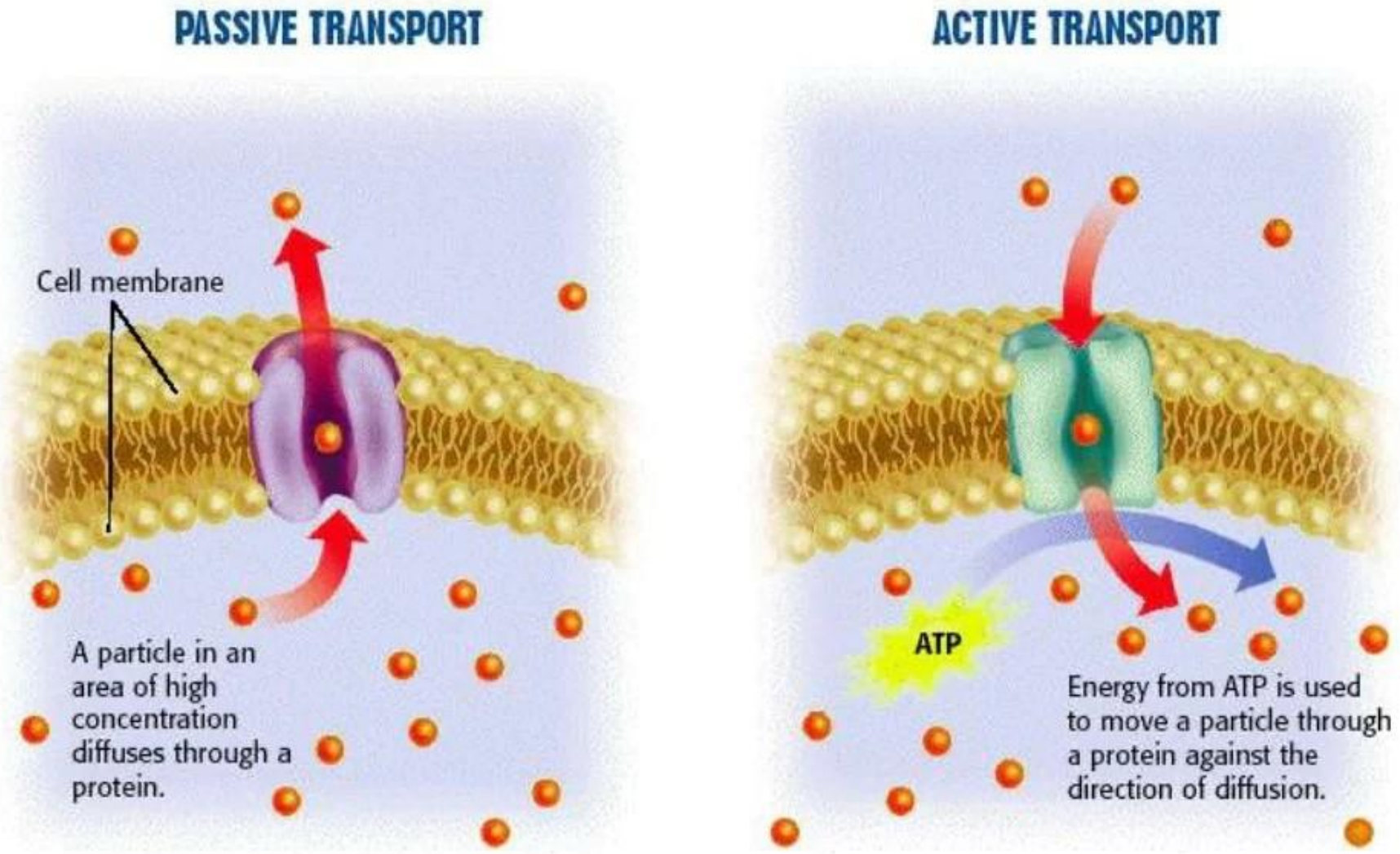
Pharmacokinetics

- **Absorption**

2. Active transport.

This mode of drug entry involves specific carrier protein that spans the membrane. This is energy dependent and is driven by the hydrolysis of adenosine triphosphate (ATP).

Passive and Active Transport



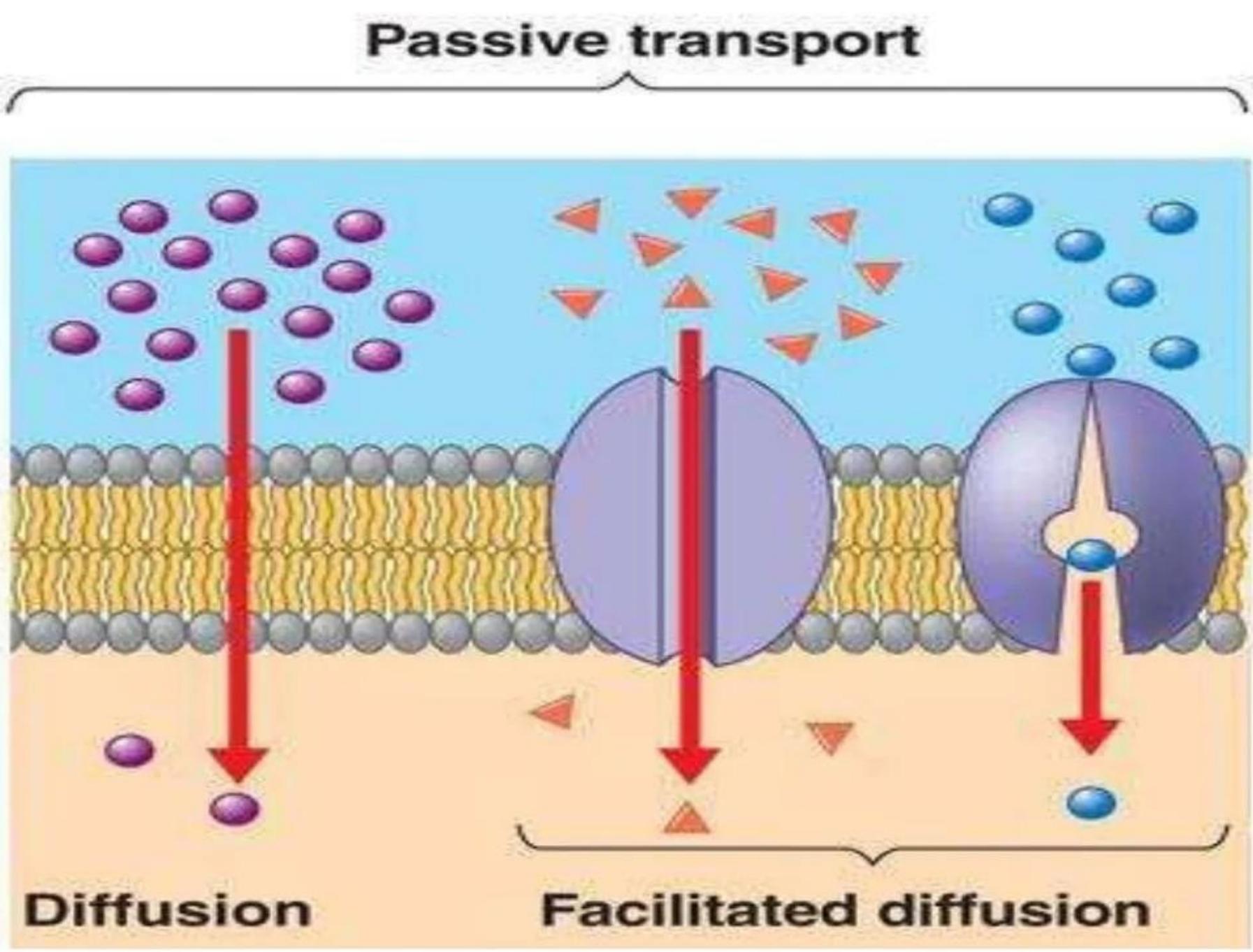
Passive transport	Active transport
Along concentration gradient (From high to low)	against concentration gradient (From low to high)
No carriers	Needs carriers
Not selective Not saturable	Selective, saturable
No energy	energy is required

Pharmacokinetics

- **Absorption**

3. Facilitated diffusion.

Facilitated diffusion is a form of facilitated transport involving the passive movement of molecules along their concentration gradient, guided by the presence of another molecule – usually an integral membrane protein forming a pore or channel.

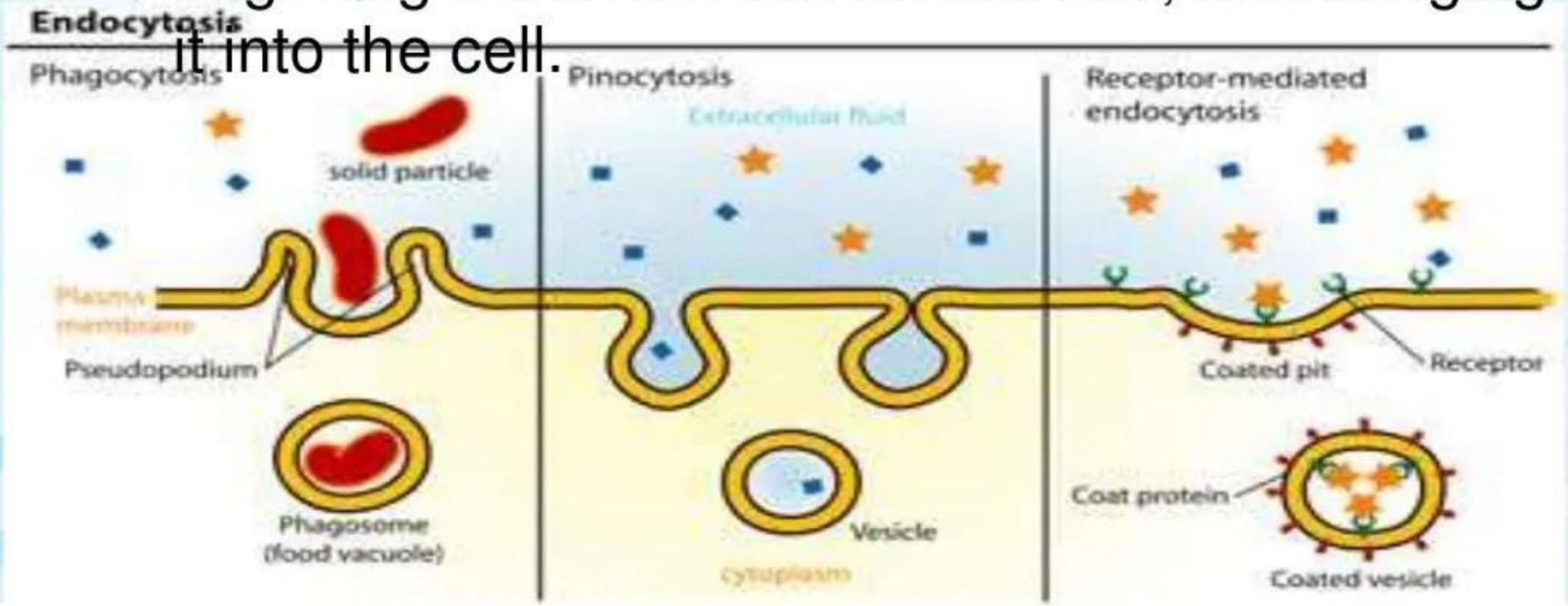

Passive transport
Diffusion
Facilitated diffusion

Pharmacokinetics

- **Absorption**

4. Endocytosis.

Endocytosis is the process of capturing a substance or particle from outside the cell by engulfing it with the cell membrane, and bringing it into the cell.



Pharmacokinetics

- **Absorption**

4. Endocytosis.

There are three main kinds of endocytosis:

- **Phagocytosis**, or *cellular eating,* occurs when the dissolved materials enter the cell. The plasma membrane engulfs the solid material, forming a phagocytic vesicle.
- **Pinocytosis**, or *cellular drinking,* occurs when the plasma membrane folds inward to form a channel allowing dissolved substances to enter the cell. When the channel is closed, the liquid is encircled within a pinocytic vesicle.

Effect of pH on drug absorption:

- Most drugs are either **weak acids** or **weak bases**.

All nonionized drugs are **lipid soluble** and the **ionized drug is water soluble.**

The **cell membrane** is a **phospholipid** in nature so that the **nonionized** drug can be **diffusion** through the lipid membrane by simple diffusion without energy

- Drug **weak base** in pH (medium) **acidic** like in stomach, **ionized** form greater than unionized ⟹ **low absorption**.
-
- Drug **Weak base** in pH (medium) **alkalin** like in intestin, **unionized** form greater than ionized ⟹ **high absorption**.

Physical factors effected on drug absorption:

1. Route of administration
2. Blood supply to the site of absorption
3. Formulation of the drug
4. Gut transit time
5. pH in the gut
6. Solubility of the product

Bioavailability

Bioavailability is the fraction of administered drug that reaches the systemic circulation in chemically unchanged form: e.g. if 100 mg of drug is administered orally and 70 mg this is absorbed unchanged, the bioavailability is 70%.

Factors effected on drug bioavailability:

1. First-pass hepatic metabolism:

When a drug is absorbed from the GI tract**, it enters the portal circulation before entering the systemic circulation. If the drug is rapidly metabolized in the liver or gut wall during this initial passage**,

the amount of unchanged drug entering the systemic circulation is decreased. (Lidocaine, proparnolol).

2. Solubility of the drug:

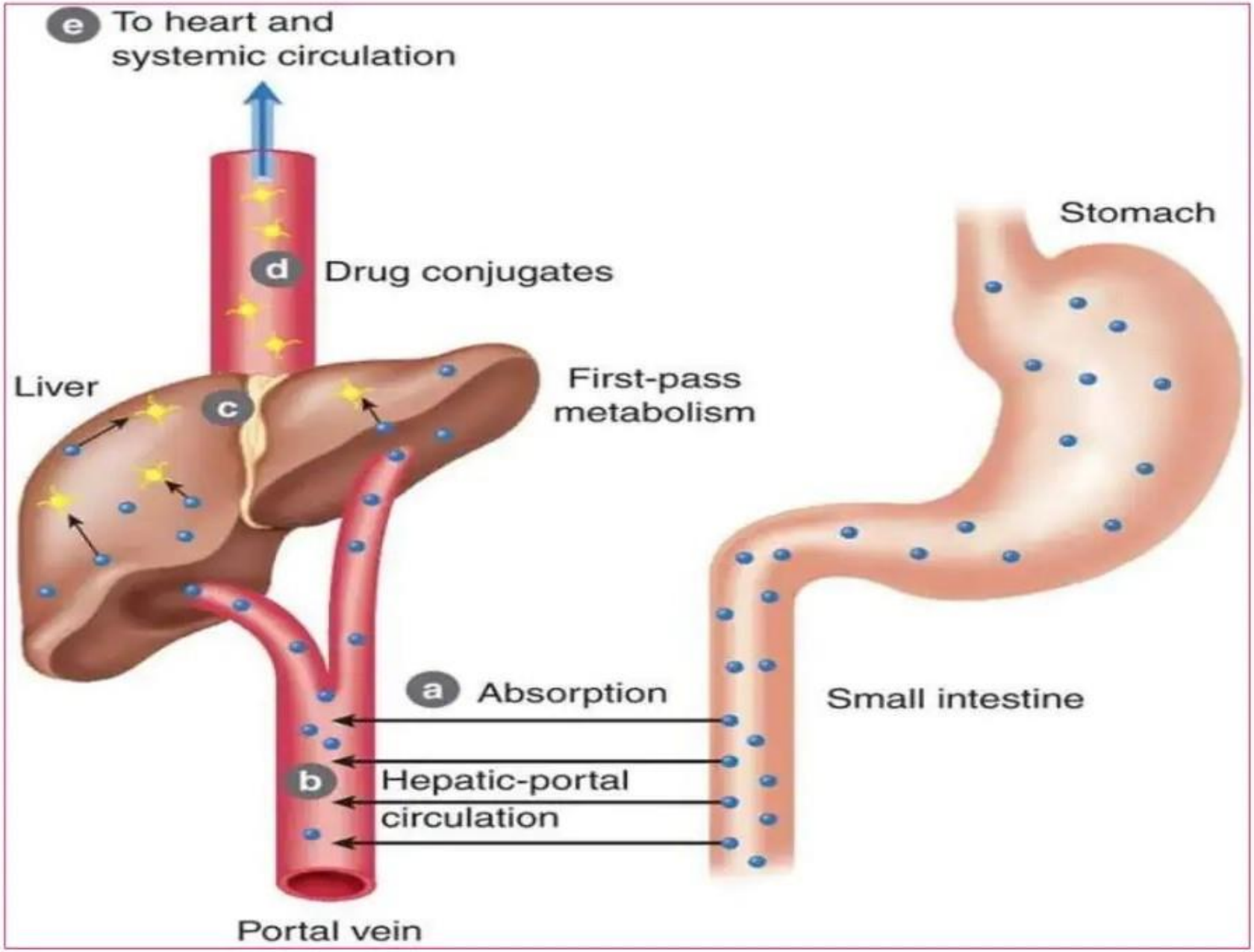
Very **hydrophilic drugs** are **poorly** absorbed because of their **inability to cross lipid-rich cell membranes.**

3. Chemical instability:

Some drugs, such as penicillin G, are unstable in the pH of the gastric contents. Others, such as insulin, are destroyed in the GI tract by digestive enzymes.

4. Nature of the drug formulation:

Drug absorption may be altered by **factors unrelated to the chemistry of the drug**. For example**: particle size, salt form, enteric coatings, and the presence of excipients. Can alter the rate of absorption.**


e To heart and systemic circulation
d Drug conjugates
Liver
c
First-pass metabolism
Stomach
a Absorption
Small intestine
b Hepatic-portal circulation
Portal vein

Pharmacokinetics

- **Distribution**

In this process drug reversibly leaves the blood streams and enters the ECF and for the cell or the tissue. Drugs will accumulate greatly in adipose or fat tissue. Usually they are not active in fat tissue; will slowly reenter the blood streams.

Various factors determine the rate and extent of distribution, they are lipid solubility, ionization, blood flow/permeability of the barriers and binding to plasma proteins and cellular protein. Unionized and lipid soluble drugs are widely distributed through out the body.

Pharmacokinetics

- **Distribution**

Plasma Protein Binding:

On reaching the circulation ,most of the drug bind to plasma protein; acidic drug mainly bind with albumin and basic drugs to alpha - acid glycoprotein, lipoprotein and beta globulin. The free or unbound fraction of the drug is the only form available for action, metabolism and excretion. The protein bound form serves as a reservoir. Protein binding prolongs the duration and action of drug. e.g warfarin 99%, morphine 35%, ethosuximide and lithium 0%.

Pharmacokinetics

❑ Distribution

Blood Brain Barrier:

The endothelial cells of the brain capillaries have tight junctions. Moreover neuroglial cells envelope the capillaries and together these form the BBB. Only lipid soluble and unionized drugs can cross BBB.

Tissue binding:

Some drugs get bound to certain tissue constituent because of special affinity for them. Tissue binding delays excretion and thus prolongs the duration of drug.

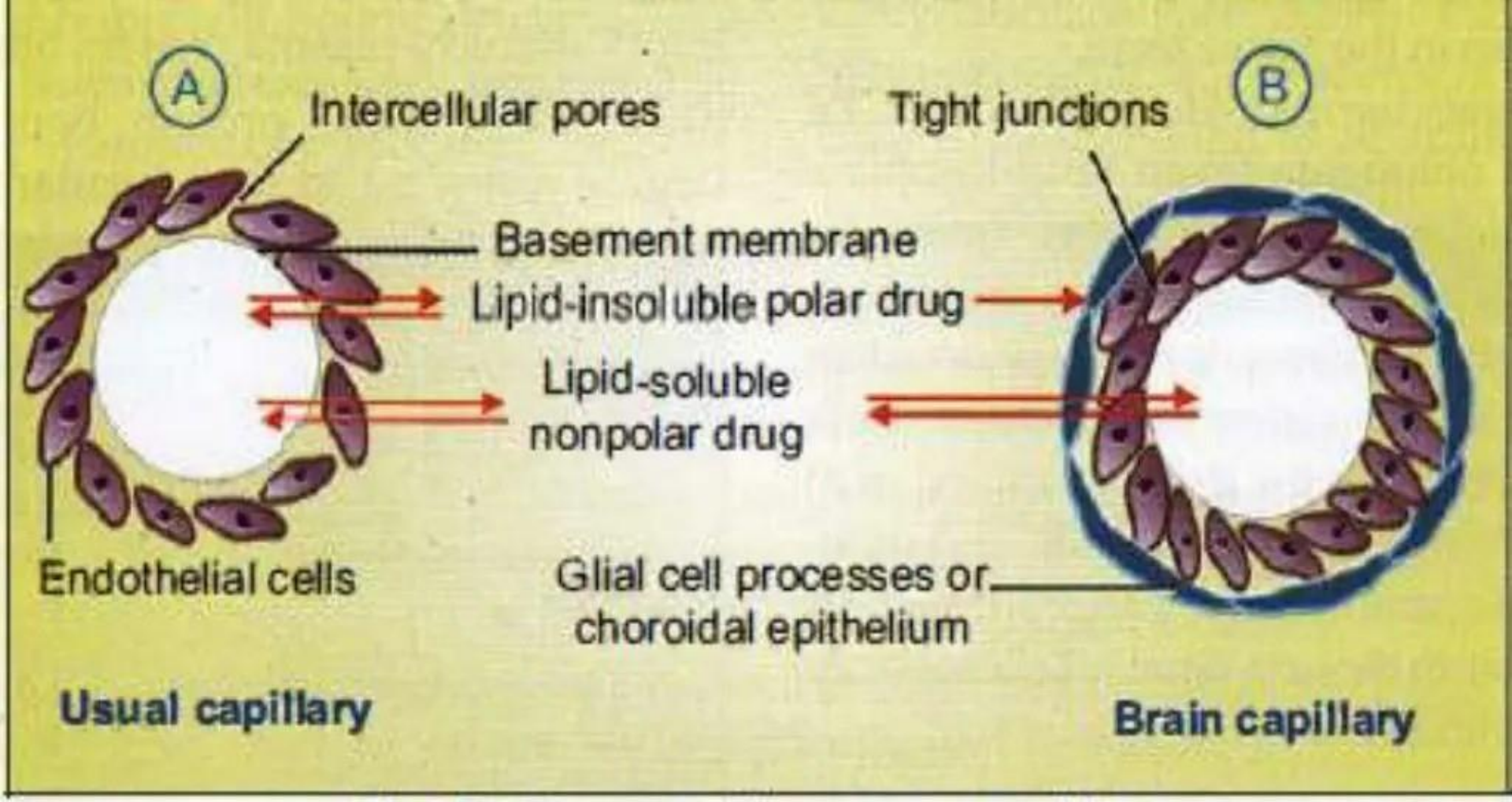


Fig. 2.8: Passage of drugs across capillaries

A. Usual capillary with large intercellular pores through which even large lipid-insoluble molecules diffuse

B. Capillary constituting blood brain or blood-CSF barrier. Tight junctions between capillary endothelial cells and investment of glial processes or choroidal epithelium do not allow passage of non lipid-soluble molecules/ions

Pharmacokinetics

- **Distribution**

Placental Barrier:

Lipid soluble ,unionized drugs readily cross the placenta while lipid insoluble drugs cross to a much lesser extent. Thus drugs taken by the mother can cause severe unwanted effects in the fetus.

Pharmacokinetics

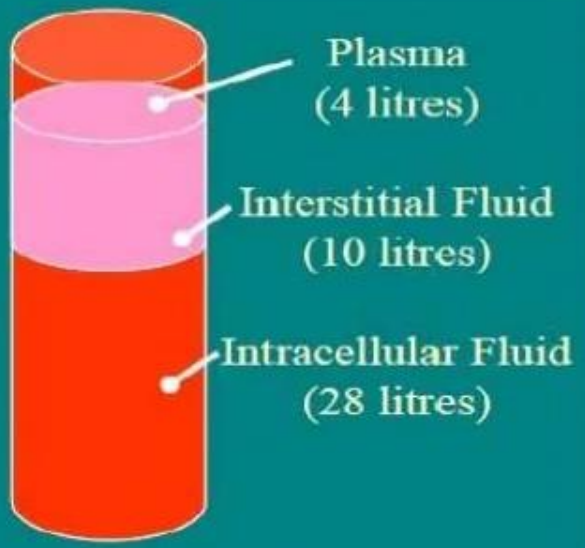
- **Distribution**

Volume of Distribution (V)

Drugs may distribute into any or all of the following compartments:

- **Plasma**
- **Interstitial Fluid**
- **Intracellular Fluid**

Total Body Fluid = 42 L (approx.)



Metabolism/Biotransformation

- **is the process of chemical alteration of the drug in the body. Body treats most of the drugs as foreign substance and tries to inactivate and eliminate them by various biochemical reactions.**
- **Theses processes convert the drugs into more polar, water soluble compounds so that they are easily excreted through the kidneys.**

The three major routes of elimination are:

- **Hepatic metabolism**
- **Biliary elimination**
- **Urinary elimination**

Together, these elimination processes **decrease the plasma concentration**.

Two type of kinetics:

- **First-order kinetics**: the rate of drug metabolism and elimination is directly proportional to the concentration of free drug. (linear kinetics)
- **Zero-order kinetics**: the rate of metabolism and rate of elimination is constant and does not depend on the drug concentration.(nonlinear kinetics)

Reactions of drug metabolism:

- The kidney cannot efficiently eliminate **lipophilic drugs** that readily cross cell membranes and are reabsorbed in the distal convoluted tubules.
- **Therefore, lipid-soluble agents are first metabolized into more polar (hydrophilic) substances in the liver via two general sets of reactions, called phase I and phase II.**

Site of Metabolism:

Mainly drugs are **metabolized in liver**. However some are metabolized in **kidneys, lungs, gut mucosa, blood and skin.**

Result:

- **Active drug to inactive metabolite. E.g. Morphine**
- **Active to more active metabolite. E.g. Digitoxin – digoxin**
- **Inactive drug (Prodrug) to active metabolite. E.g. levodopa – dopamine, cortisone - hydrocortisone**

The chemical reactions of Metabolism can take place in two phases,

1. Phase I (Non-synthetic reactions)

convert lipophilic drugs into more polar molecules by introducing a polar functional group, such as –OH or –NH2.

- **Reactions usually involve reduction, oxidation, or hydrolysis.**
- **Metabolism may increase, decrease, or have no effect on pharmacologic activity.**

2. Phase II: (conjugation reactions)

- If the **metabolite** from **phase I** metabolism is **sufficiently polar**, it can be **excreted** by the **kidneys**.
- many **phase I metabolites** are **still too lipophilic** to be excreted. A subsequent **conjugation reaction with an endogenous substrate,** such as:
  - **glucuronic acid**
  - **sulfuric acid**
  - **acetic acid.**
  - **amino acid**.
- **results in polar, usually more water-soluble compounds that are often therapeutically inactive.**
- **Some drugs may enter phase II directly and become conjugated without prior phase I metabolism. The highly polar drug conjugates are then excreted by the kidney or in bile.**

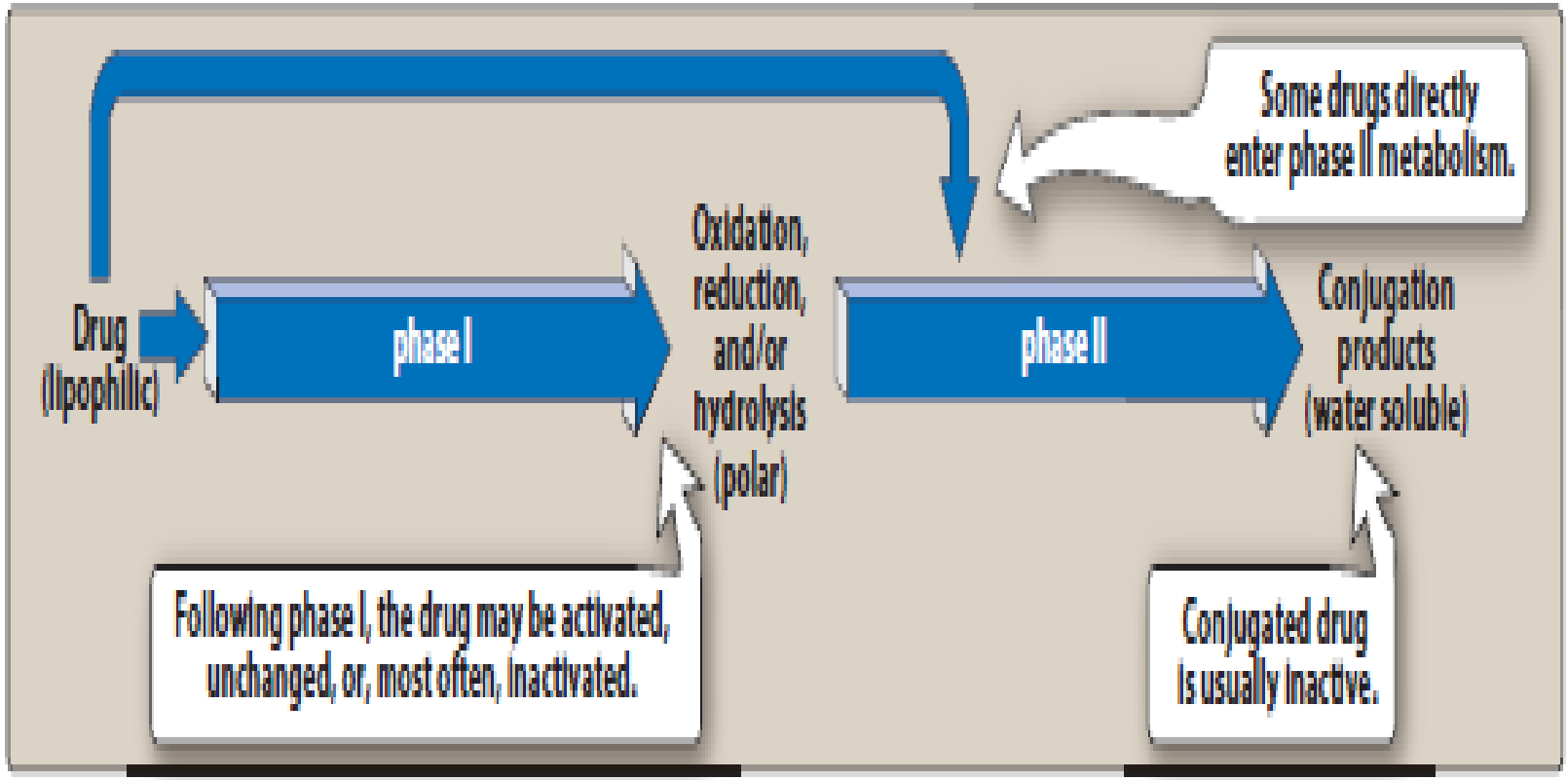


Fig. The biotransformation of drugs

Excretion of drugs

Excretion is the process of removing a drug and its metabolites from the body.

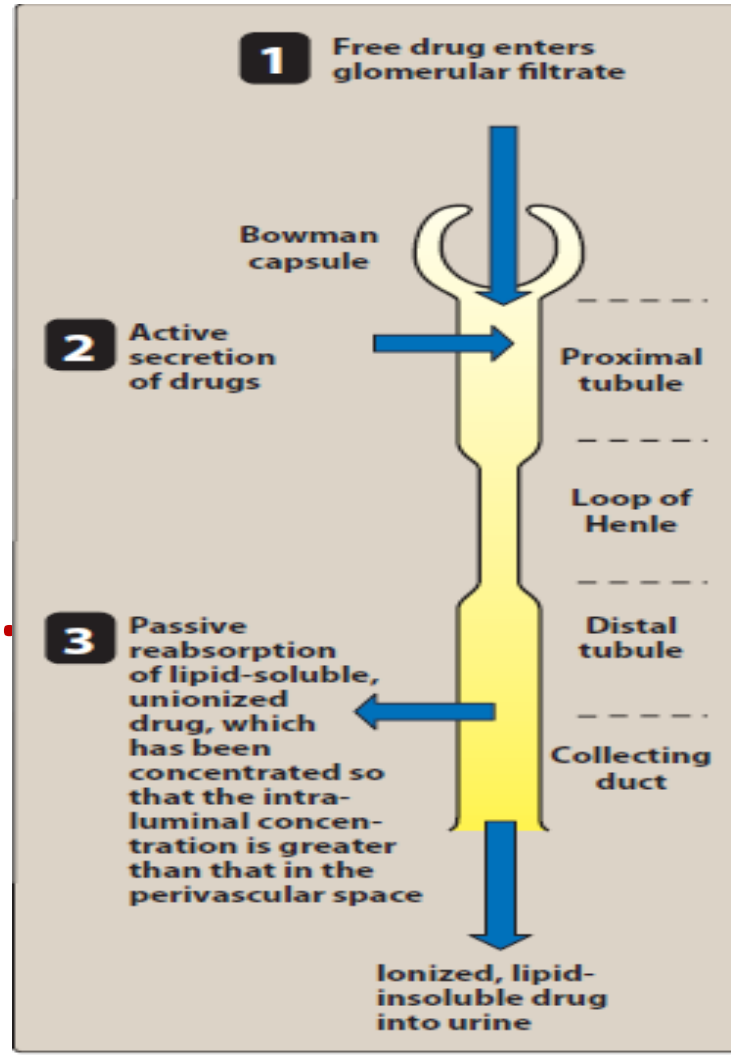
- This usually happens by the kidneys in to urine.
- Other possible routes include bile, saliva, sweat, tears, breast milk and faeces.
- The lungs are an excretion route by which volatile lipophilic substances (e.g., inhaled general anesthetics) can be excreted.
- Most drugs are insufficiently polar (and, therefore, water soluble) to be excreted directly. Instead they need to metabolism to produce more polar, water-soluble molecules
- Patients with renal dysfunction may be unable to excrete drugs and are at risk for drug accumulation and adverse effects.

- **Elimination of drugs by the kidneys into urine involves the 3 processes :**

➢ **glomerular filtration.**

➢ **active tubular secretion.**

➢ **passive tubular reabsorption.**



Drug elimination by the kidney.

Half-life

Half Life (t ½): Refers to the time required for the body to eliminate 50% of the drug.

- **It is important in planning the frequency of dosing.**
- **Short half-life (2-4 hours) : needs to be given frequently**
- **Long half life: (21-24 hours): requires less frequent dosing**

Note: It takes 5 to 6 half lives to eliminate approximately 98% of a drug from the body

- **Liver and kidney disease patients may have problems of excreting a drug.**
- **Difficulty in excreting a drug increases the half-life and increases the risk of toxicity.**

Half-life

Half-life measured in 3 ways

1) Plasma half life

2) Biological effect half life

3) Biological half life

Plasma – Half Life: Time in which the plasma concentration falls by one half

It is Influenced by various factor including **tissue diffusion, protein binding , renal excretion**

Half-life

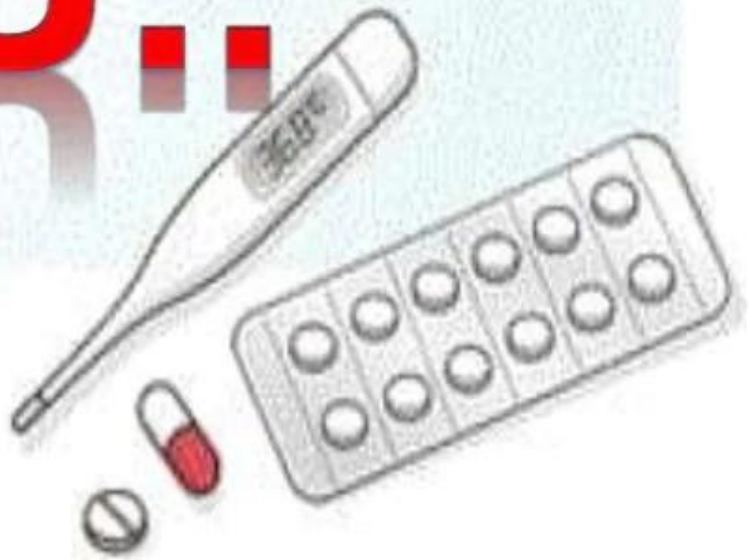
Biological effect half life:

Time in which a the pharmacological effect of the drug, and of any of the active metabolites, has declined by one half Eg. For antibiotics, varies with each infection

Biological half life

Time in which a the total amount of drug in the body after equilibrium of plasma with other compartments (fat, muscle) is halved

THANK U..



Pharmacology

Lec. 3+4 College of Dentistry

Dr Tamara Shaker hasoon ALfarabi university

Autonomic Nervous System

The nervous system is divided into two anatomical divisions: the central nervous system (CNS), which is composed of the brain and spinal cord, and the peripheral nervous system, which includes neurons located outside the brain and spinal cord—that is, any nerves that enter or leave the CNS (figure 1)

The autonomic nervous system (ANS) is largely independent (autonomous) in that its activities are not under direct conscious control. It is concerned primarily with visceral functions such as cardiac output, blood flow to various organs, and digestion, which are necessary for life.

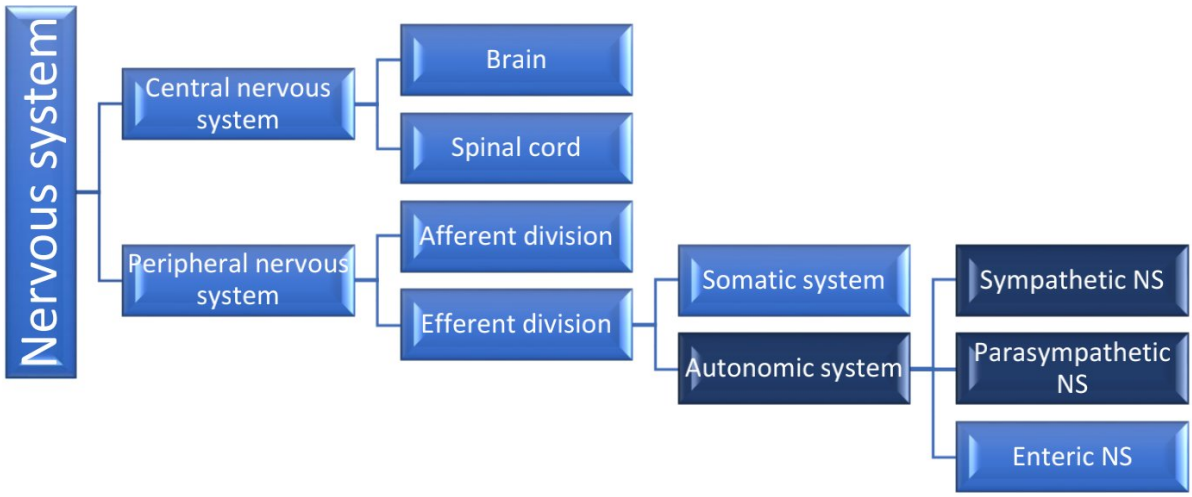


Figure 1: autonomic nervous system part of nervous system

The ANS carries nerve impulses from the CNS to the effector organs by way of two types of efferent neurons: the preganglionic neurons and the postganglionic neurons. In this pre and post ganglionic complex the ganglia function is embodied in acting as relay stations between the preganglionic neuron and the second nerve cell, the postganglionic neuron (figure 2). In the sympathetic system, the preganglionic fibres are short and postganglionic fibres are long. On the other hand, the parasympathetic preganglionic fibres are long and postganglionic fibres are short.

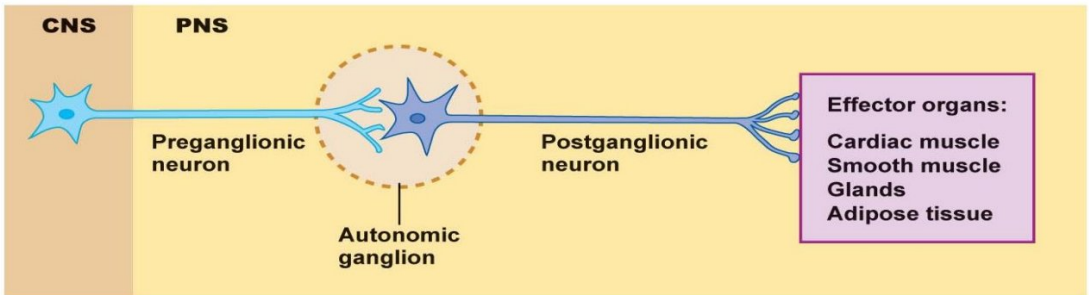


Figure 2: preganglionic and post ganglionic neurons

The function of the ANS can be explained by exploring the function of each part as the following (Figure 3):

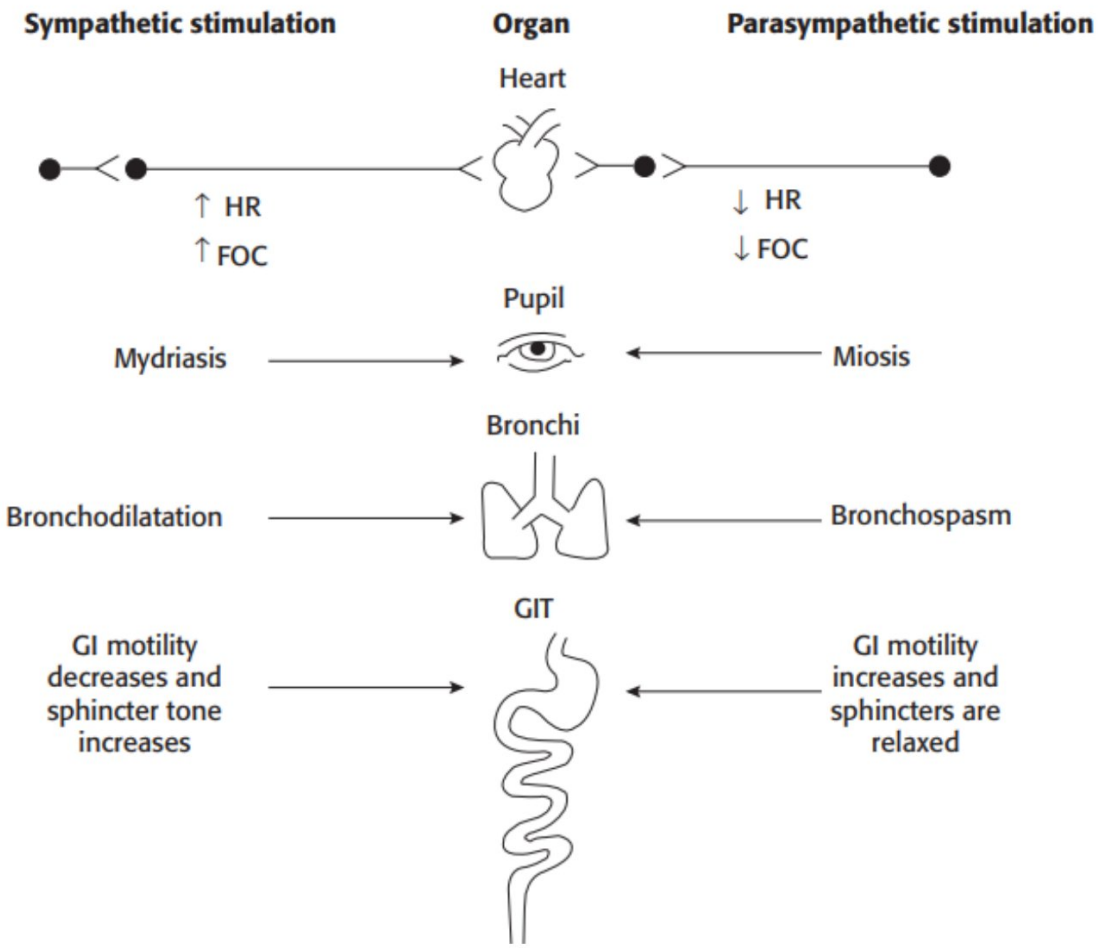


Figure 3: difference between parasympathetic and sympathetic division

A) Functions of the sympathetic nervous system

1- Effects of stimulation of the sympathetic division: The effect of sympathetic output is to:

1. Increasing heart rate and contractility, and thus, increasing blood pressure.
2. Constriction of the blood vessels of skin, mucous membranes, and splanchnic area, and dilation of skeletal muscles vessels.
3. Dilation of the pupils (mydriasis).
4. Bronchodilation.
5. Inhibit salivation.
6. Decrease GI motility.
7. Stimulation of ejaculation.
8. Inhibit bladder contraction.
9. Stimulate glucose production and release.

2- Fight-and-flight response: The changes experienced by the body during emergencies are referred to as the "fight and flight" response. These reactions are triggered both by direct sympathetic activation of the effector organs and by stimulation of the adrenal

medulla to release epinephrine and lesser amounts of norepinephrine. Hormones released by the adrenal medulla directly enter the bloodstream and promote responses in effector organs that contain adrenergic receptors. The sympathetic nervous system tends to function as a unit and often discharges as a complete system, for example, during severe exercise or in reactions to fear.

Accordingly, the sympathetic division has the property of adjusting in response to stressful situations, such as trauma, fear, hypoglycaemia, cold, and exercise.

B) **Functions of the parasympathetic nervous system**

The parasympathetic division is involved with maintaining homeostasis within the body. It is required for life, since it maintains essential bodily functions, such as digestion and elimination of wastes. The parasympathetic division usually acts to oppose or balance the actions of the sympathetic division and generally predominates the sympathetic system in "rest-and-digest" situations. Unlike the sympathetic system, the parasympathetic system never discharges as a complete system. If it did, it would produce massive, undesirable, and unpleasant symptoms, such as involuntary urination and defecation. Instead, parasympathetic fibres innervating specific organs such as the gut, heart, or eye are activated separately, and the system functions to affect these organs individually.

So, the effect of parasympathetic output can be summarised in:

1- Pupil contraction (miosis).
2- Bronchoconstriction.
3- Stimulation of erection.
4- Stimulation tears and saliva secretion.
5- Decreasing heart rate and contractility.
6- Increasing the muscle motility and tone of the gastrointestinal system.

C) **Functions of the enteric nervous system (ENS)**

The enteric nervous system is a collection of neurons in the gastrointestinal tract that constitutes the "brain of the gut" and can function independently of the central nervous system. This system controls the motility, exocrine and endocrine secretions, and microcirculation of the gastrointestinal tract.

D) **Functions of the somatic nervous system**

The somatic system is the part of the peripheral nervous system that is responsible for carrying motor and sensory information both to and from the central nervous system *without the mediation of ganglia*. This system is made up of nerves that connect to the skin, sensory organs, and all skeletal muscles. The system is responsible for nearly all voluntary muscle movements as well as for processing sensory information that arrives via external stimuli including hearing, touch, and sight. Figure 4 shows the main differences between autonomic and somatic nervous system.

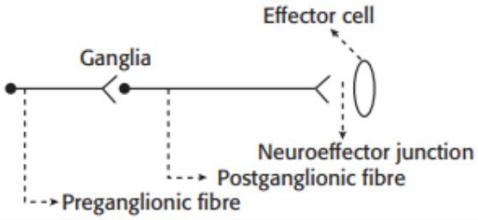
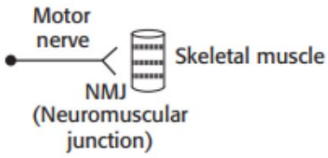
Autonomic Nervous System	Somatic Nervous System
Auto: self; *nomos*: governing; this system is involuntary and maintains homeostasis	Somatic nervous system is under voluntary control
Each autonomic fibre is made up of two neurons arranged in series	Each somatic fibre is made up of single motor neuron, which connects CNS to skeletal muscle
	
It innervates the heart, smooth muscles and exocrine glands	It innervates skeletal muscle
It controls visceral functions such as circulation, digestion, excretion, etc.	It controls skeletal muscle tone

Figure 4: main differences between autonomic and somatic nervous system

The ANS requires sensory input from peripheral structures to provide information on the current state of the body. This feedback is provided by streams of afferent impulses, originating in the viscera and other autonomically innervated structures that travel to integrating centres in the CNS, such as the hypothalamus and spinal cord. These centres respond to the stimuli by sending out efferent reflex impulses via the ANS. **This process of initiating an afferent impulse that travel to the CNS and replying by efferent impulse to get a response is called *reflex arc*** (figure 5).

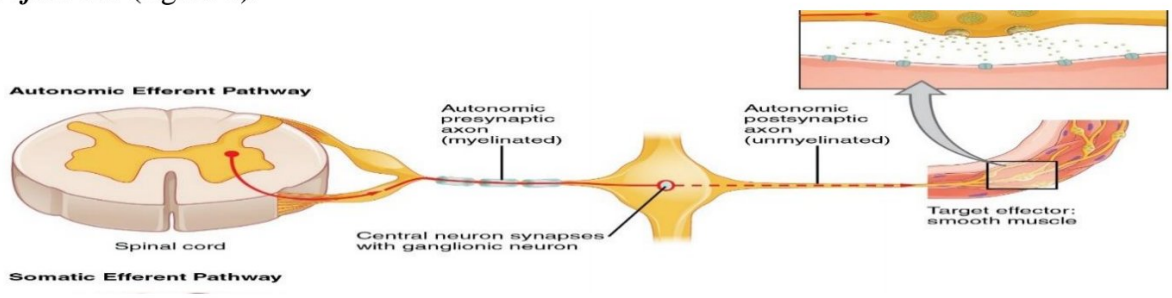


Figure 5: Somatic and autonomic reflex arc

Usually, most of the afferent impulses are involuntary translated into reflex responses. For example, a fall in blood pressure causes pressure-sensitive neurons (baroreceptors in the heart, vena cava, aortic arch, and carotid sinuses) to send fewer impulses to cardiovascular centres in the brain. This prompts a reflex response of increased sympathetic output to the heart and vasculature and decreased parasympathetic output to the heart, which results in a compensatory rise in blood pressure and tachycardia.

According to the above explanation, the reflex arcs of the ANS comprise a sensory (or afferent) arm and a motor (or efferent or effector) arm.

Neurotransmitters

Neurotransmission in the ANS is an example of the more general process of chemical signalling between cells using neurotransmitters. Neurotransmitters are specific chemical signals that are released from nerve terminals to establish the communication between nerve cells, and between nerve cells and effector organs.

In spite of recognising more than 50 signals molecules (neurotransmitters) in the nervous system, just norepinephrine (and the closely related epinephrine), acetylcholine, dopamine, serotonin, histamine, glutamate, and γ-aminobutyric acid are the most commonly involved neurotransmitters in the actions of therapeutically useful drugs. Each type of neurotransmitters can bind with a specific receptor in order to give the biological desirable response.

The primary chemical signals in the ANS are the acetylcholine and norepinephrine as they are involved in conducting wide variety functions in the CNS.

The autonomic nerve fibres can be classified to cholinergic and adrenergic neurons based on the type of the released neurotransmitters whether they are acetylcholine or epinephrine and norepinephrine.

Acetylcholine mediates the transmission of nerve impulses across autonomic ganglia in both the sympathetic and parasympathetic nervous systems. Transmission from the autonomic postganglionic nerves to the effector organs in the parasympathetic system, and a few sympathetic system organs also involve the release of acetylcholine (figure 6). In the somatic nervous system, transmission at the neuromuscular junction (the junction of nerve fibres and voluntary muscles) is also cholinergic.

In the sympathetic system, norepinephrine mediates the transmission of nerve impulses from autonomic postganglionic nerves to effector organs except few sympathetic fibres, such as those involved in sweating, are cholinergic.

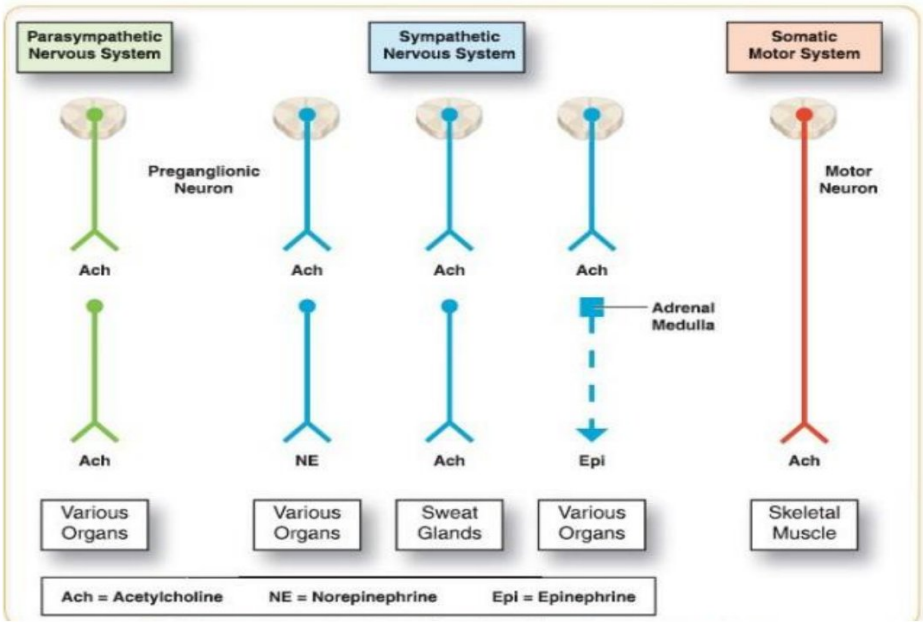


Figure 6: Neurotransmitters

Cholinergic agonists

The cholinergic drugs act on receptors that are activated by acetylcholine (ACh). These receptors include nicotinic and muscarinic receptors and can be mainly recognised in sympathetic and parasympathetic nervous system and somatic nervous system as well (Figure 7).

The two classes of receptor for Ach are defined on the basis of their preferential activation by the alkaloids *nicotine* and *muscarine.*

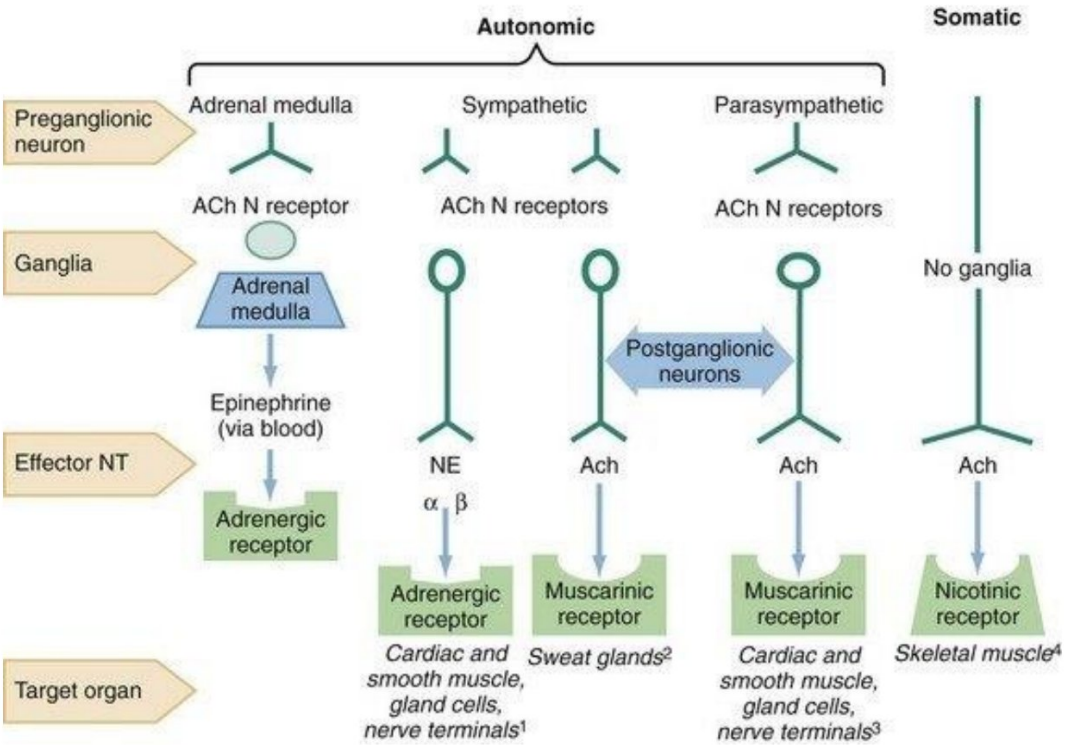


Figure 7: Ach receptors muscarinic and nicotinic receptors, the nicotinic receptors located on autonomic ganglia (Nn subtype) and on neuromuscular junction on somatic nervous system (Nm subtype)

Neurotransmission at cholinergic neurons

Neurotransmission in cholinergic neurons involves six sequential steps: 1) synthesis, 2) storage, 3) release, 4) binding of ACh to a receptor, 5) degradation of the neurotransmitter in the synaptic cleft (that is, the space between the nerve endings and adjacent receptors located on nerves or effector organs), and 6) recycling of choline and acetate (figure 8)

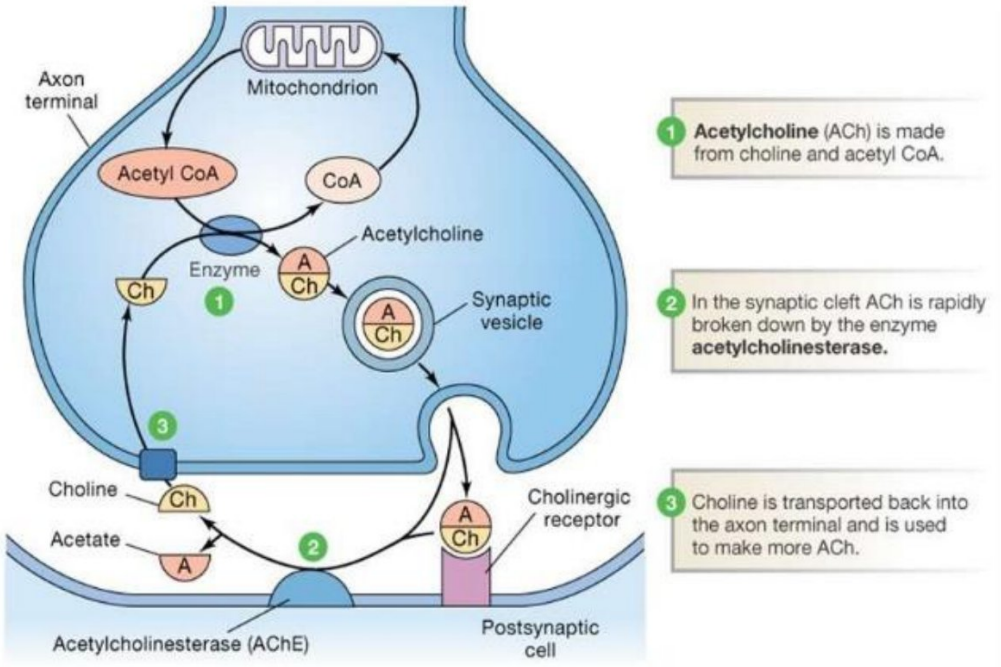


Figure 8: Ach synthesis

1.Synthesis of acetylcholine: Choline is transported from the extracellular fluid into the cytoplasm of the cholinergic neuron by an energy-dependent carrier system. Choline acetyltransferase catalyzes the reaction of choline with acetyl coenzyme A (CoA) to form ACh (an ester) in the cytosol.

2.Storage of acetylcholine in vesicles: ACh is packaged and stored into presynaptic vesicles.

3.Release of acetylcholine: When an action potential propagated at a nerve ending, voltage-sensitive calcium channels on the presynaptic membrane open, causing an increase in the concentration of intracellular calcium. Elevated calcium levels promote the fusion of synaptic vesicles with the cell membrane and the release of their contents into the synaptic space.

4.Binding to the receptor: ACh released from the synaptic vesicles diffuses across the synaptic space and binds its receptors. The postsynaptic cholinergic receptors on the surface of the effector organs are divided into two classes: muscarinic and nicotinic. Binding to a receptor leads to a biologic response within the cell, such as the initiation of a nerve impulse in a postganglionic fiber or activation of specific enzymes in effector cells.

5. Degradation of acetylcholine: The signal at the postjunctional effector site is rapidly terminated, because AChE (acetylcholine esterase) cleaves ACh to choline and acetate in the synaptic cleft.

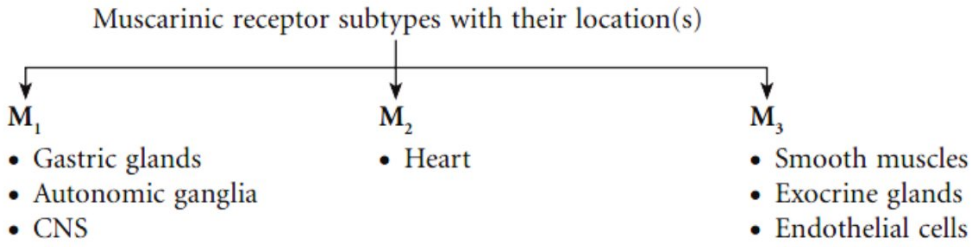
6. Recycling of choline: Choline may be recaptured by a sodium-coupled uptake system that transports the molecule back into the neuron. There, it is acetylated into ACh that is stored until released by a subsequent action potential.

CHOLINERGIC RECEPTORS (CHOLINOCEPTORS)

Cholinoceptors can be classified into two types: muscarinic and nicotinic receptors. They are different mainly in their affinities for agents that mimic the action of ACh (cholinomimetic agents).

1- **Muscarinic receptors:** It is one of the G protein–coupled receptors that have high affinity to bind with muscarine (an alkaloid that is present in certain poisonous mushrooms) and ACh but low affinity to bind with nicotine. Five sub-classes are recognised for this receptor family; however, only M1, M2, and M3 receptors have been functionally characterised.

   a- **Locations of muscarinic receptors:**

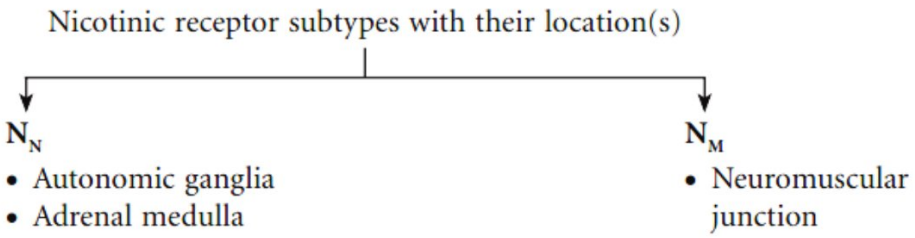


b- Muscarinic agonists: *Pilocarpine* is an example of a nonselective muscarinic agonist used in clinical practice to treat xerostomia and glaucoma. Attempts are currently underway to develop muscarinic agonists and antagonists that are directed against specific receptor subtypes. M1 receptor agonists are being investigated for the treatment of Alzheimer's disease.

2- Nicotinic receptors

These receptors, in addition to binding ACh, also recognise nicotine but show only a weak affinity for muscarine. Nicotine at low concentration stimulates the receptor, whereas nicotine at high concentration blocks the receptor. The nicotinic receptor functions as a ligand-gated ion channel.

Location: Nicotinic receptors are located in the CNS, the adrenal medulla, autonomic ganglia, and the neuromuscular junction (NMJ) in skeletal muscles.



Those at the NMJ are sometimes designated N_M, and the others, N_N. The nicotinic receptors of autonomic ganglia differ from those of the NMJ. For example, ganglionic receptors are selectively blocked by *mecamylamine*, whereas NMJ receptors are specifically blocked by *atracurium.*

Below is a table summarizing the function of each cholinergic receptor

Receptor Type(s)	Functional Response
M_1 and M_3	Promotes glandular secretion and smooth muscle contraction
M_2	Depressant effect on heart
N_N	Depolarization
N_M	Skeletal muscle contraction

DIRECT-ACTING CHOLINERGIC AGONISTS

Definition: Materials that mimic the effects of ACh by binding directly to cholinoceptors (muscarinic or nicotinic).

Types:

1) endogenous choline esters, which include ACh and synthetic esters of choline, such as *carbachol* and *bethanechol*.

2) Naturally occurring alkaloids, such as *nicotine* and *pilocarpine.* The main advantage of this group of drugs that have a longer duration of action than ACh.

The more therapeutically useful drugs (*pilocarpine* and *bethanechol*) preferentially bind to muscarinic receptors and are sometimes referred to as muscarinic agents. As a group, the direct-acting agonists demonstrate little specificity in their actions, which limits their clinical usefulness.

Acetylcholine

Acetylcholine is a quaternary ammonium compound; hence it cannot penetrate membranes. In spite of considering the ACh as a neurotransmitter of parasympathetic and somatic nerves as well as autonomic ganglia, it lacks therapeutic importance because of its pluralism of actions and its rapid inactivation by the cholinesterases. ACh has both muscarinic and nicotinic activity. Its actions include the following:

1- **Decrease in heart rate and cardiac output:** The actions of ACh on the heart imitate the effects of vagal stimulation. For example, if injected intravenously, ACh produces a brief decrease in cardiac rate (negative chronotropy) and stroke volume as a result of a reduction in the rate of firing at the sinoatrial (SA) node.

2- **Decrease in blood pressure:** As a result of ACh injection, vasodilation and lowering of blood pressure can be observed. This is due to an indirect mechanism of action because the ACh activates M3 receptors that found on endothelial cells lining the smooth muscles of blood vessels. This leads to produce a nitric oxide that act as a vasodilator from arginine. In the absence of administered cholinergic agents, the vascular cholinergic receptors have no known function, because ACh is never released into the blood in significant quantities. *Atropine* blocks these muscarinic receptors and prevents ACh from producing vasodilation.

3- **Other actions**

ACh administration can stimulate:

a- Salivary secretion stimulates intestinal secretions and motility.

b- Bronchiolar secretions.

c- Urination.

Moreover, ACh causes miosis (marked constriction of the pupil). Accordingly, ACh (1% solution) is instilled into the anterior chamber of the eye to produce miosis during ophthalmic surgery.

Therapeutic uses of direct-acting cholinergic agonists:

✓ bethanechol is used to stimulate the atonic bladder, particularly in postpartum or postoperative, nonobstructive urinary retention.

- ✓ Carbachol eye as a miotic agent to treat glaucoma by causing pupillary contraction and a decrease in intraocular pressure.
- ✓ Pilocarpine is used to treat glaucoma and is the drug of choice in the emergency lowering of intraocular pressure in glaucoma. It is also beneficial in promoting salivation in patients with xerostomia (dry mouth) resulting from irradiation therapy of the head and neck cancer or due to Sjogren's syndrome (an autoimmune disease in which the moisture-producing glands of the body are affected causing mainly symptoms of dry eyes and dry mouth).

Adverse effects of Ach and other cholinergic agonists: causes the effects of generalized cholinergic stimulation.

- Bronchospasm and increase secretions.
- GI: nausea, vomiting, and diarrhea.
- Miosis.
- Urinary urgency.
- Sweating (diaphoresis) and salivation.
- *Pilocarpine* can enter the brain (because it's a tertiary amine (unionized)) and cause CNS disturbances. Poisoning with this agent is characterized by exaggeration of various parasympathetic effects.

To counteract the poisoning effect of the pilocarpine and Bethanechol, Parenteral *atropine*, at doses that can cross the blood–brain barrier, is administered to counteract the toxicity of *the cholinergic material.*

INDIRECT-ACTING CHOLINERGIC AGONISTS (ANTICHOLINESTERASE AGENTS (REVERSIBLE))

ACh is uaually deactivated by the AChE (Acetylcholine esterase), which is an enzyme that specifically cleaves ACh to acetate and choline. It can be found at both pre- and postsynaptically in the nerve terminal where it is membrane bound.
Accordingly, inhibition of AchE can indirectly provide a cholinergic action by preventing the degradation of ACh. This results in an accumulation of ACh in the synaptic space. This process can be carried out by using the anticholinesterase agents or cholinesterase inhibitors. These drugs can provoke a response at all cholinoceptors in the body, including both muscarinic and nicotinic receptors of the ANS, as well as at the NMJ and in the brain.

Therapeutic uses of acetylcholinesterase inhibitors (reversible)

Edrophonium, pyridostigmine, and ambenonium: They are used in the diagnosis and management of myasthenia gravis, which is an autoimmune disease caused by antibodies to the nicotinic receptor at NMJs. This causes their degradation, making fewer receptors available for interaction with the neurotransmitter.

Physostigmine

- It increases intestinal and bladder motility, which serve as its therapeutic action in atony of either organ.
- used to treat glaucoma, but *pilocarpine* is more effective.
- as an antidote for drugs with anticholinergic actions.

Neostigmine

- used to stimulate the bladder and GI tract.
- as an antidote for *tubocurarine* and other competitive neuromuscularblocking agents.
- also used to treat myasthenia gravis.

Tacrine, donepezil, rivastigmine, and galantamine

Patients with Alzheimer disease have a deficiency of cholinergic neurons in the CNS. This observation led to the development of anticholinesterases as possible remedies for the loss of cognitive function. *Tacrine* was the first to become available, but it has been replaced by others because of its hepatotoxicity. Despite the ability of *donepezil*, *rivastigmine,* and *galantamine* to delay the progression of Alzheimer disease, none can stop its progression.

Adverse effects of acetylcholinesterase inhibitors (reversible):

- Adverse effects include those of generalized cholinergic stimulation, such as salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm.
- Inhibition of AChE at the skeletal NMJ causes the accumulation of ACh and, ultimately, results in paralysis of skeletal muscle.
- *Physostigmine* can enter and stimulate the cholinergic sites in the CNS. The effects on the CNS may lead to convulsions when high doses are used. Bradycardia and a fall in cardiac output may also occur.

INDIRECT-ACTING CHOLINERGIC AGONISTS (ANTICHOLINESTRASE AGENTS (IRREVERSIBLE))

A number of synthetic organophosphate compounds have the capacity to bind covalently to AChE. The result is a long-lasting increase in ACh at all sites where it is released. Many of these drugs are extremely toxic and were developed by the military as nerve agents. Related compounds, such as *parathion* and *malathion*, are used as insecticides.

Table: Summary of echothiophate actions, therapeutic uses and its adverse effect.

Anticholinesterase agent (Irreversible)	Actions	Therapeutic uses	Adverse effect
Echothiophate	*Covalently binds to the AChE.	*A topical solution of the drug is for the treatment of open-angle glaucoma.	*Represented by the generalised cholinergic stimulation. *Paralysis of motor function (causing breathing difficulties). *Convulsions.

Cholinergic Antagonists

Cholinergic antagonist is a general term for agents that bind to cholinoceptors (muscarinic or nicotinic) and prevent the effects of acetylcholine (ACh) and other cholinergic agonists.

There are three types of cholinergic antagonist drugs, which are:

1- Antimuscarinic agents (anticholinergic drugs) block muscarinic receptors, causing inhibition of muscarinic functions. Because they do not block nicotinic receptors, the anticholinergic drugs (more precisely, antimuscarinic drugs) have little or no action at skeletal neuromuscular junctions (NMJs).

2- Ganglionic blockers (specifically act on the nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia)

3- The neuromuscular-blocking agents (mostly nicotinic antagonists), which block cholinergic transmission between motor nerve endings and the nicotinic receptors on the skeletal muscle

1- Atropine (antimuscarinic agents): It is an alkaloid with a high affinity for muscarinic receptors. It binds competitively and prevents ACh from binding to those sites. Atropine acts both centrally and peripherally. Its general actions last about 4 hours, except when placed topically in the eye, where the action may last for days. Neuroeffector organs have varying sensitivity to atropine.

Effects:

- CNS: confusion, delirium.
- Decrease GI motility and acid secretions without interfering with hydrochloric secretion.

- **Increase heart rate at high doses, i.e. higher than (0.5 mg). At low doses slight decrease in heart rate:** At low doses, the predominant effect is a slight decrease in heart rate. This effect results from blockade of the M1 receptors on the inhibitory prejunctional (or presynaptic) neurons, thus permitting increased ACh release. Higher doses of atropine cause a progressive increase in heart rate by blocking the M2 receptors on the sinoatrial node
- Decrease body secretions like saliva (xerostomia), bronchial secretions, and sweat (elevate body temperature).
- Mydriasis (cycloplegic to permits the measurement of refractive errors without interference by the accommodative capacity of the eye).

Therapeutic uses:

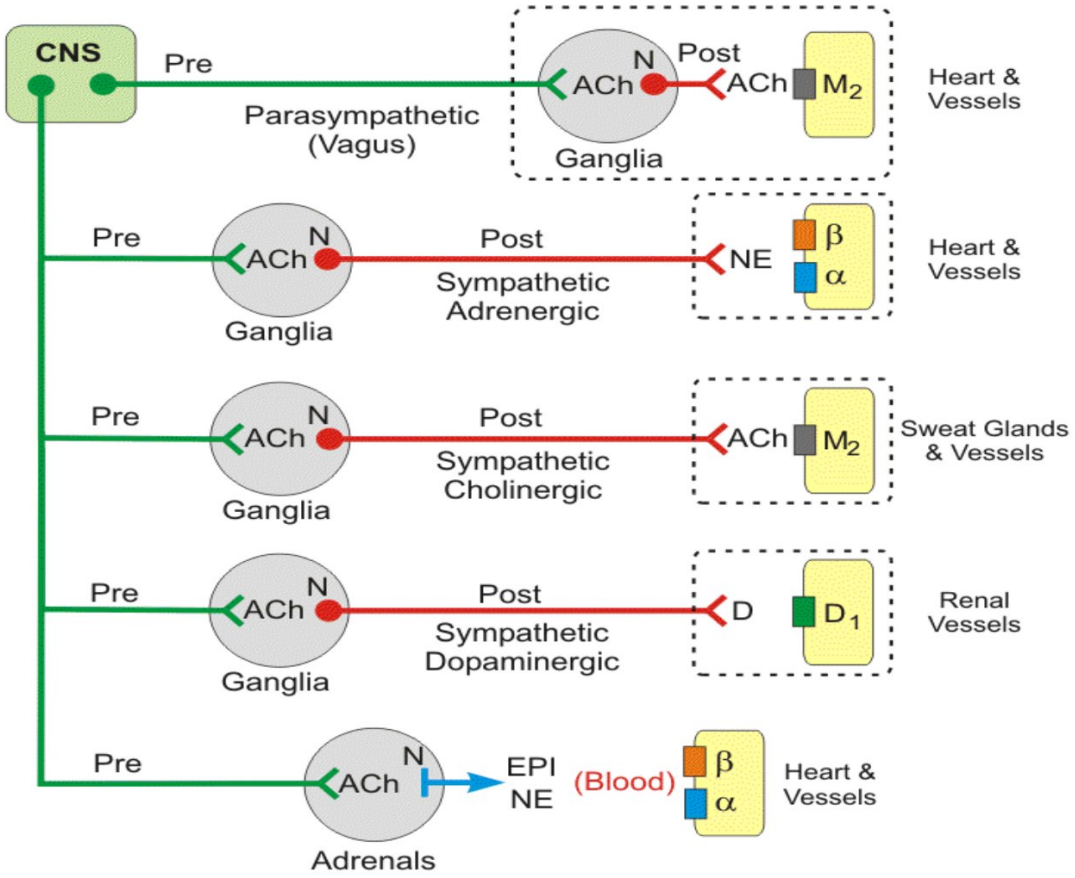
- As mydriatic and cycloplegic: Atropine is used topically for producing mydriasis and cycloplegia. The action of atropine lasts 7–10 days.
- As preanaesthetic medication: Atropine is used prior to the administration of general anaesthetics: To prevent vagal bradycardia during anaesthesia. To prevent laryngospasm by decreasing respiratory secretions. Antisecretory agent to block the secretions in the upper and lower respiratory tracts before surgery.
- Anticholinergics are useful as antispasmodics in dysmenorrhoea, intestinal and renal colic.
- Poisoning: a. In organophosphorous poisoning, atropine is the life-saving drug. b. In some types of mushroom poisoning, atropine is the drug of choice . c. Atropine is used in curare poisoning with neostigmine to counteract the muscarinic effects of neostigmine.
- As vagolytic: Atropine is used to treat sinus bradycardia and partial heart block due to increased vagal activity.

Side effects: Blurred vision, decrease secretions, hyperthermia, constipation, urinary retention, delirium, and hallucinations.

- ✓ ***Scopolamine*** is another antagonist used for motion sickness.
- ✓ ***Ipratropium*** used as inhaler to decrease bronchoconstriction and bronchial secretions in COPD (chronic obstructive pulmonary disease) and asthma.

2- Nicotine (Ganglionic blockers)**:** although nicotine considers as an agonist at nicotinic receptors, but at higher dose it blocks the autonomic ganglia (figure 9). Nicotine produces initial stimulation and varying degrees of subsequent block through a mechanism analogous to that of succinylcholine (see later).

Nicotine is a component of cigarette smoke, is a poison with many undesirable actions. However, it can be used in a controlled way to help in giving up smoking. It is found in more than one pharmaceutical dosage forms like sublingual tablets, lozenges and as chewing gum. Its action can be summarised in these points: Increasing the blood pressure and cardiac rate and at higher doses, the blood pressure falls because of ganglionic blockade, and activity in both the GI tract and bladder musculature ceases.



CNS = central nervous system; Pre = preganglionic; Post = postganglionic; ACh = acetylcholine; N = nicotinic receptor; NE = norepinephrine; EPI = epinephrine; D = dopamine; M_2 = muscarinic receptor; β = β-adrenoceptor; α = α-adrenoceptor; D_1 = dopaminergic receptor

Figure 9: position of nicotinic receptor in autonomic ganglia

3- The neuromuscular-blocking agents: These drugs block cholinergic transmission between motor nerve endings and the nicotinic receptors on the skeletal muscle. They possess some chemical similarities to ACh, and they act either as antagonists (nondepolarising type) or as agonists (depolarising type) at the receptors on the endplate of the NMJ. Neuromuscular blockers are clinically useful during surgery to facilitate tracheal intubation and provide complete muscle relaxation at lower anaesthetic doses, allowing for more rapid recovery from anesthesia and reducing postoperative respiratory depression.

1- Nondepolarising (competitive) blockers: At low doses: Nondepolarising agents competitively block ACh at the nicotinic receptors. That is, they compete with ACh at the receptor without stimulating it. Thus, these drugs prevent depolarisation of the muscle cell membrane and inhibit muscular contraction. On the other hand, **on high doses**, these drugs can lead to complete blockade and the muscle does not respond to direct electrical stimulation. All neuromuscular-blocking agents are injected intravenously or occasionally intramuscularly since they are not effective orally. In general, these agents are safe with minimal side effects; however, they can rarely cause bronchospasm.

2- **Depolarising agents:** Depolarising blocking agents work by depolarising the plasma membrane of the muscle fibre, similar to the action of ACh. However, these agents are more resistant to degradation by acetylcholinesterase (AChE) and can thus more persistently depolarise the muscle fibres. *Succinylcholine* is the only depolarising muscle relaxant in use today. *Succinylcholine* attaches to the nicotinic receptor and acts like ACh to depolarise the junction. This leads to a transient twitching of the muscle. Continued binding of the depolarising agent renders the receptor incapable of transmitting further impulses leading to flaccid paralysis. Therapeutically, *succinylcholine (which is administered IV)* is useful when rapid endotracheal intubation is required during the induction of anaesthesia. The main side effects of this drug are the hyperthermia, apnea and hyperkalaemia.

ADRENERGIC AGONISTS

Lec. 5+6

The sympathetic nervous system is an important regulator of virtually all organ systems. This is particularly evident in the regulation of blood pressure. The autonomic nervous system is crucial for the maintenance of blood pressure even under relatively minor situations of stress (eg, the gravitational stress of standing).

The ultimate effects of sympathetic stimulation are mediated by release of norepinephrine from nerve terminals, which then activates adrenoceptors on postsynaptic sites.

Also, in response to a variety of stimuli such as stress, **the adrenal medulla releases epinephrine, which is transported in the blood to target tissues.**

The adrenergic drugs affect receptors that are stimulated by norepinephrine (noradrenaline) or epinephrine (adrenaline).

These receptors are known as adrenergic receptors or adrenoceptors. Drugs that activate adrenergic receptors are termed **sympathomimetics**, and drugs that block activation of adrenergic receptors are termed **sympatholytics**.

The sympathomimetics are readily divided into subgroups on the basis of **their spectrum of action (α-, β-, or dopamine-receptor affinity) or mode of action (direct or indirect).**Most of the actions of catecholamines and sympathomimetic agents can be classified into seven broad types:

1. A peripheral excitatory action on certain types of smooth muscle, such as those in blood vessels supplying skin, kidney, and mucous membranes; and on gland cells, such as those in salivary and sweat glands.

2. A peripheral inhibitory action on certain other types of smooth muscle, such as those in the wall of the gut, in the bronchial tree, and in blood vessels supplying skeletal muscle.

3. A cardiac excitatory action that increases heart rate and force of contraction.

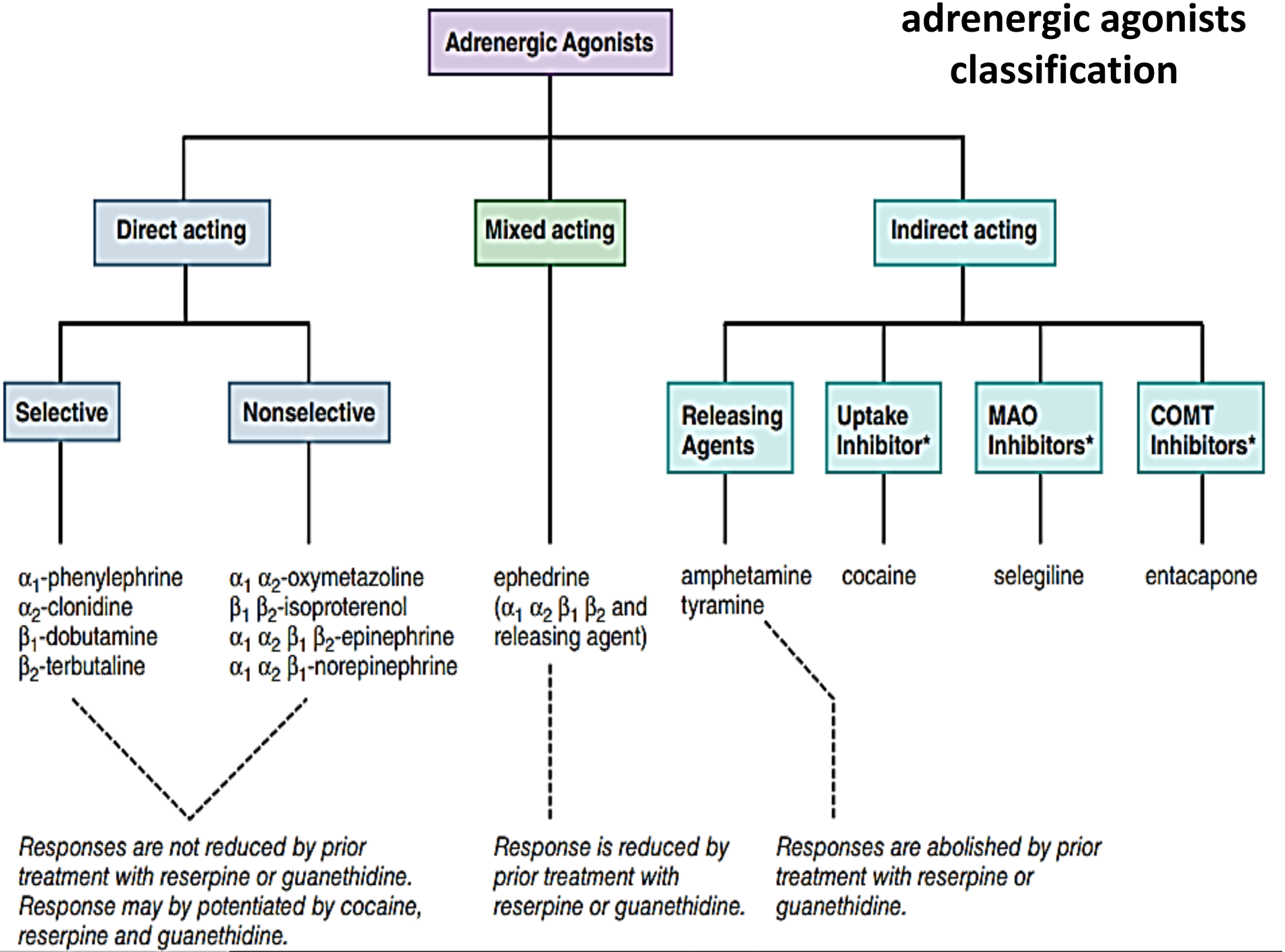
4. Metabolic actions, such as an increase in the rate of glycogenolysis in liver and muscle and liberation of free fatty acids from adipose tissue.

5. Endocrine actions, such as modulation (increasing or decreasing) of the secretion of insulin, renin, and pituitary hormones.

6. Actions in the CNS, such as respiratory stimulation, an increase in wakefulness and psychomotor activity, and a reduction in appetite.

7. Pre junctional actions that either inhibit or facilitate the release of neurotransmitters.

adrenergic agonists classification



Neurotransmission at adrenergic neurons

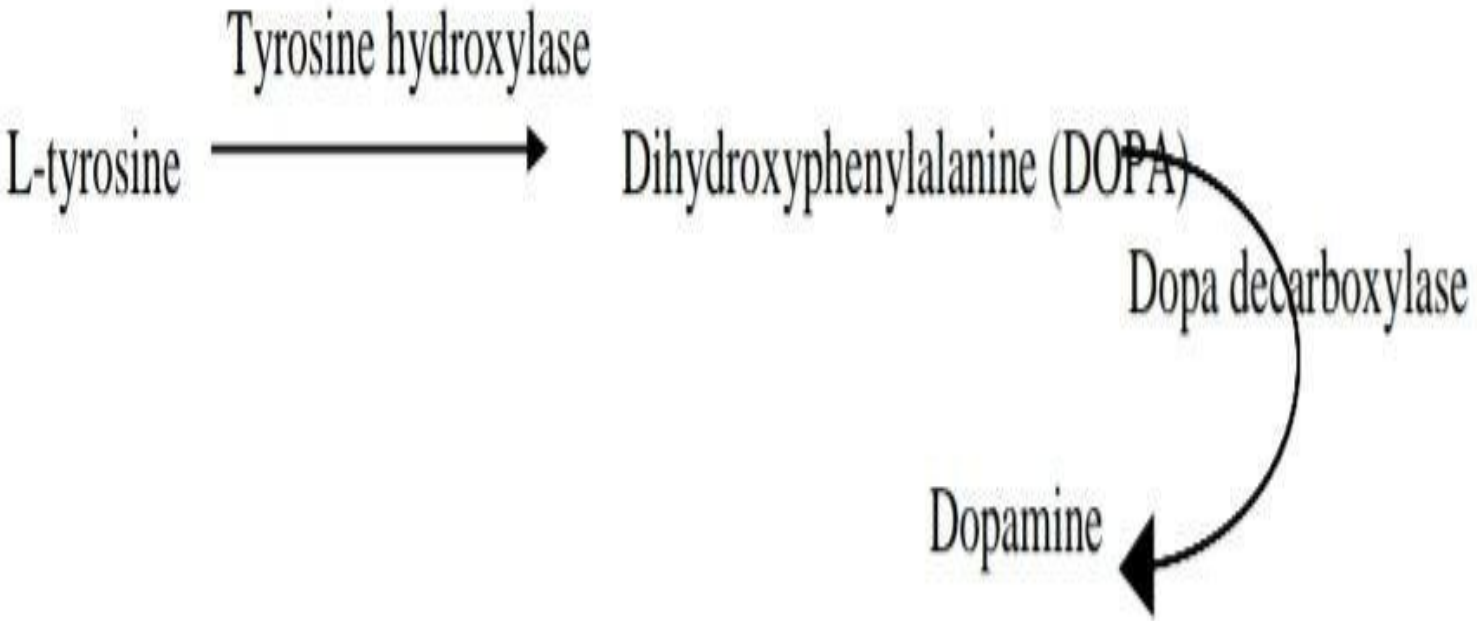
Neurotransmission at adrenergic neurons is similar to what was describe in cholinergic neurons, **except that norepinephrine (noradrenaline) is the neurotransmitter instead of acetylcholine.**

The neurotransmission involves the following steps: synthesis, storage, release, and receptor binding of norepinephrine, followed by removal of the neurotransmitter from the synaptic gap.

Synthesis of norepinephrine

The metabolic precursor for norepinephrine (noradrenaline) is L-tyrosine, which is transported by a Na+ linked carrier into adrenergic neurons. **Tyrosine hydroxylase**, a cytosolic enzyme that catalyses the conversion of tyrosine to **dihydroxyphenylalanine (dopa).**

decarboxylase in the presynaptic neuron.



The next step, conversion of dopa to dopamine, is catalysed by dopa decarboxylase in the presynaptic neuron.

Storage of norepinephrine in vesicles

Dopamine is then transported into synaptic vesicles by an amine transporter system. **Dopamine is next hydroxylated to form norepinephrine by the enzyme dopamine β-hydroxylase.**

In the adrenal medulla, norepinephrine is methylated to form epinephrine (adrenaline), which is stored in chromaffin cells along with norepinephrine. On **stimulation,** the adrenal medulla releases about 80% epinephrine and 20% norepinephrine directly into the circulation.

Release of norepinephrine

An action potential arriving at the nerve junction triggers an influx of calcium ions from the extracellular fluid into the cytoplasm of the neuron. The increase in calcium causes synaptic vesicles to fuse with the cell membrane and to undergo exocytosis to expel their contents into the synapse.

Binding to receptors

Norepinephrine released binds to postsynaptic receptors on the effector organ or to presynaptic receptors on the nerve ending. Binding of norepinephrine to receptors results in the formation of intracellular second messengers (the cyclic adenosine monophosphate (cAMP) second messenger system and the phosphatidylinositol cycle) to transduce the signal into an effect.

Norepinephrine also binds to presynaptic receptors (mainly α2 subtype) that modulate the release of the neurotransmitter.

Removal of norepinephrine

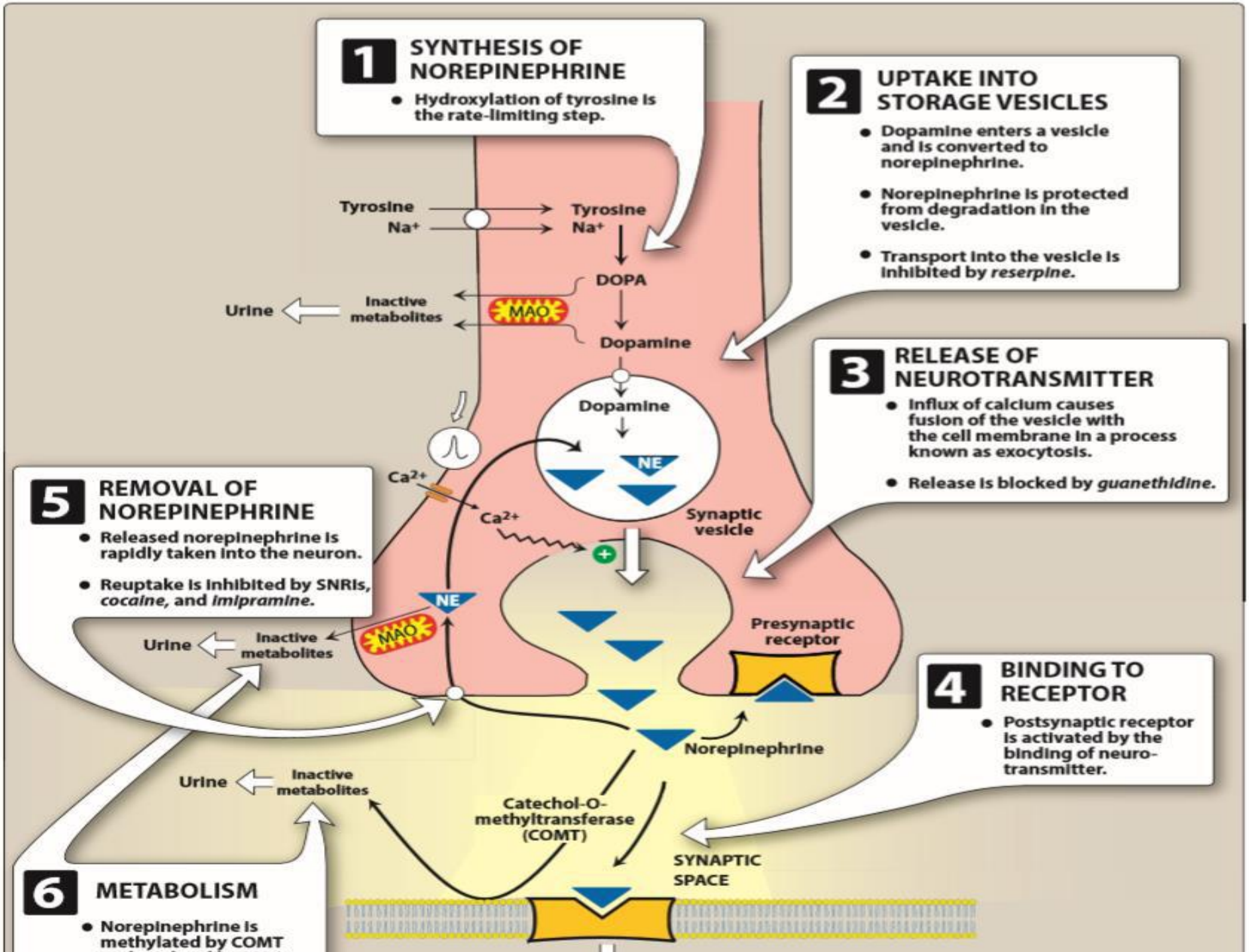
Norepinephrine may

1) diffuse out of the synaptic space and enter the systemic circulation;
2) be metabolized to inactive metabolites by catechol-O-methyltransferase (COMT) in the synaptic space; or
3) undergo reuptake back into the neuron. Reuptake of norepinephrine into the presynaptic neuron is the primary mechanism for termination of its effects.

Potential fates of recaptured norepinephrine

Once norepinephrine reenters the adrenergic neuron, it may be taken up into synaptic vesicles via the amine transporter system and be sequestered for release by another action potential, or it may persist in a protected pool in the cytoplasm.

Alternatively, norepinephrine can be oxidized by monoamine oxidase (MAO) present in neuronal mitochondria.


1 SYNTHESIS OF NOREPINEPHRINE
Hydroxylation of tyrosine is the rate-limiting step.
2 UPTAKE INTO STORAGE VESICLES
Dopamine enters a vesicle and is converted to norepinephrine.
Norepinephrine is protected from degradation in the vesicle.
Transport into the vesicle is inhibited by reserpine.
3 RELEASE OF NEUROTRANSMITTER
Influx of calcium causes fusion of the vesicle with the cell membrane in a process known as exocytosis.
Release is blocked by guanethidine.
4 BINDING TO RECEPTOR
Postsynaptic receptor is activated by the binding of neuro-transmitter.
5 REMOVAL OF NOREPINEPHRINE
Released norepinephrine is rapidly taken into the neuron.
Reuptake is inhibited by SNRIs, cocaine, and imipramine.
6 METABOLISM
Norepinephrine is methylated by COMT
Tyrosine
Na+
Tyrosine
Na+
DOPA
MAO
Urine
Inactive metabolites
Dopamine
Dopamine
NE
Ca2+
Ca2+
Synaptic vesicle
NE
MAO
Urine
Inactive metabolites
Presynaptic receptor
Norepinephrine
Urine
Inactive metabolites
Catechol-O-methyltransferase (COMT)
SYNAPTIC SPACE

Adrenergic receptors

Two main families of receptors designated α and β, are classified based on response to the adrenergic agonists epinephrine, norepinephrine, and isoproterenol.

α-Adrenoceptors:

divided into two subtypes, α1 and α2, based on their affinities for α agonists and antagonists. For example, α1 receptors have a higher affinity for phenylephrine than α2 receptors.

α1 Receptors These receptors are present on the postsynaptic membrane of the effector organs and mediate many of the classic effects, originally designated as α-adrenergic, involving constriction of smooth muscle.

α2 Receptors These receptors are located primarily on sympathetic presynaptic nerve endings and control the release of norepinephrine (inhibit). This inhibitory action serves as a local mechanism for modulating norepinephrine output when there is high sympathetic activity.

β-Adrenoceptors

For β receptors, the rank order of potency is isoproterenol > epinephrine > norepinephrine.

The β-adrenoceptors can be subdivided into three major subgroups, β1, β2, and β3, based on their affinities for adrenergic agonists and antagonists.

Dopamine Receptors

The D 1 receptor is typically associated with the stimulation of adenylyl cyclase for example, D 1 - receptor–induced smooth muscle relaxation is presumably due to cAMP accumulation in the smooth muscle of those vascular beds in which dopamine is a vasodilator.

D 2 receptors have been found to inhibit adenylyl cyclase activity, open potassium channels, and decrease calcium influx.

Figure 3: adrenergic receptors

Type	Tissue	Actions
α_1	Most vascular smooth muscle (innervated)	Contraction
	Pupillary dilator muscle	Contraction (dilates pupil)
	Pilomotor smooth muscle	Erects hair
	Prostate	Contraction
	Heart	Increases force of contraction
α_2	Postsynaptic CNS neurons	Probably multiple
	Platelets	Aggregation
	Adrenergic and cholinergic nerve terminals	Inhibits transmitter release
	Some vascular smooth muscle	Contraction
	Fat cells	Inhibits lipolysis
β_1	Heart, juxtaglomerular cells	Increases force and rate of contraction; increases renin release
β_2	Respiratory, uterine, and vascular smooth muscle	Promotes smooth muscle relaxation
	Skeletal muscle	Promotes potassium uptake
	Human liver	Activates glycogenolysis
β_3	Fat cells	Activates lipolysis
D_1	Smooth muscle	Dilates renal blood vessels
D_2	Nerve endings	Modulates transmitter release

Desensitization of receptors

Prolonged exposure to the catecholamines reduces the responsiveness of these receptors, a phenomenon known as **desensitization.** Three mechanisms have been suggested to explain this phenomenon:

1) sequestration of the receptors so that they are unavailable for interaction with the ligand;

2) down-regulation, that is, a disappearance of the receptors either by destruction or by decreased synthesis; and

3) an inability to couple to G-protein, because the receptor has been phosphorylated on the cytoplasmic side.

Characteristic of adrenergic agonists (catecholamine and non)

Most adrenergic drugs are derivatives of β-phenylethylamine. Substitutions on the benzene ring or on the ethylamine side chains produce a variety of **compounds with varying abilities to differentiate between α and β receptors and to penetrate the CNS.**

Catecholamines are compounds containing a catechol moiety (a benzene ring with two adjacent hydroxyl groups) and an amine side chain. Pharmacologically, the most important ones are: noradrenaline (norepinephrine), adrenaline (epinephrine), dopamine, and isoprenaline (also known as isoproterenol).

These compounds share the following properties:

1. High potency: Catecholamines show the highest potency in directly activating α or β receptors.

2. Rapid inactivation: Catecholamines are metabolized by COMT postsynaptically and by MAO intraneuronally, by COMT and MAO in the gut wall, and by MAO in the liver. Thus, catecholamines have only a brief period of action when given parenterally, and they are inactivated (ineffective) when administered orally.

3. Poor penetration into the CNS: Catecholamines are polar and, therefore, do not readily penetrate into the CNS. Nevertheless, most catecholamines have some clinical effects (anxiety, tremor, and headaches) that are attributable to action on the CNS.

Noncatecholamines: Compounds lacking the catechol hydroxyl groups have longer half-lives, because they are not inactivated by COMT. These include phenylephrine, ephedrine, and amphetamine.

Adrenergic agonists classification

1. Direct-acting agonists These drugs act directly on α or β receptors, producing effects similar to those that occur following stimulation of sympathetic nerves or release of epinephrine from the adrenal medulla. Examples epinephrine, norepinephrine, isoproterenol, dopamine, and phenylephrine.

2. Indirect-acting agonists :These agents may block the reuptake of norepinephrine (cocaine)or cause the release of norepinephrine from the cytoplasmic pools or vesicles of the adrenergic neuron (amphetamine). The norepinephrine then binds to α or β receptors.

3. Mixed-action agonists Ephedrine and its stereoisomer, pseudoephedrine, both stimulate adrenoceptors directly and enhance release of norepinephrine from the adrenergic neuron.

CATECHOLAMINES

- Rapid onset of action
- Brief duration of action
- Not administered orally
- Do not penetrate the blood-brain barrier

NONCATECHOL-AMINES

Compared to catecholamines:

- Longer duration of action
- All can be administered orally or via inhalation

DRUG	RECEPTOR SPECIFICITY	THERAPEUTIC USES
Epinephrine	α_1, α_2 β_1, β_2	Acute asthma Anaphylactic shock In local anesthetics to increase duration of action
Norepinephrine	α_1, α_2 β_1	Treatment of shock
Isoproterenol	β_1, β_2	As a cardiac stimulant
Dopamine	Dopaminergic α_1, β_1	Treatment of shock Treatment of congestive heart failure Raise blood pressure
Dobutamine	β_1	Treatment of acute heart failure
Oxymetazoline	α_1	As a nasal decongestant
Phenylephrine	α_1	As a nasal decongestant Raise blood pressure Treatment of paroxysmal supraventricular tachycardia
Clonidine	α_2	Treatment of hypertension
Albuterol *Terbutaline*	β_2	Treatment of bronchospasm (short acting)
Salmeterol *Formoterol*	β_2	Treatment of bronchospasm (long acting)
Amphetamine	α, β, CNS	As a CNS stimulant in treatment of children with attention deficit syndrome, narcolepsy, and for appetite control
Ephedrine *Pseudoephedrine*	α, β, CNS	As a nasal decongestant Raise blood pressure

Direct-acting agonists

Direct-acting agonist: bind to adrenergic receptors on effector organs without interacting with the presynaptic neuron. As a group, these agents are widely used clinically.

A. Epinephrine:

Epinephrine interacts with both α and β receptors. At low doses, β effects (vasodilation) on the vascular system predominate, whereas at high doses, α effects (vasoconstriction) are the strongest.

1. Actions:

a. Cardiovascular: increase contractility of the myocardium (positive inotrope: β1 action) and increases its rate of contraction (positive chronotrope: β1 action). Therefore, cardiac output increases. Epinephrine activates β1 receptors on the kidney to cause renin release (an enzyme involved in the production of angiotensin II, a potent vasoconstrictor).

Epinephrine constricts arterioles in the skin, mucous membranes, and viscera (α effects), and it dilates vessels going to the liver and skeletal muscle (β2 effects).

b. Respiratory: Epinephrine causes powerful bronchodilation by acting directly on bronchial smooth muscle (β2 action). It also inhibits the release of allergy mediators such as histamines from mast cells.

c. Hyperglycemia: Epinephrine increases glycogenolysis in the liver (β2 effect), increased release of glucagon (β2 effect), and a decreased release of insulin (α2 effect).

d. Lipolysis: Epinephrine initiates lipolysis through β receptors of adipose tissue.

2. Therapeutic uses: a. (Bronchospasm)acute asthma and anaphylactic shock.

b. Anaphylactic shock: type I hypersensitivity reactions (including anaphylaxis)

c. Cardiac arrest

d. Anesthetics: Local anesthetic solutions may contain low concentrations (for example, 1:100,000 parts)

3. Pharmacokinetics: Epinephrine has a rapid onset but a brief duration of action (due to rapid degradation). It can be given IV , IM, and by inhalation. It is rapidly metabolized by MAO and COMT.

4. Adverse effects: Epinephrine can produce adverse CNS effects that include anxiety, fear, tension, headache, and tremor. It can trigger cardiac arrhythmias, particularly if the patient is receiving digoxin, and can lead to myocardial ischemia or infarction (MI). Epinephrine can also induce pulmonary edema.

B. Norepinephrine

when administered in therapeutic doses, the α-adrenergic receptor is most affected (α1=α2>β1).

1. Cardiovascular actions:

a. Vasoconstriction: Norepinephrine causes a rise in peripheral resistance due to intense vasoconstriction of most vascular beds (α1 effect). Both systolic and diastolic blood pressures increase.

b. Baroreceptor reflex: Norepinephrine increases blood pressure, and this stimulates the baroreceptors, inducing a rise in vagal activity. The increased vagal activity produces a reflex bradycardia, which is sufficient to counteract the local actions of norepinephrine on the heart, although the reflex compensation does not affect the positive inotropic effects of the drug.

When atropine, which blocks the transmission of vagal effects, is given before norepinephrine, stimulation of the heart by norepinephrine is evident as tachycardia.

2. Therapeutic uses: Norepinephrine is used to treat shock.

3. Pharmacokinetics: Norepinephrine is given IV. It is rapidly metabolized by MAO and COMT. 4. Adverse effects: These are similar to epinephrine. In addition, it may cause blanching and sloughing of skin along an injected vein.

C. Isoproterenol:

Isoproterenol is a direct-acting synthetic catecholamine that stimulates both β1- and β2-adrenergic receptors. Its action on α receptors is insignificant. Isoproterenol produces intense stimulation of the heart, increasing heart rate, contractility, and cardiac output.

D. Dopamine:

Dopamine can activate α- and β-adrenergic receptors. For example, at higher doses, it causes vasoconstriction by activating α1 receptors, whereas at lower doses, it stimulates β1 cardiac receptors. In addition, D1 and D2 dopaminergic receptors in the peripheral mesenteric and renal vascular beds, where binding of dopamine produces vasodilation.

1- Actions:

a. **Cardiovascular:** Dopamine exerts a stimulatory effect on the β1 receptors of the heart, having both positive inotropic and chronotropic effects.

b. **Renal and visceral:** Dopamine dilates renal and splanchnic arterioles by activating dopaminergic receptors, thereby increasing blood flow to the kidneys and other viscera. Therefore, dopamine is clinically useful in the treatment of shock, in which significant increases in sympathetic activity might compromise renal function.

2. **Therapeutic uses:** Dopamine is the drug of choice for cardiogenic and septic shock and is given by continuous infusion. It raises blood pressure by stimulating the β1 receptors on the heart to increase cardiac output and α1 receptors on blood vessels to increase total peripheral resistance.

Adverse effects: nausea, hypertension, and arrhythmias.

E. Dobutamine:

Is a synthetic, direct-acting catecholamine that is a β1 receptor agonist. It increases cardiac rate and output with few vascular effects. Dobutamine is used to increase cardiac output in acute heart failure, as well as for inotropic support after cardiac surgery.

F. Phenylephrine:

Is a direct-acting, synthetic adrenergic drug that binds primarily to α1 receptors. Phenylephrine is a vasoconstrictor that raises both systolic and diastolic blood pressures. It has no effect on the heart itself but, rather, induces reflex bradycardia when given parenterally . The drug is used to treat hypotension in hospitalized or surgical patients

G. Clonidine: Clonidine is an α2 agonist that is used for the treatment of hypertension. It can also be used to minimize the symptoms that accompany withdrawal from opiates, tobacco smoking, and benzodiazepines.

H. Albuterol and terbutaline: are short-acting β2 agonists used primarily as bronchodilators and administered by a metered-dose inhaler. Albuterol is the short-acting β2 agonist of choice for the management of acute asthma symptoms.

I.Salmeterol and formoterol: are long-acting β agonists (LABAs) that are β2 selective. A single dose by a metered-dose inhalation device, such as a dry powder inhaler, provides sustained bronchodilation over 12 hours, compared with less than 3 hours for albuterol.

These agents are not recommended as monotherapy, but are highly efficacious when combined with a corticosteroid.

Indirect-Acting Adrenergic Agonists

Indirect-acting adrenergic agonists cause the release, inhibit the reuptake, or inhibit the degradation of epinephrine or norepinephrine. They potentiate the effects of epinephrine or norepinephrine produced endogenously, but do not directly affect postsynaptic receptors (Amphetamine, tyramine, and cocaine).

Amphetamine: The marked central stimulatory action of amphetamine is often mistaken by drug abusers as its only action. However, the drug can also increase blood pressure significantly by α1 agonist action on the vasculature, as well as β1 - stimulatory effects on the heart.

Its actions are mediated primarily through an increase in nonvesicular release of catecholamines such as dopamine and norepinephrine from nerve terminals.

Therapeutic uses: in attention deficit hyperactivity disorder (ADHD), CNS stimulatory effects, suppression of appetite.

Tyramine: Tyramine is not a clinically useful drug, but it is important because it is found in fermented foods, such as aged cheese and Chianti wine. It is a normal by-product of tyrosine metabolism.

Cocaine: Block reuptake of catecholamine at adrenergic nerve terminal. Effect of cocaine on CNS is general stimulation, euphoria, dysphoria, followed by depression. On CVS in small doses it causes bradycardia, and at higher doses tachycardia; vasoconstriction; and myocardial infarction. Cocaine causes local anaesthesia by blocking Na+ channels.

Mixed-action agonists

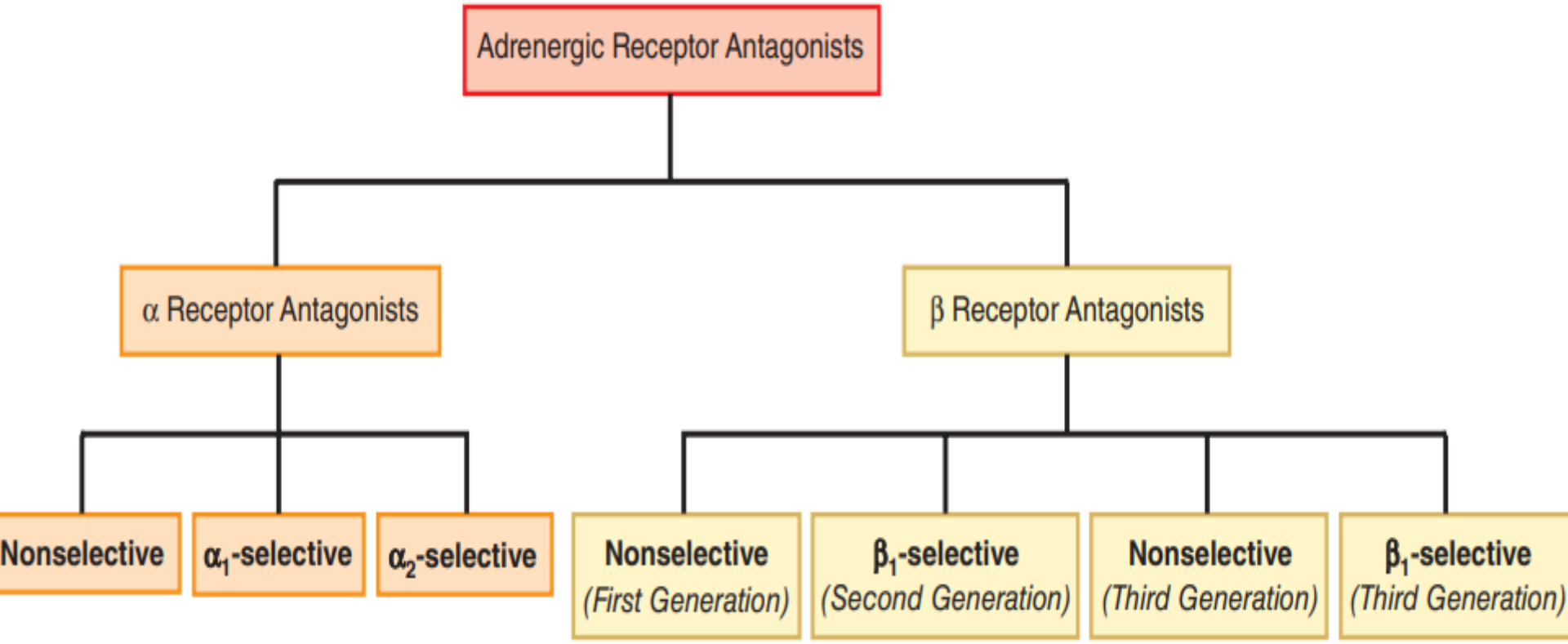
Ephedrine and pseudoephedrine:

Mixed-Action Adrenergic Agonists Ephedrine and pseudoephedrine. They not only enhance release of stored norepinephrine from nerve endings but also directly stimulate both α and β receptors. Thus, a wide variety of adrenergic actions ensue that are similar to those of epinephrine, although less potent.

ADRENERGIC ANTAGONISTS

Also called **adrenergic blockers or sympatholytics** bind to adrenoceptors but do not trigger the usual receptor-mediated intracellular effects. These drugs act by either reversibly or irreversibly attaching to the adrenoceptors, thus preventing activation by endogenous catecholamines.

Like the agonists, the adrenergic antagonists are classified according to their relative affinities for α or β receptors in the sympathetic nervous system.
Numerous adrenergic antagonists have important roles in clinical medicine, primarily to treat diseases associated with the cardiovascular system



lassification of adrenergic receptor antagonists. Drugs marked by an asterisk (*) also block α_1 receptors.

α-Adrenergic blocking agents

Phentolamine, Phenoxybenzamine, Prazosin, Terazosin, Doxazocin, Tamsulosin, Alfuzocin, Yohimbine.

1-Non –selective:

Irreversible, long-acting—Phenoxybenzamine is the prototypical long-acting α blocker; it differs from other adrenoceptor blockers in being irreversible in action. It is slightly α1-selective.

Pharmacological action: Peripheral vascular resistance is reduced due to the blockade of vascular α1-receptors.

Reversible, shorter-acting—Phentolamine is a competitive, reversible blocking agent that does not distinguish between α1 and α2 receptors.

2-Alpha1-selective—Prazosin is a highly selective, reversible pharmacologic α1 blocker. Doxazosin, terazosin, and tamsulosin are similar drugs.

3-Alpha2-selective—Yohimbine

Clinical Uses:

Drugs that block α adrenoceptors profoundly affect blood pressure. Because normal sympathetic control of the vasculature occurs in large part through agonist actions on α-adrenergic receptors, blockade of these receptors reduces the sympathetic tone of the blood vessels, resulting in decreased peripheral vascular resistance. This induces a reflex tachycardia resulting from the lowered blood pressure:

1. Nonselective α blockers—Nonselective α blockers have limited clinical applications. The best-documented application is in the presurgical management of pheochromocytoma (Beta-blockers (propranolol) are used to control the cardiac manifestations—tachycardia and arrhythmias due to excess catecholamines.

2. Selective α blockers—Prazosin, doxazosin, and terazosin are used in hypertension. These α1 blockers, as well as tamsulosin and silodosin are also used to reduce urinary hesitancy and prevent urinary retention in men with benign prostatic hyperplasia.

3. Yohimbine is a selective competitive α2-blocker. Has been used as a sexual stimulant and in the treatment of erectile dysfunction.

β-ADRENERGIC BLOCKING AGENTS

They can be classified in to:

1. Non-selective β1 and β2 antagonists (e.g. propanolol, Nadalol, Timolol, Pindolol).

2. β1-selective (e.g. Metoprolol, Atenolol,Bisoprlol, Esmolol, Acebutolol, Betaxolol).

3.Non-selective or selective β-blockers with vasodilating effect (due to α1-blocking effect) Labetalol and carvedilol: Antagonists of both α and β adrenoceptors

All of the clinically available β-blockers are competitive antagonists. Nonselective β-blockers act at both β1 and β2 receptors, whereas cardio-selective β antagonists primarily block β1 receptors. **[Note: There are no clinically useful β2 antagonists.]**

These drugs also differ in intrinsic sympathomimetic activity, CNS effects, blockade of sympathetic receptors, vasodilation, and pharmacokinetics.

Although all β-blockers lower blood pressure, they do not induce postural hypotension, because the α adrenoceptors remain functional. Therefore, normal sympathetic control of the vasculature is maintained.

Therapeutic uses of β-blockers

1.Hypertension: β-Blockers are useful for all grades of hypertension. These drugs are preferred especially in patients with coexisting angina, myocardial infarction or cardiac arrhythmias.

The advantages of β-blockers are: Sodium and water retention is rare, cheaper, have a long duration of action and well tolerated.

2. Angina pectoris and MI: β-Blockers reduce myocardial O2 demand by decreasing heart rate, myocardial contractility and blood pressure. They improve exercise tolerance and reduce frequency of anginal episodes. Use of β-blockers early in acute phase of MI may limit infarct size. Long-term use of β-blockers may reduce mortality and reinfarction.

3. Cardiac arrhythmias: β-Blockers are mainly used in atrial arrhythmias such as atrial fibrillation, atrial flutter, etc.; but rarely for ventricular arrhythmias.

4. Congestive cardiac failure: Chronic use of β-blockers such as carvedilol, metoprolol and bisoprolol has shown to reduce the mortality rate in chronic heart failure.

6. Glaucoma: β-Blockers decrease the IOP by reducing the production of aqueous humour. They are useful in the treatment of glaucoma. Timolol, carteolol, levobunolol, betaxolol, etc. are used topically in glaucoma. Timolol is the most frequently used β-blocker in glaucoma.

7. Prophylaxis of migraine: Propranolol, atenolol and metoprolol are effective in reducing the frequency of migraine headache. The mechanism is not known.

8. Hyperthyroidism: The signs and symptoms of hyperthyroidism such as tachycardia, palpitation, tremor, anxiety, etc. are reduced due to blockade of β-receptors. Propranolol is used in thyroid storm.

9. Essential tremors: Oral propranolol may give some benefit in patients with essential tremors.

10. Acute anxiety states: β-Blockers are useful in controlling the symptoms of acute anxiety such as palpitation, tachycardia, tremor, sweating,

Propranolol is the prototype. The adverse effect of propranolol include:

a. Bronchoconstriction: Propranolol has the potential to cause significant bronchoconstriction due to blockade of β2 receptors. Death by asphyxiation has been reported for patients with asthma whom were inadvertently administered the drug.

b. Arrhythmias: Treatment with β-blockers must never be stopped abruptly because of the risk of precipitating cardiac arrhythmias, which may be severe. The β-blockers must be tapered off gradually over a period of at least a few weeks.

c. Sexual impairment: Because ejaculation in the male is mediated through α-adrenergic activation, β-blockers do not affect ejaculation or internal bladder sphincter function. On the other hand, so me men do complain of impaired sexual activity.

d. Metabolic disturbances: β Blockade leads to decreased glycogenolysis and decreased glucagon secretion. Fasting hypoglycemia may occur. In addition, β-blockers can prevent the counter regulatory effects of catecholamines during hypoglycemia.

e. CNS effects: Propranolol has numerous CNS-mediated effects, including depression, dizziness, lethargy, fatigue, weakness, visual disturbances, hallucinations, short-term memory loss, emotional lability, vivid dreams (including nightmares), and depression.

DRUG SUMMARY TABLE: Adrenoceptor Blockers

Subclass	Mechanism of Action	Clinical Applications
Nonselective ` blockers		
Phentolamine	Competitive pharmacologic antagonism at α receptors	Pheochromocytoma, antidote to overdose of α agonists
Phenoxybenzamine	Irreversible (covalent) binding to α receptors	Pheochromocytoma, carcinoid, mastocytosis, Raynaud's phenomenon
Alpha$_1$-selective blockers		
Prazosin	Competitive antagonism at α_1 receptors	Hypertension, benign prostatic hyperplasia
Doxazosin, terazosin: like prazosin; longer duration of action (12–24 h)		
Tamsulosin, silodosin: like prazosin, approved only for benign prostatic hyperplasia		
Alpha$_2$-selective blockers		
Yohimbine	Competitive antagonism at α_2 receptors	Obsolete use for erectile dysfunction - research use
Nonselective a blockers		
Propranolol	Competitive block of β receptors, local anesthetic effect	Angina, arrhythmias (treatment and prophylaxis), hypertension, thyrotoxicosis, tremor, stage fright, migraine
Timolol, betaxolol, others: lack local anesthetic action; useful in glaucoma		
Pindolol: partial agonist action; possibly safer in asthma		
Nadolol: like propranolol but longer action (up to 24 h) and less CNS effect		
Beta$_1$-selective blockers		
Atenolol	Competitive block of β_1 receptors	Hypertension, angina, arrhythmias
Esmolol: IV agent for perioperative and thyroid storm arrhythmias, hypertensive emergency		
Metoprolol: like atenolol, oral, shown to reduce mortality in heart failure		
Nebivolol: oral β_1-selective blocker with additional nitric oxide-dependent vasodilating action		
Beta$_2$-selective blockers		
Butoxamine	Competitive block of β_2 receptors	None - research use only
Alpha + beta blockers		
Labetalol	Four isomers; 2 bind and block both α and β receptors	Hypertension, hypertensive emergencies (IV)
Carvedilol: like labetalol, 2 isomers; shown to reduce mortality in heart failure		

Adrenergic Agonists

I. OVERVIEW

- The adrenergic drugs affect receptors that are stimulated by norepinephrine NE (noradrenaline) or epinephrine (adrenaline).
- These receptors are known as adrenergic receptors or adrenoceptors.
- Adrenergic drugs that activate adrenergic receptors are termed **sympathomimetics**.
- Drugs that block the activation of adrenergic receptors are termed **sympatholytics.**
- Some sympathomimetics **directly** activate adrenergic receptors (direct- acting agonists), while others act **indirectly** by enhancing release **or** blocking reuptake of norepinephrine NE (indirect-acting agonists).

II. THE ADRENERGIC NEURON

A. Neurotransmission at adrenergic neurons

- It involves the following steps: **synthesis** of NE, **storage** of NE, **release** of NE, and **receptor binding** of norepinephrine, followed by **removal** of the neurotransmitter from the synaptic gap.

- NE can be removed either by enzymatic degradation by Catechol-O-methyl transferase **(COMT)** extraneuronally or by Mono-Amine Oxidase enzyme **(MAO)** intraneuronally, or by reuptake back the neuron by **Na/Cl** dependent NE transporter **(NET).**

- NET can be **inhibited** by tricyclic antidepressants (TCAs), such as **imipramine**, by serotonin–norepinephrine reuptake inhibitors such as **duloxetine**, or by **cocaine.** Such agents will increase the NE concentration in the synaptic junction, hence, increasing NE effect.

B. Adrenergic receptors (adrenoceptors)

Two main families of receptors, designated **α** and **β,** are classified on the basis of their responses to the adrenergic agonists epinephrine, norepinephrine, and isoproterenol.

1. **α-Adrenoceptors**: they show a weak response to the synthetic agonist isoproterenol, but they are responsive to the naturally occurring catecholamines epinephrine and norepinephrine. The rank order of potency and affinity is epinephrine ≥ norepinephrine >> isoproterenol. The α-adrenoceptors are subdivided into **two subgroups**, α1 and α2, based on their affinities for α agonists and blocking drugs. For example, the **α1** receptors have a higher affinity for **phenylephrine** than α2 receptors. Conversely, the drug **clonidine** selectively binds to **α2** receptors and has less effect on α1 receptors.

   Moreover, α1 Receptors are found **postsynaptically** on effector organs, while α2 Receptors are mainly found **presynaptically** on the adrenergic neuron controlling the release of NE (acting as inhibitory receptor).

   Further subtypes: **α1A** arefound mainly in the **prostate** gland, **α1B** are found mainly in **blood vessels**, their activation leads to vasoconstriction and elevate the bloodpressure.
2. **β-Adrenoceptors**: Responses of β receptors differ from those of α receptors and are characterized by a strong response to isoproterenol, with less sensitivity to epinephrine and norepinephrine. For β receptors, the rank order of potency is isoproterenol > epinephrine > norepinephrine. The β-adrenoceptors can be subdivided into three major subgroups, β1, β2, and β3, based on their affinities for adrenergic agonists and antagonists. β1 receptors have approximately equal affinities for epinephrine and norepinephrine, whereas β2 receptors have a higher affinity for epinephrine than for norepinephrine.
   β3 receptors are involvedin lipolysis and also have effects on the bladder.

C. Desensitization of receptors:

Prolonged exposure to the catecholamines reduces the responsiveness of these receptors, a phenomenon known as desensitization. Three mechanisms have been suggested to explain this phenomenon:

1. Sequestration of the receptors so that they are unavailable for interaction with the ligand.
2. Down-regulation, that is, a disappearance of the receptors either by destruction or by decreased synthesis.
3. Inability to couple to G protein.

III. Adrenergic agonists:

Agents that increase the adrenergic neurotransmission called adrenergic agonists or sympathomimetics, they are of three types: Direct acting (act on adrenergic receptor directly), Indirect acting (cannot interact with receptor but they indirectly increase NE release or inhibit reuptake) and Mixed action (act both directly and indirectly).

A. Direct acting adrenergic agonists:

1. Epinephrine: Epinephrine interacts with both α and β receptors. At low doses, β effects, whereas at high doses, α effects. Its actions are:

Cardiovascular:

- The major actions of epinephrine are on the cardiovascular system. Epinephrine strengthens the contractility of the myocardium (positive **inotrope:** β1 action) and increases its rate of contraction (positive **chronotrope:** β1 action). Epinephrine activates β1 receptors on the kidney to cause renin release which leads to the production of angiotensin II that causes vasoconstriction and increase blood pressure.

- while it dilates vessels going to skeletal muscle(β2 effects).

- **Respiratory:** Epinephrine causes powerful bronchodilation by acting directly on bronchial smooth muscle (β2 action). It also inhibits the release of allergy mediators such as histamines from mast cells.
- **Hyperglycemia:** Epinephrine increases the blood glucose levels.
- **Lipolysis:** Epinephrine causes lipolysis in adipose tissue.

Therapeutic uses:

- **Bronchospasm:** Epinephrine is the primary drug used in the emergency treatment of respiratory conditions when bronchoconstriction has resulted in diminished respiratory function, e.g. acute asthma and anaphylactic shock, epinephrine is the drug of choice and can be lifesaving in this setting. Within a few minutes after subcutaneous administration, respiratory function greatly improves.
- **Anaphylactic shock:** Epinephrine is the drug of choice for the treatment of hypersensitivity reactions which occurs in response to allergens.
- **Cardiac arrest:** Epinephrine may be used to restore cardiac rhythm in patients with cardiac arrest.

- **Anesthetics:** Local anesthetic solutions may contain low concentrations (for example, 1: 100,000 parts) of epinephrine. Epinephrine greatly increases the duration of local anesthesia by producing vasoconstriction at the site of injection.

- ## Adverse effects:

1. CNS effects that include anxiety, fear, tension, headache, and tremor.
2. It can trigger cardiac arrhythmias, particularly if the patient is receiving digoxin.
3. Epinephrine can also induce pulmonary edema.
4. Epinephrine may have enhanced cardiovascular actions in patients with **hyperthyroidism**, and the dose must be reduced in these individuals.

5. Inhalation anesthetics also sensitize the heart to the effects of epinephrine, which may lead to tachycardia.
6. Epinephrine increases the release of endogenous stores of glucose. In diabetic patients, dosages of insulin may have to be increased.
7. Nonselective β-blockers prevent vasodilator effects of epinephrine on β2 receptors, leaving α receptor stimulation unopposed. This lead to increased blood pressure.

2. Norepinephrine:

Therapeutic uses: Norepinephrine is used to treat shock, because it increases vascular resistance and, therefore, increases blood pressure. It has no other clinically significant uses.

Adverse effects: These are similar to epinephrine. In addition, norepinephrine is a potent vasoconstrictor and may cause blanching and sloughing of skin along an injected vein. If extravasation (leakage of drug from the vessel into tissues surrounding the injection site) occurs, it can cause tissue necrosis. It should not be administered in peripheral veins, if possible. Impaired circulation from norepinephrine may be treated with the α receptor antagonist phentolamine.

3. Isoproterenol: is a direct-acting synthetic catecholamine that stimulates both β1- and β2-adrenergic receptors. Its non-selectivity is one of its drawbacks and the reason why it is rarely used therapeutically. Its action on α receptors is insignificant. Isoproterenol produces intense stimulation of the heart, increasing heart rate, contractility, and cardiac output.

4. Dopamine:

Dopamine is the drug of choice for cardiogenic and septic shock and is given by continuous infusion. It raises blood pressure by stimulating the β1 receptors on the heart to increase cardiac output and α1 receptors on blood vessels to increase total peripheral resistance. In addition, it enhances perfusion to the kidney and splanchnic areas. Increased blood flow to the kidney enhances the glomerular filtration rate and causes diuresis. In this regard, dopamine is far superior to norepinephrine, which diminishes blood supply to the kidney and may cause renal shutdown.

It is also used to treat hypotension and severe heart failure, primarily in patients with low or normal peripheral vascular resistance and in patients who have oliguria. Its adverse effects (nausea, hypertension, arrhythmias).

5. Oxymetazoline: is a direct-acting synthetic adrenergic agonist that stimulates both α1- and α2-adrenergic receptors. Oxymetazoline is found in many over-the-counter short-term nasal spray decongestants, as well as in ophthalmic drops for the relief of redness of the eyes associated with swimming, colds, and contact lenses. Oxymetazoline directly stimulates α receptors on blood vessels supplying the nasal mucosa and conjunctiva, thereby producing vasoconstriction and decreasing congestion. Rebound congestion and dependence are observed with long-term use.

6. Phenylephrine: is a direct-acting, synthetic adrenergic drug that binds primarily to α1 receptors. Phenylephrine is a vasoconstrictor that raises both systolic and diastolic blood pressures. The drug is used to treat hypotension in hospitalized or surgical patients. Large doses can cause hypertensive headache and cardiac irregularities. Phenylephrine acts as a nasal decongestant when applied topically or taken orally. Phenylephrine is also used in ophthalmic solutions for mydriasis.

7. Clonidine: α2 agonist that is used for the treatment of hypertension. Clonidine acts centrally on presynaptic α2 receptors to produce inhibition of sympathetic vasomotor centers, decreasing sympathetic outflow to the periphery. The most common side effects of clonidine are lethargy, sedation, constipation, and xerostomia. Abrupt discontinuance must be avoided to prevent rebound hypertension.

8. Albuterol and terbutaline: are short-acting β2 agonists (SABA) used primarily as bronchodilators and administered by a metered-dose inhaler. Albuterol is the short-acting β2 agonist of choice for the management of acute asthma symptoms. They are also used off-label as a uterine relaxant to suppress premature labor. Side effects of these agents is tremor, restlessness, apprehension, and anxiety. When these drugs are administered orally, they may cause tachycardia or arrhythmia (due to β1 receptor activation).

9. Salmeterol and formoterol: are long acting β agonists (LABAs) that are β2 selective. A single dose by a metered-dose inhalation device, such as a dry powder inhaler, provides sustained bronchodilation over 12 hours, they are used for long term management of asthma often in combination with inhaled corticosteroids.

B. INDIRECT-ACTING ADRENERGIC AGONISTS:

1. Amphetamine: The marked central stimulatory action of amphetamine is often mistaken by drug abusers as its only action. However, the drug can also increase blood pressure significantly. Its actions are mediated primarily through an increase in the release of catecholamines such as dopamine and norepinephrine from nerve terminals.

2. Tyramine: is not a clinically useful drug, but it is important because it is found in fermented foods, such as aged cheese. It can precipitate serious vasopressor episodes. Like amphetamines, tyramine also increase the release of catecholamines from nerve terminals.

3. Cocaine: is unique among local anesthetics in having the ability to block the sodium-chloride (Na+/Cl-)-dependent norepinephrine transporter required for cellular uptake of norepinephrine into the adrenergic neuron. Consequently, norepinephrine accumulates in the synaptic space, resulting in enhanced sympathetic activity and potentiation of the actions of epinephrine and norepinephrine.

C. MIXED-ACTION ADRENERGIC AGONISTS:

Ephedrine and pseudoephedrine are mixed-action adrenergic agents. They not only release stored norepinephrine from nerve endings but also directly stimulate both α and β receptors. They are used orally primarily to treat nasal and sinus congestion.

ADRENERGIC ANTAGONISTS

The adrenergic antagonists (also called **blockers or sympatholytic** agents) bind to **adrenoceptors** but do not trigger the usual receptor-mediated intracellular effects. These drugs act by either reversibly or irreversibly attaching to the receptor, thus preventing its activation by endogenous catecholamines. The adrenergic antagonists are classified according to their relative affinities for **α** or **β** receptors in the peripheral nervous system. These drugs will interfere with the functions of the sympathetic nervous system.

α-Adrenergic blocking agents:

a- Non-selective α- blocker drugs

Phentolamine

Non selective competitive antagonists of α-adrenoceptors.

α-blockade → dilation of vascular smooth muscle → ↓SVR (systemic vascular resistance) → ↓BP.

Uses:

Antihypertensive, particularly in patients with pheochromocytoma (neuroendocrine tumor of the adrenal glands medulla that secretes high amounts of catecholamines, mostly norepinephrine, plus epinephrine to a lesser extent).

S/E:

- orthostatic hypotention
- Reflex tachycardia (caused by α2-blockade, which causes ↑NE release and thereby ↑ β1-adrenoceptor stimulation.

Phenoxybenzamine similar to Phentolamine but binds irreversibly to α-adrenoceptors, thus, it is ideal for treatment of pheochromocytoma.

b- α selective blockers:

1- α1 selective blockers

Prazosin, Terazosin, Doxazocin, Tamsulosin, Alfuzocin:

Reversible α1-adrenoceptor antagonist. Blockade on vascular smooth muscle → arteriolar and venous vasodilation → ↓BP & ↓ venous return.

Low affinity for α2-adrenoceptors may explain relative lack of reflex tachycardia compared with non-selective α-blockers (α2-blockade would prevent negative feed-back and thereby allow ↑ NE release, leading to β1 stimulation of the heart).

Inhibition of smooth muscle contraction in prostate → relief of urinary symptoms caused by benign prostatic hyperplasia (BPH).

Uses:

- HT (hypertention)
- Benign prostatic hyperplasia (BPH)
- Treatment of raynaud's phenomenon (vasospasm that can lead to digital ischemia).

S/E: orthostatic hypotention, dry mouth, nightmares, sexual dysfunction, lethargy.

2- α2- blockers

Yohimbine:

Is α2-antagonist that causes ↑ NE release and has been used to treat erectile dysfunction.

β-adrenergic blocking agents

Nonselective **β** blockers act at both **β1** and **β2** receptors, whereas cardioselective **β** antagonists primarily block **β1** receptors [Note: There are no clinically useful β2 antagonists.]

Although all β blockers lower blood pressure in hypertension, they do not induce **postural hypotension**, because the α-adrenoceptors remain functional. Therefore, normal sympathetic control of the vasculature is maintained.

β blockers are also effective in treating angina, cardiac arrhythmias, myocardial infarction, congestive heart failure, hyperthyroidism, and glaucoma as well as serving in the prophylaxis of migraine headaches. [Note: The names of all β-blockers end in **"-olol":** Propranolol, Nadolol Atenolol **except** for *labetalol* and *carvedilol*.]

They can be classified in to:

- **1st generation:** Non-selective β 1 and β2 antagonists (e.g. propranolol, Nadalol, Timolol, Pindolol.
- **Propranolol**

Therapeutic uses:

1- Hypertension: -Lowers blood pressure in hypertension by several different mechanisms of action which are:

-Decreasing cardiac output (which is the primary mechanism).

- Inhibition of renin release from the kidney leads to decrease total peripheral resistance with long term use.

2- Angina pectoris:

↓**O2** demand by heart muscles → ↓chest pain. So, it is used in chronic management of stable angina.

3- Myocardial infarction (MI):

Prophylactic use of β-blockers can prevent a second attack of MI. Immediate administration following a MI reduces infarct size and hastens recovery.

4- Migraine:

Reduces migraine episodes when used prophylactically due to its hydrophobic property.

- **2nd generation:** β1-selective (e.g. Metoprolol, Atenolol, Bisoprlol, Esmolol, Acebutolol, Betaxolol).

- **3rd generation:** non-selective or selective **β-blockers** with vasodilating effect (due to **α1-blocking** effect)
- (e.g. **Carvidilol, Labetlol**→ (nonselective + vasodilating effect) **Nebivolol**→ (Selective β1-blocker + vasodilating effect).

DRUG	RECEPTOR SPECIFITY	THERAPEUTIC USES	SIDE EFFECTS
Propranolol	β1, β2	Hypertension Migraine Hyperthyroidism Angina pectoris Myocardial infarction	Bradycardia, hypotension, fatigue, impotence, Bronchospasm
Nadolol		Hypertension	
Timolol		Glaucoma, hypertension	
Pindolol		Hypertension	
Acebutolol Atenolol Esmolol Metoprolol	β1	Hypertension	Bradycardia, hypotension, fatigue, impotence
Nebivolol	β 1, α1	Hypertension	
Carvedilol Labetalol	β1, β2, α1	Hypertension Congestive heart failure	Bradycardia, hypotension, fatigue, impotence, Bronchospasm

Pharmacology

Lec 1+2
Dr. Raida Noori

General Pharmacology

Pharmacology: Is a branch in science studies the interaction between substances and living organisms through chemical processes, especially by binding to regulatory molecules and activating or inhibiting normal body processes.

A **drug** can be defined as any substance or products that make changes in biologic function through its chemical actions. Usually, the drug molecule interacts with a specific molecule in the biological system that plays a regulatory role. This molecule is called a receptor.

Clinical pharmacology can be defined as the science that studies the clinical actions and applications of the drugs, by exploring:

- The drug **pharmacokinetics** (represents what the body does to a drug).
- The drug **pharmacodynamics** (represents what the drug does to the body) of the drugs.

Pharmacokinetics

1- Absorption

To enter the bloodstream, a drug must be absorbed from its site of administration (unless the drug has been injected directly into the vascular compartment). The rate and efficiency of absorption differ depending on a drug's route of administration, the chemical characteristic of the drug and the environment where a drug is absorbed.

So, **bioavailability** is defined as the fraction of an administered dose of unchanged drug that reaches the systemic circulation. When a medication is administered intravenously (IV), its bioavailability is 100%.

Routes of drug administration:

The route of administration of a drug is determined primarily by the properties of the drug (water or lipid soluble, ionised), and the aims of the treatment (rapid onset of action, or restriction of treatment to localised area). There are two major routes of drug administration, enteral and parenteral. In addition to other routes.

Enteral include oral, sublingual buccal, rectal.

Parenteral: intravenous, intramuscular, and subcutaneous injections.

Other include inhalation, topical, intranasal, transdermal, intrathecal, eyedrops and others

Mechanisms of absorption of drugs from the GI tract

Depending on their chemical properties, drugs may be absorbed from the GI (gastrointestinal) tract by passive diffusion, facilitated diffusion, active transport, or endocytosis.

1-**Passive diffusion**: A drug moves from region of high concentration to one of lower concentration. Water-soluble drugs penetrate the cell membrane through aqueous channels or pores, whereas lipid-soluble drugs readily move across most biologic membranes due to their solubility in the membrane lipid bilayers (figure1).

2- **Facilitated diffusion:** Other agents can enter the cell through specialized transmembrane carrier proteins that facilitate the passage of large molecules. This process is known as facilitated diffusion. It does not require energy, can be saturated, and may be inhibited by compounds that compete for the carrier.

3- **Active transport:** It also involves specific carrier proteins that span the membrane. A few drugs that closely resemble the structure of naturally occurring metabolites are actively transported across cell membranes using these specific carrier proteins. Energy-dependent active transport is driven by the hydrolysis of ATP (adenosine triphosphate).

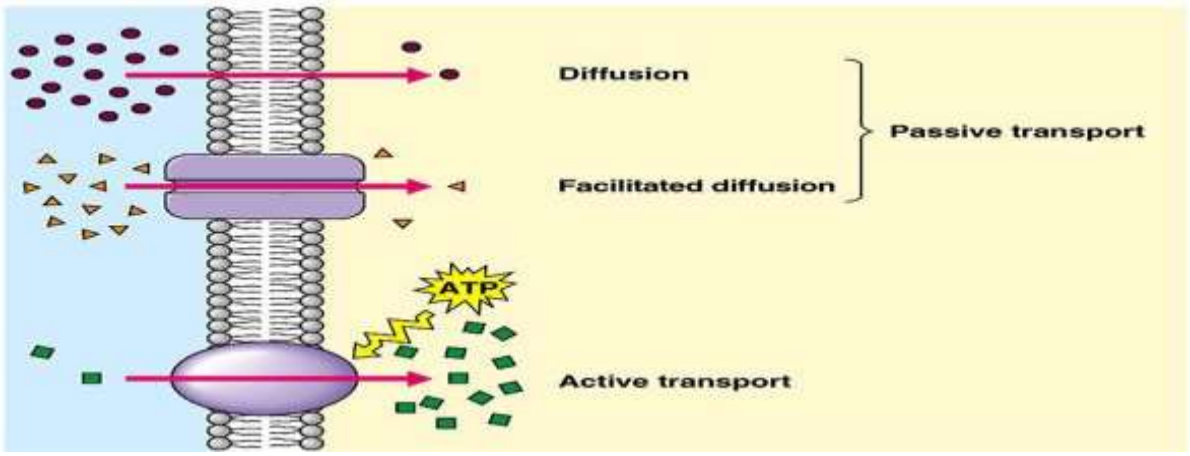


Figure 1: passive and active transport.

Endocytosis: Endocytosis occurs through binding of the transported molecule to specialized components (receptors) on cell membranes, with subsequent internalization by infolding of that area of the membrane. The contents of the resulting intracellular vesicle are subsequently released into the cytoplasm of the cell. Endocytosis permits very large or very lipid-insoluble chemicals to enter cells. Exocytosis is the reverse process, that is, the expulsion of material that is membrane-encapsulated inside the cell from the cell. Most neurotransmitters are released by exocytosis (figure 2).

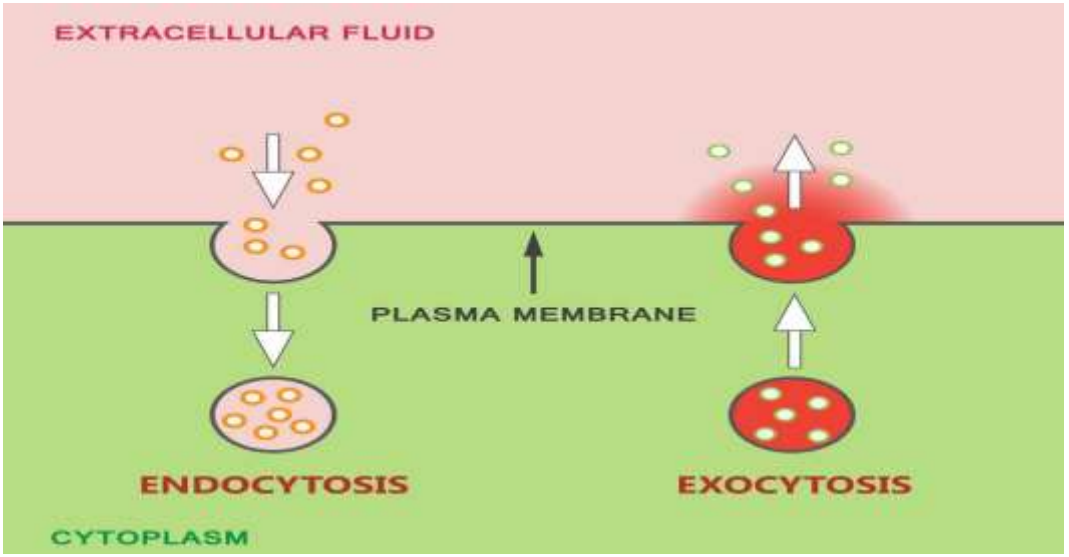


Figure 2: endo and exocytosis

Factors influencing absorption

1- Effect of the pH (pH of the medium) on drug absorption

Basically, the majority of drugs are either weak acids or weak bases.

Acidic drugs (HA) always release a proton (H+), causing a charged anion (A−) to form:

$$HA \leftrightarrow H^{+} + A^{-}$$

On the other hand, Weak bases (BH^{+}) can also release an H^{+}. However, the protonated form of basic drugs is usually charged, and loss of a proton produces the uncharged base (B):

$$BH^{+} \leftrightarrow H^{+} + B$$

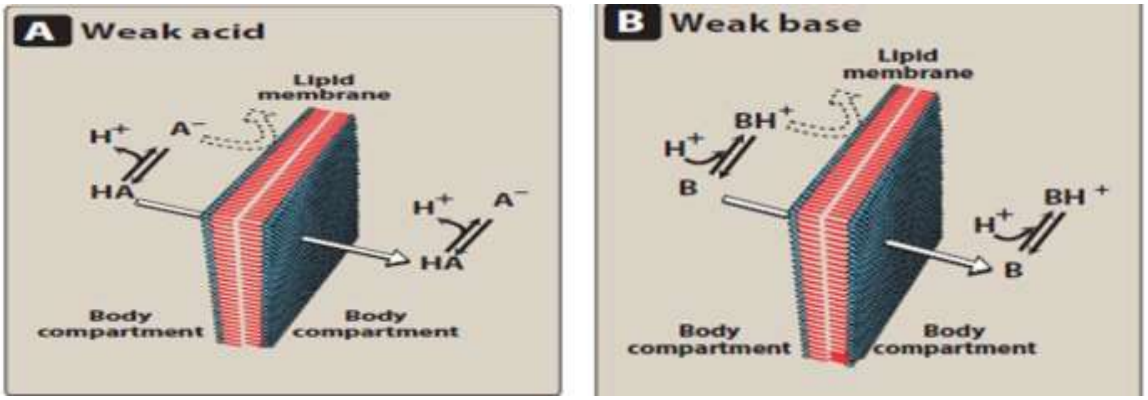


Figure 3: Diffusion of ionized and non-ionized drugs through cell membrane.

2-Blood flow to the absorption site: Because blood flow to the intestine is much greater than the flow to the stomach, absorption from the intestine is favored over that from the stomach.

3-Total surface area available for absorption: the intestine has a surface area about 1000-fold that of the stomach, making absorption of the drug across the intestine more efficient.

4- Contact time at the absorption surface: If a drug moves through the GI tract very quickly, as can happen with severe diarrhea, it is not well absorbed.

5- Expression of P-glycoprotein: P-glycoprotein is a multidrug transmembrane transporter protein responsible for transporting various molecules, including drugs, from the intracellular space to the extracellular. P-glycoprotein reduces drug absorption.

Bioavailability (F or BA)

It refers to the degree and rate at which an administered drug is absorbed by the systemic circulation. For instance, if 100 mg of a drug is administered orally and 60 mg is absorbed unchanged, the bioavailability is 0.6 or 60%. Determining bioavailability is important for calculating drug dosages for non-intravenous routes of administration. The bioavailability can be determined by the following equation:

$$\text{Bioavailability} = \frac{\text{AUC oral}}{\text{AUC injected}} \text{X } 100$$

Where the AUC oral refers to the area under the blood concentration-time curve of orally administered drugs while the AUC injected represents the area under the blood concentration-time curve of intravenous (IV) injected drugs (figure 4). The F value of the IV drugs usually equals to 100%;

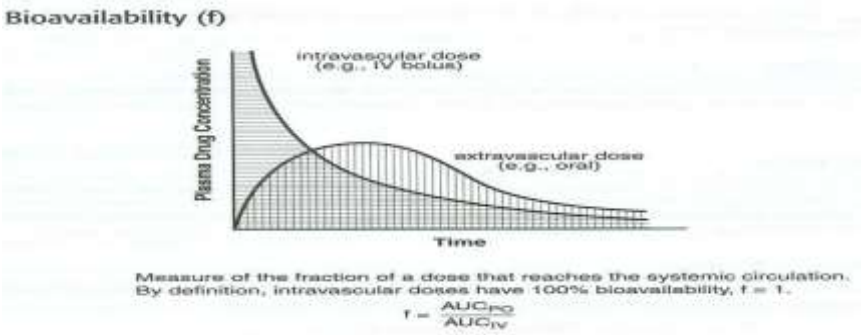


Figure 4: AUC for IV and oral route, and the calculation of bioavailability.

Factors that influence bioavailability

a- First-pass hepatic metabolism: After absorption of a drug from the GI tract, it will enter the portal circulation before entering the systemic circulation (figure 5). If the drug is rapidly metabolized in the liver or gut wall, a marked decrease in the amount of the unchanged drug will be recorded in the systemic circulation.

. For example, more than 90% of nitroglycerin is cleared during first-pass metabolism. Therefore, it is primarily administered via the sublingual or transdermal route. So, drugs that extensively metabolise by liver or intestine should be given in doses sufficient to ensure that enough active drug reaches the desired site of action.

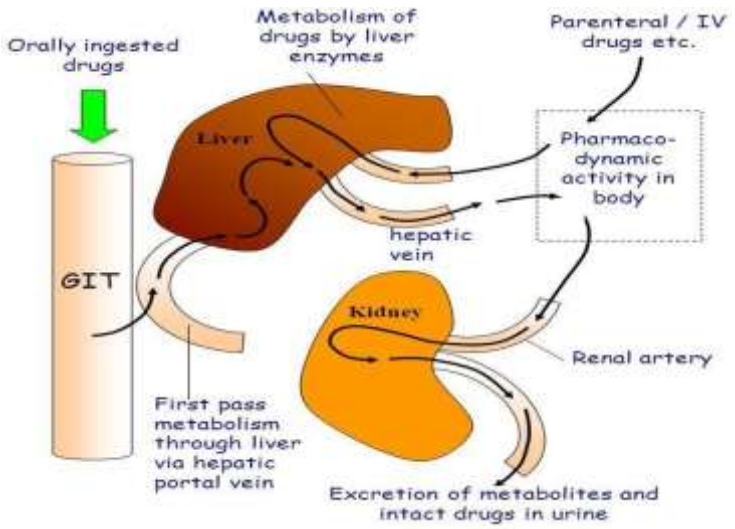


Figure 5: First pass metabolism.

b- Solubility of the drug: Very hydrophilic (water-soluble) drugs are poorly absorbed because of their inability to cross the lipid-rich cell membranes. Paradoxically, drugs that are extremely hydrophobic (lipophilic, lipid-soluble) are also poorly absorbed, because they are totally insoluble in aqueous body fluids and, therefore, cannot gain access to the surface of cells.

c- Chemical instability: Some drugs, such as *penicillin G*, are unstable in the pH of the gastric contents. Others, such as *insulin*, are destroyed in the GI tract by degradative enzymes.

d- Nature of the drug formulation: Drug absorption may be altered by factors unrelated to the chemistry of the drug. For example, particle size, salt form, crystal polymorphism, enteric coatings, and the presence of excipients, can influence the ease of dissolution and, therefore, alter the rate of absorption.

2-Distribution

Drug distribution is the process by which a drug reversibly leaves the bloodstream and enter the interstitium (extracellular fluid) and then the cells of tissue.

There are four main elements to this:

1- **Distribution into body fluids.** mainly plasma, interstitial fluid and intracellular fluid.

2- **Uptake into body tissues/organs.** Some drugs are concentrated or accumulated in tissues or some organs of the body, which can lead to toxicity on chronic use. For example, tetracyclines—bones and teeth; thiopentone —adipose tissue; chloroquine—liver and retina; digoxin—heart, etc.

3- **Extent of plasma protein binding.** Plasma proteins such as albumin can bind drug molecules. This varies widely among drugs. Drugs bound to plasma proteins are pharmacologically inert. Some are highly bound (e.g. warfarin which is 99 per cent bound to plasma proteins).

4- **Passage through barriers.** The two main examples are the placenta and the blood brain barrier (BBB). Drugs must be highly lipid soluble to pass across these barriers. If not, they may not be able to reach their site of action.

3-Metabolism (Biotransformation)

Biotransformation of drugs is the process of metabolizing the parent drug compound and occurs mainly in the liver to different compounds called metabolites. The drug metabolite may have decreased, increased or undergone no change in pharmacological activity compared to the

parent drug. Some drugs are what are termed *pro-drugs* that is the drug itself is pharmacologically inactive until it is metabolized by the liver to its active form. A good example is codeine, which is metabolized to the active form morphine by the body.

Enzyme Induction: Repeated administration of certain drugs increases the synthesis of microsomal enzymes. This is known as enzyme induction. The drug is referred to as an enzyme inducer, e.g. rifampicin, phenytoin, barbiturates, carbamazepine, griseofulvin, etc.

Enzyme Inhibition: Certain drugs inhibit the activity of drug-metabolizing enzymes and are known as enzyme inhibitors, e.g. chloramphenicol, ciprofl oxacin, erythromycin, etc. Enzyme inhibition is a rapid process as compared to enzyme induction.

4- Elimination

Removal of the drug and its metabolite from the body is known as drug excretion. The main channel of excretion of drugs is the kidney; others include lungs, bile, faeces, sweat, saliva, tears, milk, etc.

Kidney: The processes involved in the excretion of drugs via kidney are glomerular filtration, passive tubular reabsorption and active tubular secretion.

Pharmacodynamics

The effect of the drugs can be one of the following:

1. Stimulatory: Some drugs act by increasing the activity of specialized cells, e.g. adrenaline stimulates the heart resulting in an increase in heart rate and force of contraction.

2. Depressive: Some drugs act by decreasing the activity of specialized cells, e.g. alcohol, barbiturates, general anaesthetics, etc. depress the central nervous system.

3. Irritant: Certain agents on topical application can cause irritation of the skin and adjacent tissues.

4. Replacement: When there is a deficiency of endogenous substances, they can be replaced by drugs, e.g. insulin in diabetes mellitus, thyroxine in cretinism and myxedema, etc.

5. Cytotoxic: Drugs are selectively toxic for the infecting organism/cancer cells, e.g. antibiotics/ anticancer drugs.

Mechanism of action of drugs

Although the majority of drugs work through interaction with specialized biological molecules called receptors, there are few groups of drugs that do not relay on receptors to mediate their effect.

For example, medication that depend on **physical properties** (osmosis, adsorption, radioactivity), **chemical properties** (antacids, chelating agents).

Drug with receptors mediated mechanisms

Cells have different types of receptors, each of which is specific for a particular ligand. The term "ligand" refers to a small molecule that binds to a site on a receptor protein and produces a unique response.

Drug + Receptor ⟷ Drug–receptor complex → Biologic effect

The receptors may be divided into four families: A) Ligand-gated ion channels, B) G protein–coupled receptors, C) Enzyme–linked receptors, and D) Intracellular receptors (figure 6)**.**

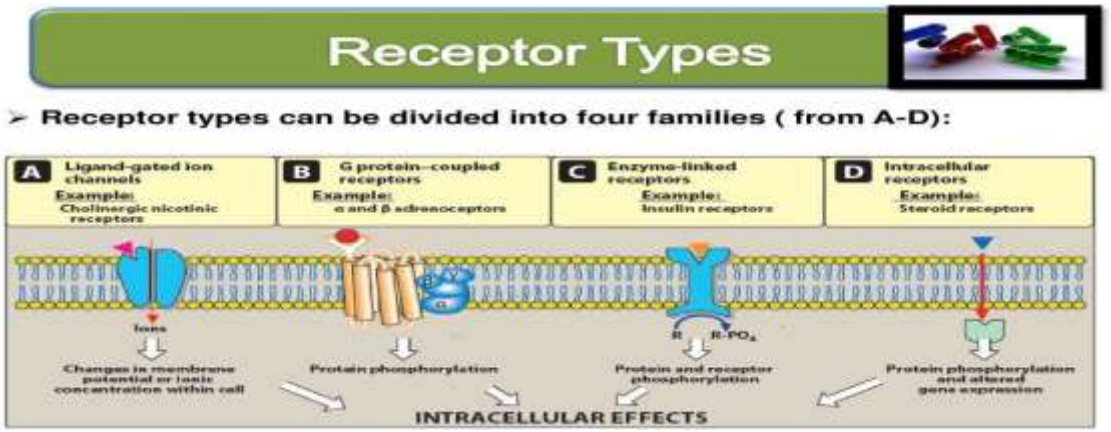


Figure 6: types of receptors.

According to the intrinsic activity of the drugs, they are classified into agonist and antagonist drugs. An agonist drug can be defined as a chemical that binds to and activates the receptor to produce a biological response. Agonist drugs has been sub-classified into:

1- **Full agonist**: If a drug binds to a receptor and produces a maximal biologic response that mimics the response to the endogenous ligand, it is a full agonist.
2- P**artial agonists**: drugs that bind to and activate a given receptor but have only partial efficacy at the receptor relative to a full agonist.
3- **Inverse agonist**: is a ligand that binds to the same receptor-binding site as an agonist; however, it produces an opposite effect by suppressing spontaneous receptor signalling (when present).

Agonists That Inhibit Their Binding Molecules: Some drugs mimic agonist drugs by

inhibiting the molecules responsible for terminating the action of an endogenous agonist. For example, acetylcholinesterase inhibitors , by slowing the destruction of endogenous acetylcholine, cause cholinomimetic effects that closely resemble the actions of cholinoceptor agonist molecules even though cholinesterase inhibitors do not bind or only incidentally bind to cholinoceptors. Because they amplify the effects of physiologically released agonist ligands, their effects are sometimes more selective and less toxic than those of exogenous agonists.

The antagonists are type of receptor ligands or **drugs** that block a biological response by binding to and blocking the receptors rather than activating them like an agonist. They are sometimes called blockers. Different types of antagonist drugs were recognised, which are:

1- **Competitive antagonists** can be defined as the drugs that bind to receptors at the same binding site as the endogenous ligand or agonist, but without activating the receptor. Agonists and antagonists "compete" for the same binding site on the receptor. Once bound, an antagonist will block agonist binding.

2- **Irreversible antagonists can be defined as the drugs that** bind to the receptors or targets molecule in a manner which makes them impossible to reverse the binding (bind by covalent bond). No amount of agonist will overcome this sort of bond.

3- And finally, **the functional antagonisms or physiological antagonism, which can be observed when** an antagonist may act at a completely separate receptor, initiating effects that are functionally opposite those of the agonist. Take for example the

4- glucocorticoids which increase the blood sugar while the insulin lowers it, but the two drugs act by completely different pathways.

5- **Duration of Drug Action** Termination of drug action is a result of one of several processes. In some cases, the effect lasts only as long as the drug occupies the receptor, and dissociation of drug from the receptor automatically terminates the effect. In many cases, however, the action may persist after the drug has dissociated because, for example, some coupling molecule is still present in activated form. In the case of drugs that bind covalently to the receptor site, the effect may persist until the drug-receptor complex is destroyed and new receptors or enzymes are synthesized. In addition, many receptor-effector systems incorporate desensitization mechanisms for preventing excessive activation when agonist molecules continue to be present for long periods.

Ischemic heart disease

&

Antihyperlipidemic Drugs

By

Dr. Samir Al-Shujairy

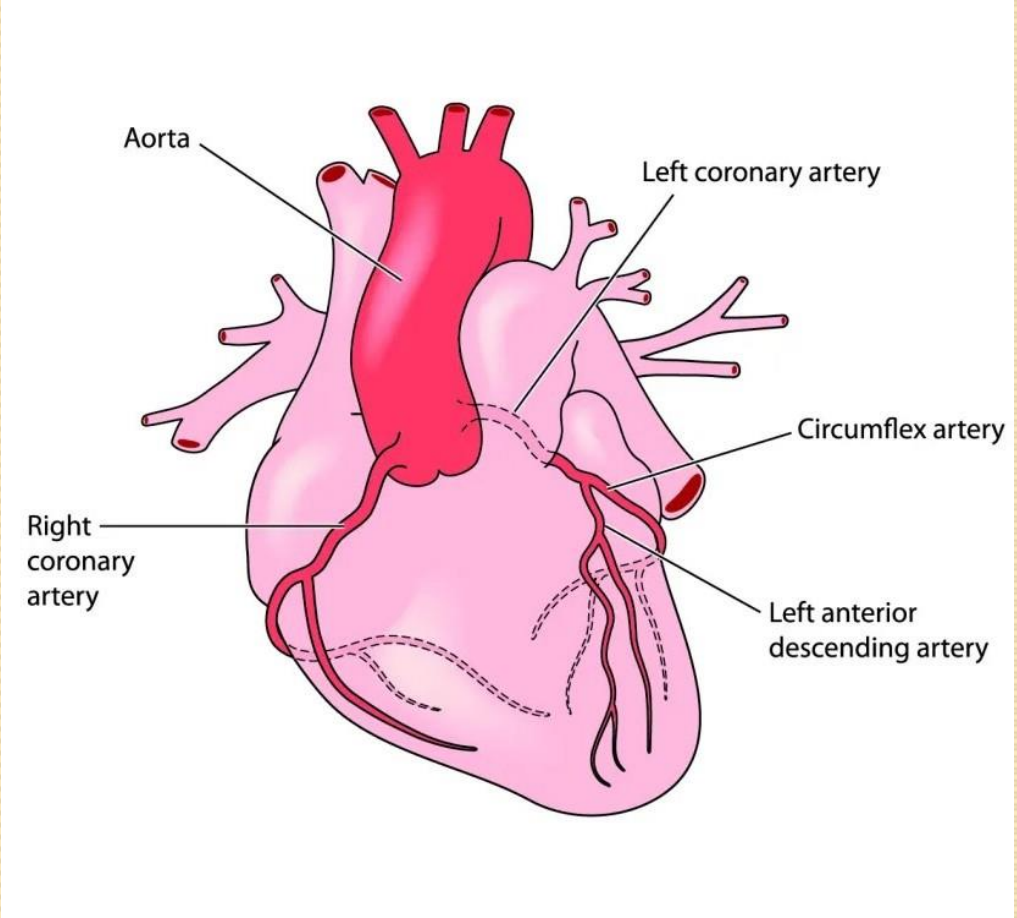
PhD. Pharmacology & Toxicology

General Pharmacology

Collage of Pharmacy /University of Anbar

Ischemic heart disease

PhD. Pharmacology & Toxicology



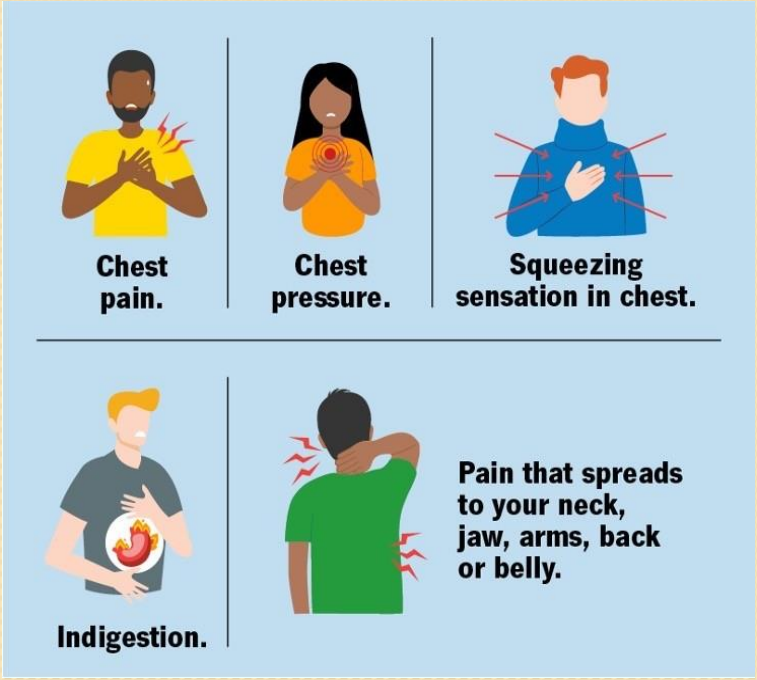
:Ischemic heart disease includes

1) Chronic stable angina)Classic; exertional angina)
2) Acute coronary syndromes (ACS)
3) Prinzmetal's angina (Variant angina; angina of rest; α-mediated angina.(

They are caused by varying combinations of **increased myocardial demand** and **decreased myocardial perfusion**

1. Chronic stable angina (Classic; exertional angina)

- Its the most common form of angina ,therefore, is also called **typical angina**.
- When the pattern of the chest pains and the amount of effort needed to trigger the chest pains do not vary over time, the angina is named "**stable angina**".



- It is due to atheromatous narrowing of the coronary artery.
- Pain is induced by effort and disappears with rest.

- Site and radiation: retrosternal, radiating to the left shoulder and the left arm.
- Precipitated by 3E: exertion, emotion, eating, and relieved by rest and nitrates.
- Duration: usually **< 10-15 min**. If longer than 15 min →suspect ACS.

)2. Acute coronary syndromes (ACS

A- Unstable angina: It is due to rupture of atheromatous plaque and formation of thrombus. The patient experiences acceleration in the frequency or severity of chest pain, or new-onset angina pain.

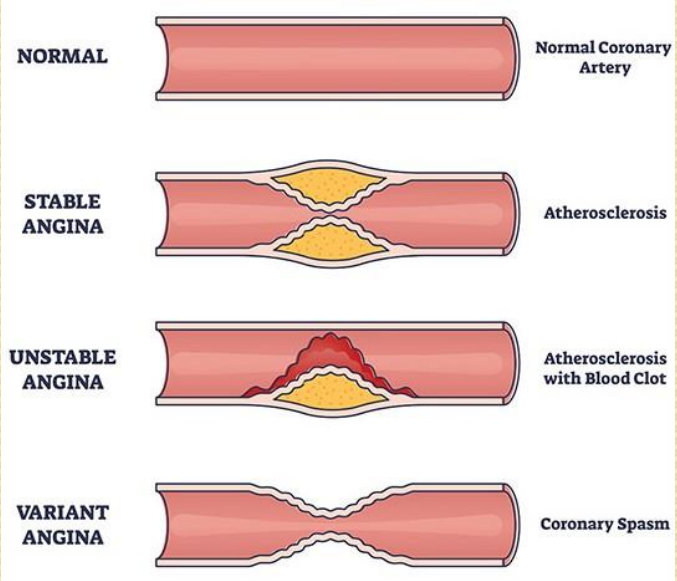
B- Myocardial infarction: An intraluminal thrombus completely occludes the epicardial coronary artery at the site of plaque rupture leading to irreversible coagulative necrosis.

3. Prinzmetal's angina (Variant angina; angina of rest;)α-mediated angina

- Prinzmetal angina is an **uncommon** form of angina that occurs restat and is due to **coronary artery spasm** causing decreased blood flow to the heart muscle.

May occur due to:

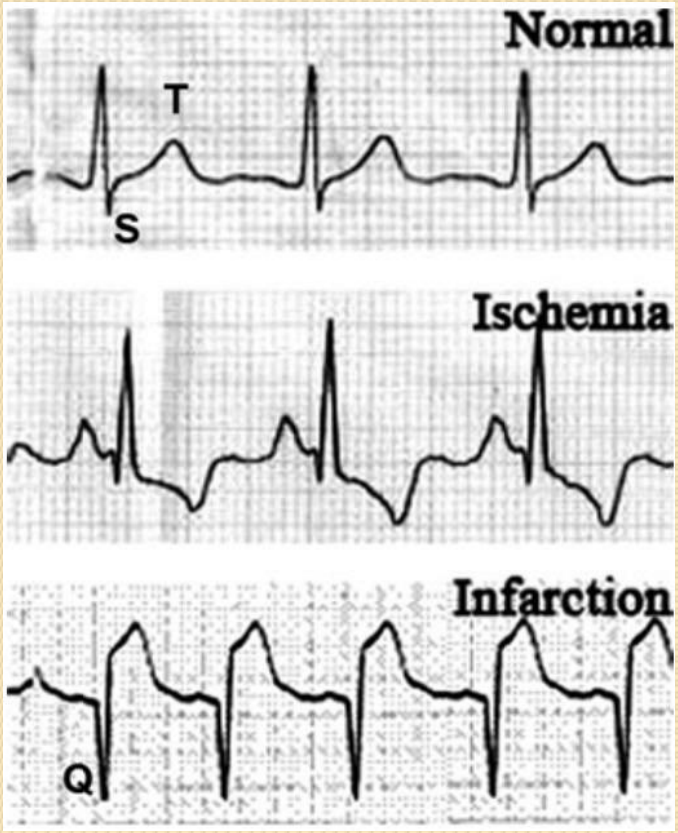
1. Predominant of α-1 on β-.2
2. Inability of Ach to stimulate M.3
3. High level TXA2 which cause VC.



Diagnosis:

-1ECG:

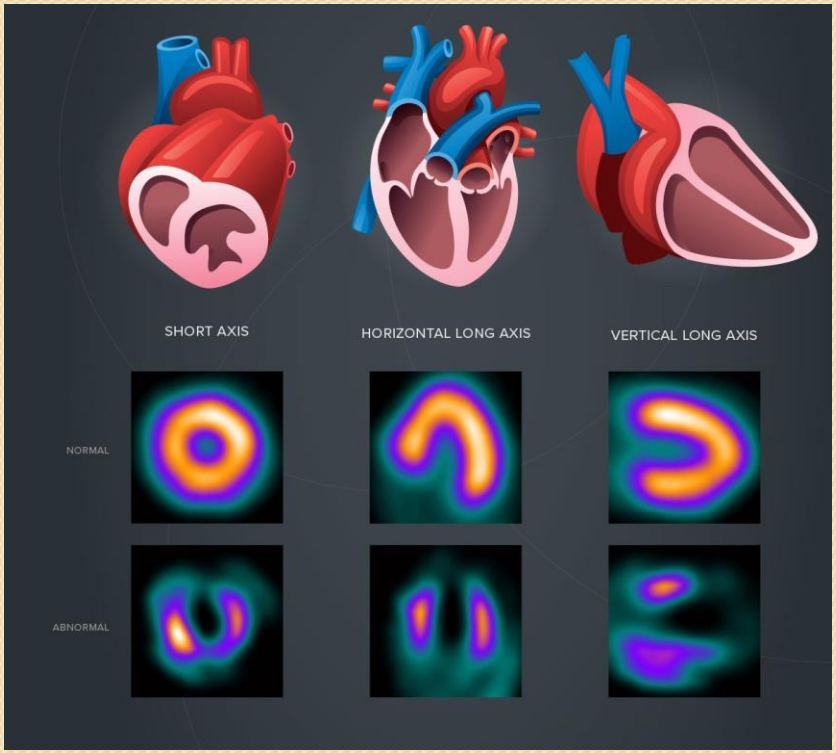
- Resting -12lead ECG: this is **often normal** and does not exclude ischemic heart disease.
- During attack: there is ST segment depression and T-wave inversion.
- **In myocardial infarction**: ST elevation and deep Q-wave.

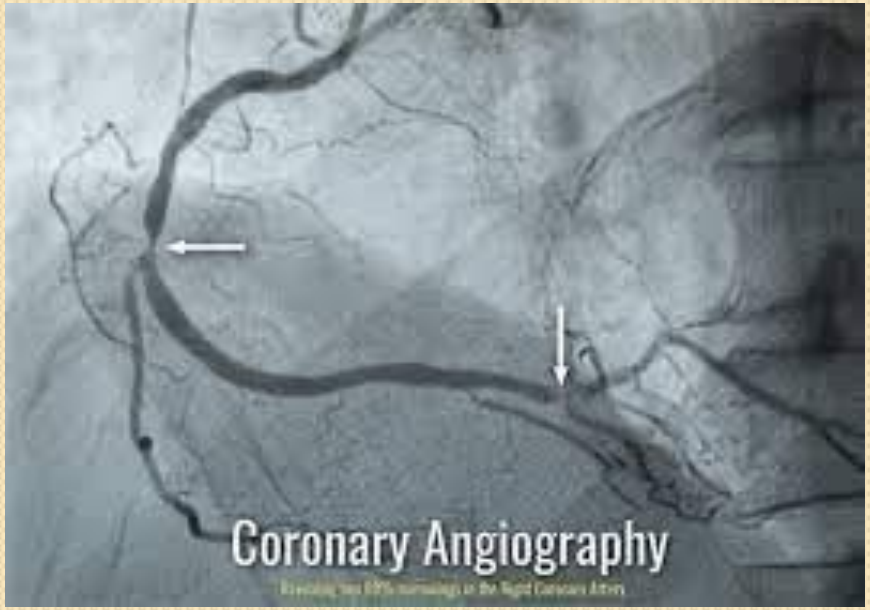


2Exercise ECG: recording ECG under controlled physical effort to record ischemic changes.

3Nuclear isotope stress imaging) use radiopaque substance e.g. thalidium.(

4 Coronary angiography.





Management of stable angina

i. **Non-drug therapy** = lifestyle modification :

The same as hypertension. In addition to low fat diet.

i. **Pharmacological therapy**:

- - I Immediate treatment of acute chest pain:

a. Glyceryl trinitrate (GTN): sublingual or spray.

b. Aspirin 300 mg loading dose as soon as possible. It reduces the risk of progression to MI.

c. Refer the patient to hospital if an ACS is suspected.

2- Long-term therapy:

a. Beta-blockers: the first-line agents for chronic stable (exertional) angina.

:b. CCBs the second-line agents for chronic stable angina

c. Long and intermediate acting nitrates.

d. pFOX inhibitors: trimetazidine

.e Newer antianginal drugs ranolazine and nicorandil :

f. Lipid lowering drugs: statins.

g. Antiplatelet drugs: e.g. aspirin, clopidogrel.

iii- Surgical treatment (myocardial revascularization)

Organic nitrates and nitrites

- Classification:

	Dose	Onset	Duration
Short-acting nitrates:			
Amyl nitrite crushable ampoules	0.3 ml inhalation	1-2 min	5-10 min
Glyceryl trinitrate tablets or spray	0.5 mg SL	1-5 min	10-20 min
Isosorbide dinitrate	5 mg SL	3-5 min	60 min
Glyceryl trinitrate (Tridil®)	5 µg/min i.v.i.		
Intermediate-acting nitrates:			
Isosorbide dinitrate	10 mg oral	15 min	3-6 hrs
	40 mg oral SR	30 min	6-10 hrs
Long-acting nitrates:			
Isosorbide mononitrate	20 mg oral	30 min	6-8 hrs
	60 mg oral SR	30 min	6-10 hrs
Transdermal patches	Nocturnal angina	30 min	12-18 hrs

:Pharmacokinetics

1. **Absorption:** nitrates are **rapidly absorbed** from all sites of administration.

2. **Metabolism:** in the liver:

–If given oral → extensive first-pass metabolism (oral bioavailability <(10%

–If given sublingual → no first-pass metabolism → high bioavailability.

– Mononitrate: has no hepatic metabolism →long duration of action.

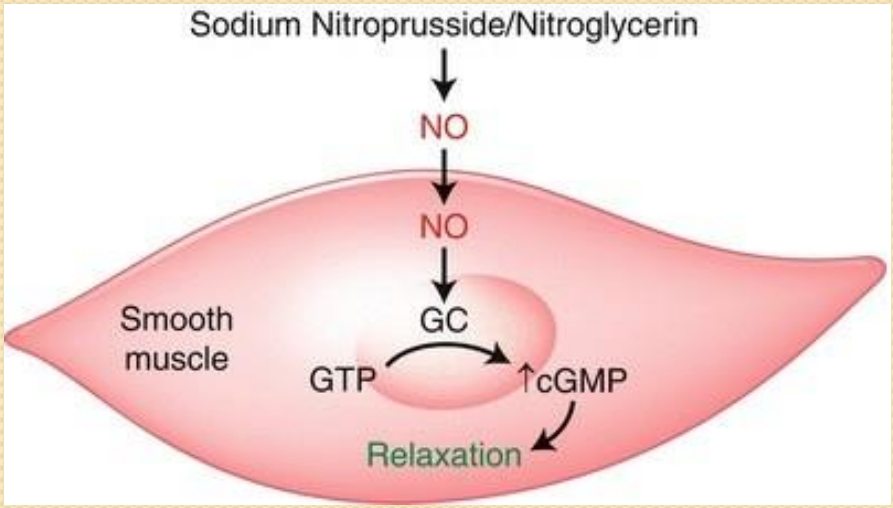
3. **Excretion:** via the kidney.

Mechanism of action

1. Nitrates converted by mitochondrial aldehyde dehydrogenase (MALDH) to (NO) which is **identical** to the endothelial derived relaxing factor (EDRF)

→ ↑cGMP →VD (more on **veins 90 %** than arteries)

.2 They also ↑ formation of vasodilator PGE2 and PGI.2



Pharmacological effects:

1. CVS:

a. Blood vessels:

–VD of the venous (and to lesser extent the arterial side(leading to ↓preload which leading to ↓ cardiac work.

–VD of coronary arteries leading to increased coronary blood flow.

–VD of arteries in the face and neck leading to flushing of the face (Flushing.(

– VD of meningeal vessels leading to throbbing headache.

b. Heart: Reflex tachycardia)in high dose) due to ↓ BP.

2. Smooth muscles: Relaxation of all sm. (bronchial, GIT, uterine, and biliary) due to cGMP activation.

3. Respiratory: Reflex tachypnea due to hypotension **in high doses**.

4. Blood: Methemoglobinemia in high doses due to oxidation of Hb into met- Hb.

Therapeutic uses:

1. **Angina pectoris:** (NO, PGE2 and PGI2 formation) lead to decrease cardiac work & myocardial O2 demand through:

- Venodilatation → ↓ venous return (preload = ↓ end-diastolic pressure)
- Arteriolodilatation → ↓ peripheral resistance (afterload).

2. Enhancement of coronary blood flow (perfusion) through: Coronary VD. and redistribution of blood from large epicardial vessels to ischemic subendocardial vessels.

2. MI: to limit the area of myocardial damage.

3.Acute heart failure: to↓preload and afterload.

4. Treatment of cyanide poisoning:

NO oxidate Hb to produce met-Hb, cyanide have higher affinity to bind with oxidized Hb, that will be resulted in cynomet-Hb formation,

The later structure detoxed with Sodium thiosulfate which convert it to thiocyanate which well **excreted readily by kidney**.

Adverse effects:

1.Hypotension and reflex tachycardia: may aggravate angina (high doses)

2.Throbbing headache: due to VD of meningeal arteries.

3. Flushing of the face.

4. Methemoglobinemia: rare and require high doses.

5.Nitrate tolerance: means diminished response to nitrates with continuous administration which cannot be corrected by increasing the dose. With unclear mechanisms, but 2 theories explain this:

1. Continuous administration of nitrates leads to formation of **free radicals (ROS)** leading to oxidation and inhibition of the enzyme MALDH responsible for bioactivation of nitrites into the vasoactive NO.

2. **Prolonged VD** by nitrates leads to reflex sympathetic stimulation and activation of RAAS→ VC and salt & water retention.

- Prevention of nitrate tolerance: make a **daily nitrate-free interval** (10–12 h) to give chance for bioactivating enzymes to regenerate. During this period, give another anti-anginal drug e.g. BBs or CCBs.

Precautions during nitrate therapy:

.1 Use the smallest effective dose to avoid hypotension and reflex tachycardia.

.2 The patient should **consult his doctor** if anginal pain does not improve after taking **3 SL** tablets of GTN during 15 min (the pain may be due to MI)

3. Nitroglycerine tablets should not be put in direct sunlight (light sensitive) or with cotton (to avoid formation of the explosive nitrocellulose)

4. The expiry date should be checked (active tablets have burning taste)

5. Nitrates should not be used with sildenafil. Why?

Beta-blockers:

1. Its considered first-line in classic angina (note that short acting nitrates are the first line during the acute attack.(
2. Treatment objectives include lowering the resting HR to 50-60 beats/min and limiting maximal exercise HR to ~ 100 beats/min or less.
3. There is little evidence to suggest superiority of any particular β-blocker, but β- blockers with intrensic sympathomimetic activity ISA should be avoided because the reduction in HR and O2 consumption would be minimal. E.g. Pindolol.

.4 They are contraindicated in Prinzmetal's angina because they block the β2-mediated coronary dilatation leaving the α1 receptors unopposed → ↑ coronary spasm.

Mechanism of β-blockers in exertional angina:

1. They ↓ contractility, HR, and systolic BP → ↓ myocardial work and O2 demand.
2. They ↑ diastolic (coronary) filling time.
3. Cause redistribution of blood from normal to ischemic (subendocardial) regions.
4. Cytoprotective effect: they produce metabolic switch from myocardial fat utilization to CHO utilization (i.e. improves myocardial metabolism)

Why combination of nitrate and BB preferred?

	β-blockers	Nitrates	Combination
– HR	↓	↑ (Reflex)	↓ or no effect
– Contractility	↓	↑ (Reflex)	↓ or no effect
– Diastolic filling time	↑	↓	↑ or no effect
– Blood pressure	↓	↓	↓↓

- Combination of BBs and nitrates ↑ their efficiency & ↓ their side effects (Tolerance.(

Calcium channel blockers (CCBs:(

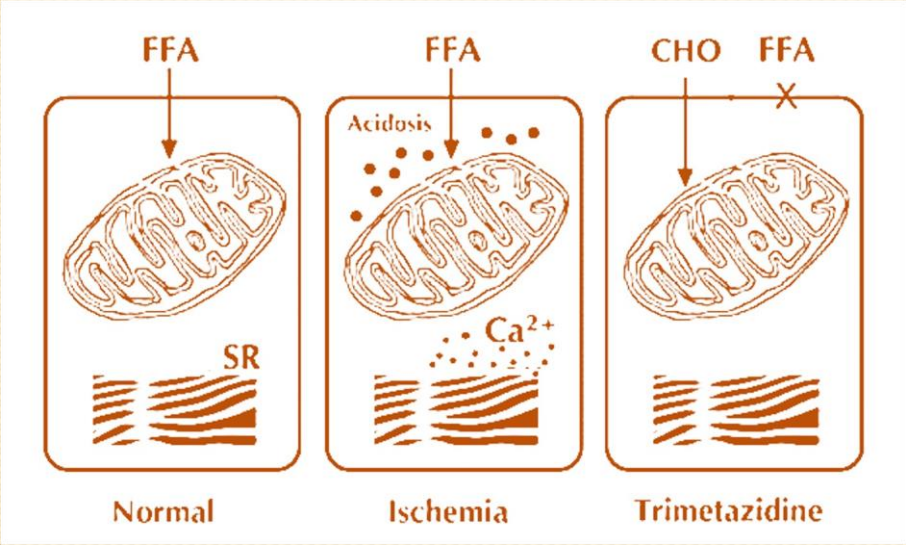
1. They are considered **first-line treatment for Prinzmetal's (variant) angina.**
2. They are considered **second-line alternative after BBs** in chronic stable angina in whom BBs are contraindicated (**Asthma**)
3. Short acting dihydropyridines e.g. nifedipine are associated with increased risk of ACS and should be avoided. Long acting dihydropyridines (e.g. amlodipine) and non-dihydropyridines (**verapamil and diltiazem) are more preferred.**
4. Amlodipine is the CCB of best choice for symptomatic treatment of angina and/or hypertension in patients with chronic heart failure.

Newer options for treatment of chronic angina:

(pFOX inhibitors, k channel openers, ranolazine)

- These drugs alter the balance between myocardial work and O2 supply by novel mechanisms of action.
- Their efficacy in treatment of angina is controversial; however they are approved for treatment of chronic stable angina in combination with βB, CCBs, and nitrates.

pFOX inhibitors (metabolic modifiers): Trimetazidine



- They prevent fatty acid oxidation in the myocardium.

-This "metabolic switch" from fats to CHO utilization requires less O2 consumption.

-By inhibition of fatty acid oxidation, they ↓ intracellular lactic acidosis leading to ↓ intracellular Ca^{+2}. So they prevent cell necrosis and preserve contractile function.

Ranolazine:

- It ↓ intracellular Ca^{2+} indirectly by reducing the late Na+ current that facilitates Ca^{+2} entry into myocardial cells.
- The reduction in intracellular Na+ and Ca^{2+} load reduces cardiac contractility and work.
- *It does not affect HR, blood pressure or coronary blood flow*.

Potassium channel openers: Nicorandil:

–Nicorandil is a new antianginal drug with 2 proposed mechanisms of action:

1. It opens ATP-dependent K+ channels in the vascular wall leading to VD of peripheral and coronary arteries.
2. Nitrate-like activity: **it has a nitrate component** and ↑cGMP like nitrates but tolerance to its effects is less marked.

–Like nitrates, it should not be used with sildenafil.

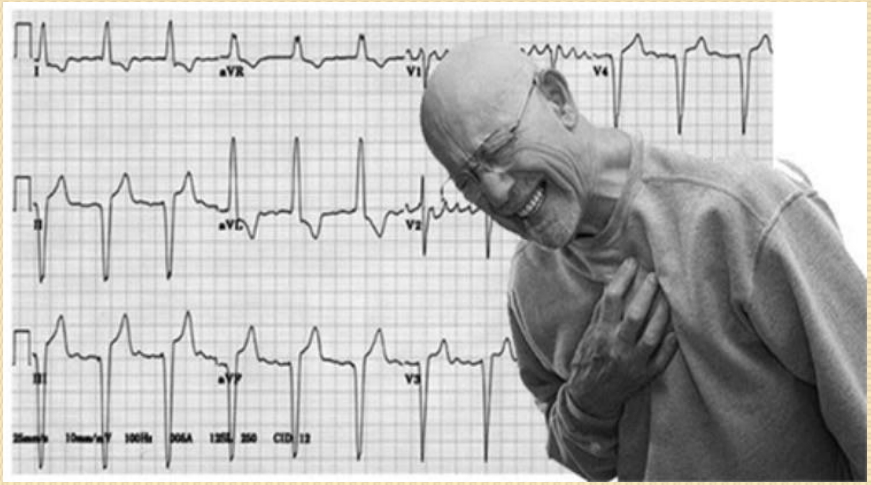
Choice of antianginal drugs in patients with another disease:

Angina with….	Most preferred	Least preferred
Bronchial asthma	Nitrates, CCBs	Beta-blockers
Heart failure	Amlodipine	Beta-blockers, Verapamil
Hypertension	Beta-blockers, CCBs	Nitrates
Diabetes mellitus	Nitrates, Nifedipine	Beta-blockers, Verapamil

MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION (AMI)

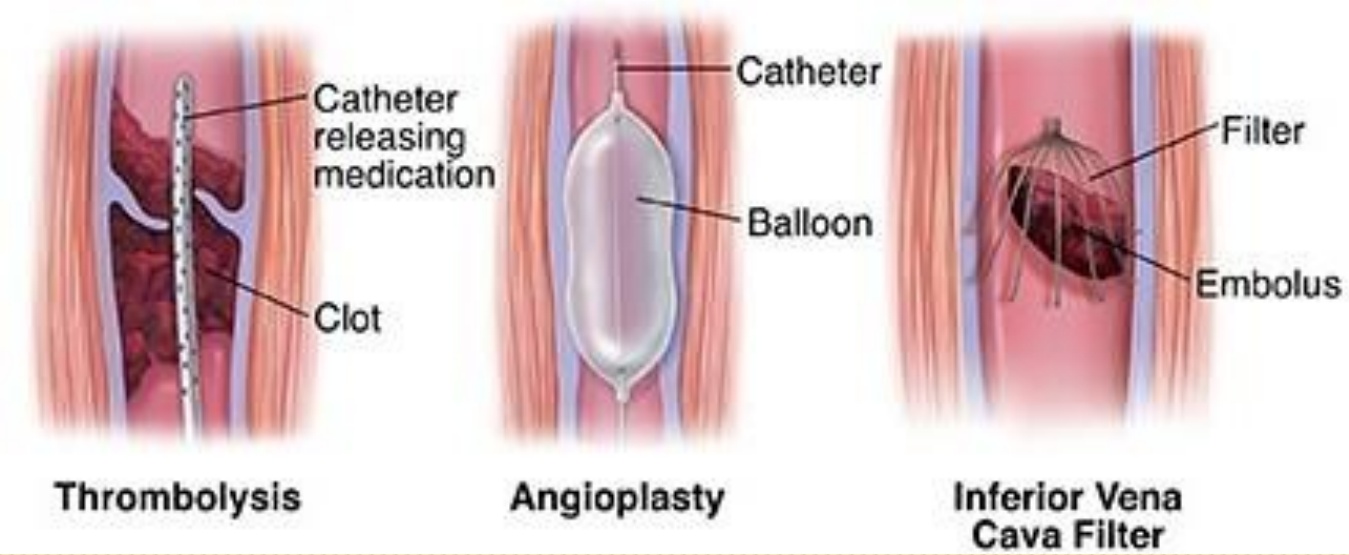
- Manifestations: persistent central crushing chest pain + ST segment elevation or depression + pathological Q wave + raised biochemical markers of myocardial cell death (troponin enzyme)

- All cases must be hospitalized in a specialized coronary care unit.

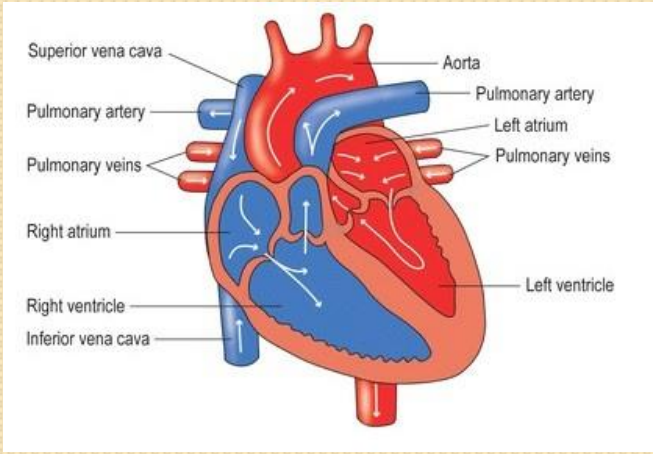


Non-pharmacologic therapy:

- Patients presenting within 12 hours of symptom onset, the treatment of choice is percutaneous coronary intervention (PCI, or coronary angioplasty)
- A balloon catheter, guided by x-ray imaging, is introduced into the occluded artery to open it.



Pharmacologic therapy: (MONATSCT)



1. **Morphine sulfate (5 mg i.v:)**

–To produce analgesia and ↓ stress of the patient ↓ →sympathetic discharge and heart work

– Morphine causes venodilatation → ↓ venous return and cardiac work.

- In case of inferior MI morphine is contraindicated and must replaced with Meperidine.

2. Oxygen: Recent evidence suggests that routine O2 administration has doubtful significance and did not reduce mortality except in hypoxia.

3.Nitroglycerine and beta-blockers: to limit the infarct size.

4.Anticoagulant drugs: heparin 10,000 IU i.v. then 5000 IU/8h s.c. especially when the patient is obese or if there is history of previous MI.

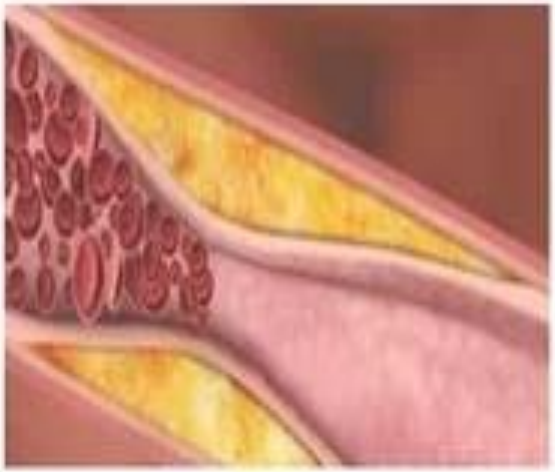
5.Thrombolytic(fibrinolytic therapy: streptokinase, urokinase, or t-PA as early as possible.

6. Sedatives: Diazepam 5 mg i.v.

7. Treatment of Complications:

- Cardiogenic shock → dobutamine i.v. (B1 agonist(
- Arrhythmia → lidocaine i.v.

INTRODUCTION



What is Hyperlipidemia?

- A condition in which there are high levels of fat particles(lipids) deposited in the blood.
- Elevated plasma levels of lipids are deposited in the form of lipoproteins.

  Eg: lipids like cholesterol and triglycerides.
- These lipids can deposit in blood vessel walls and restrict blood flow.
- This creates a risk of heart attack & stroke.

It results from abnormalities in lipid metabolism or plasma lipid transport or a disorder in the synthesis and degradation of lipoproteins

The biochemistry of Plasma lipids

What are lipids?

Lipids are the heterogenous mixtures of fatty acids and alcohol that are present in the body. The major lipids in the bloodstream are ***cholesterol*** and it's ***esters***, ***triglycerides*** and ***phospholipids.***

Cholesterol

- **Is steroid that serves as an important component of all cell membranes**

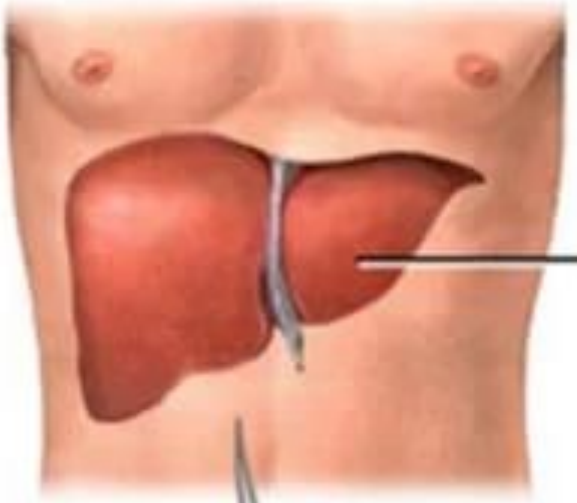
What are the normal functions of cholesterol in the body?

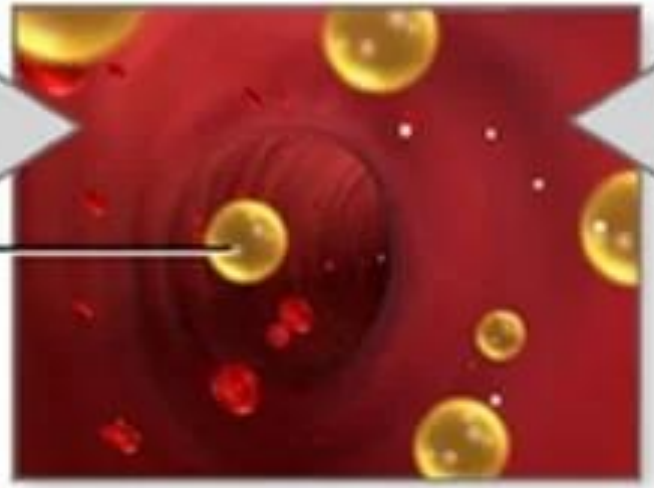
- **It is necessary in for new cells form and older cells repairing after injury.**

- **important precursor molecule for the biosynthesis of bile acids, steroid hormones, and several fat-soluble vitamins**

- **Also it used by**
  - **adrenal glands to form hormones such as cortisol**
  - **testicles to form testosterone**
  - **ovaries to form estrogen and progesterone.**

Cholesterol is produced by the liver and we consume it from meat and dairy products





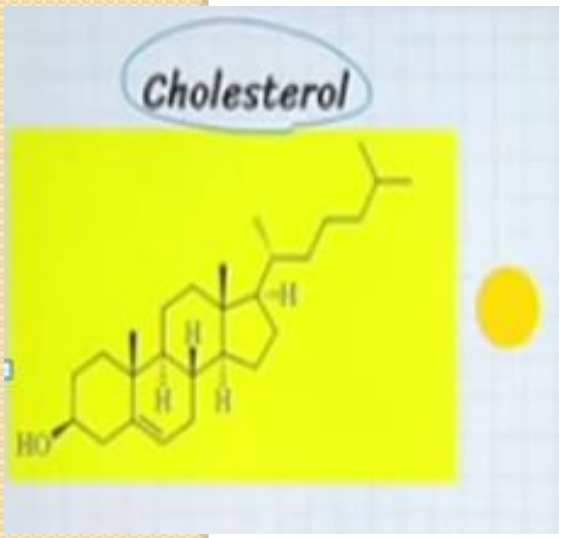
What are the normal functions of *triglycerides and Phospholipids* in the body?

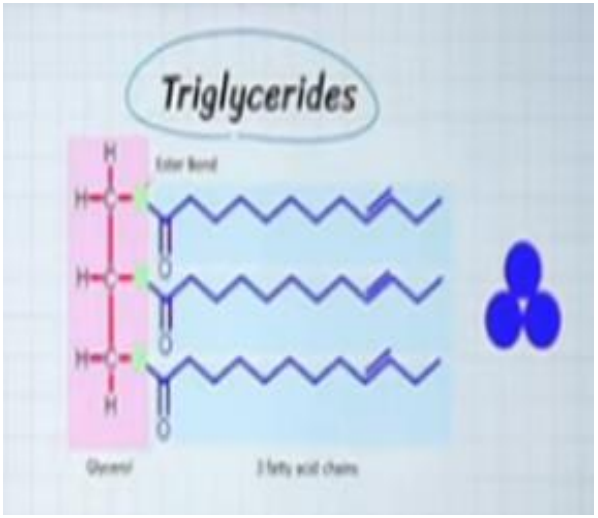
- ***Triglycerides*** supply energy for the body. Triglycerides either meet immediate energy needs in muscles or stored as fat for future energy requirements.
- ***Phospholipids*** are compounds that are used to make cell membranes, generate second messengers, and store fatty acids for the use in generation of prostaglandins

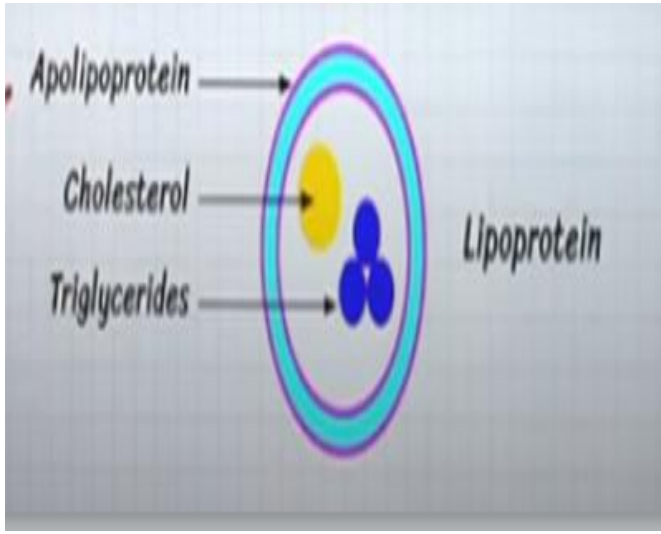
Hyperlipidemia

- Hyperlipidemia: Elevation of TG or Cholesterol or both.

- Lipoproteins consist of a **hydrophobic lipid** core **(TGs or cholesterol)** surrounded by a **hydrophilic coat** of phospholipids and proteins (apoproteins), which render them miscible in aqueous plasma.



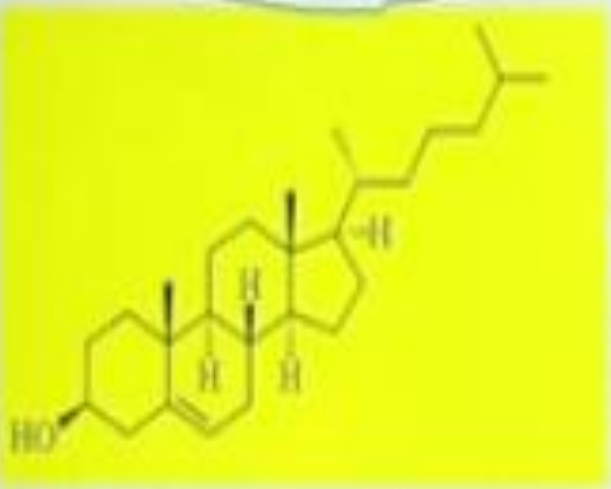




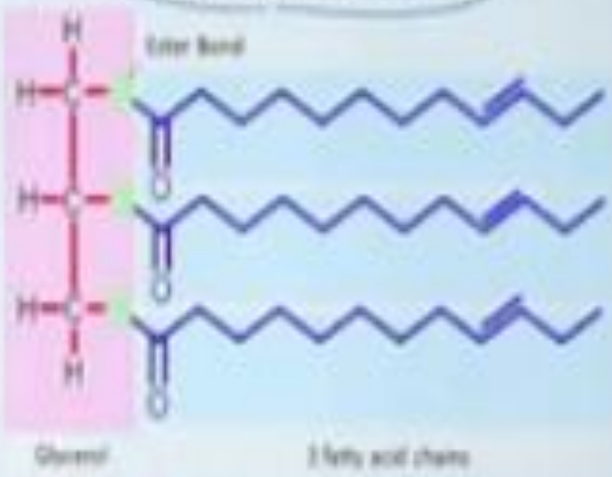
Basic information

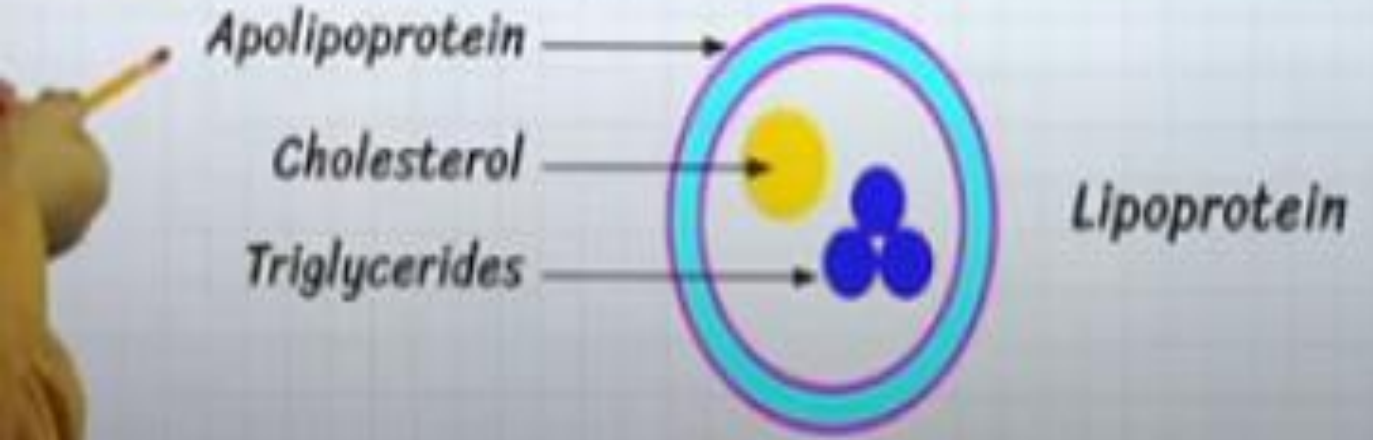
بسم الله الرحمن الرحيم

Cholesterol



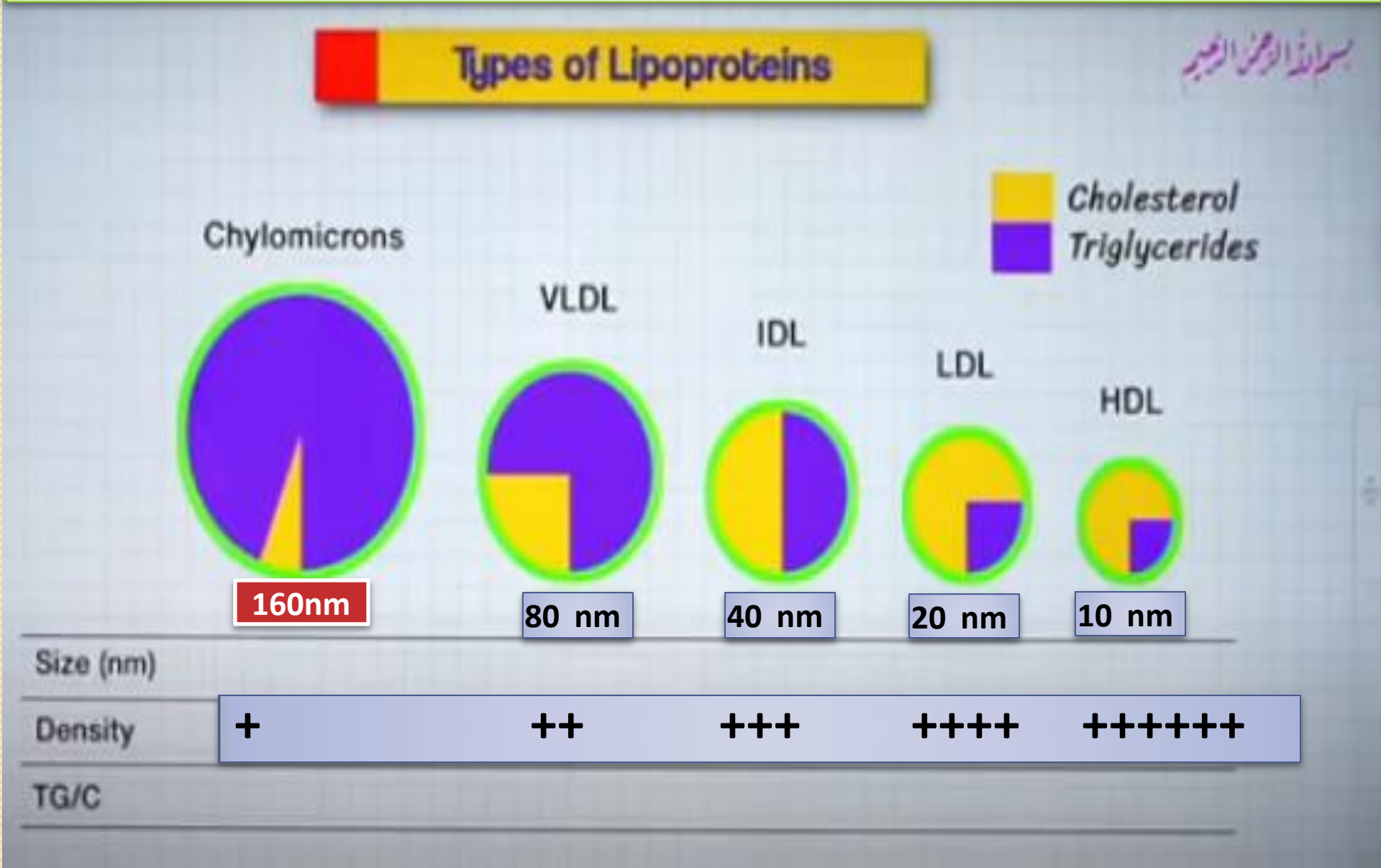
Triglycerides



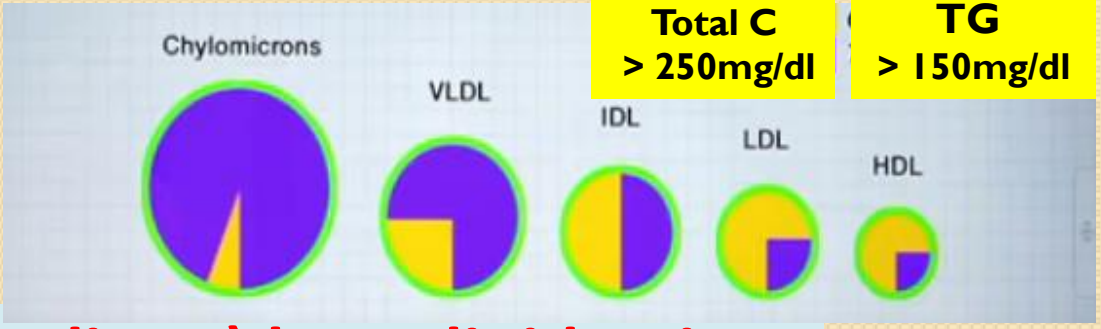


Lipoprotein

There are 5 classes of lipoproteins depending on their relative proportion of the core lipids, type of apoprotein, size, and density:



Classification of hyperlipidemia



1. Primary(familial; hereditary) hyperlipidemia:

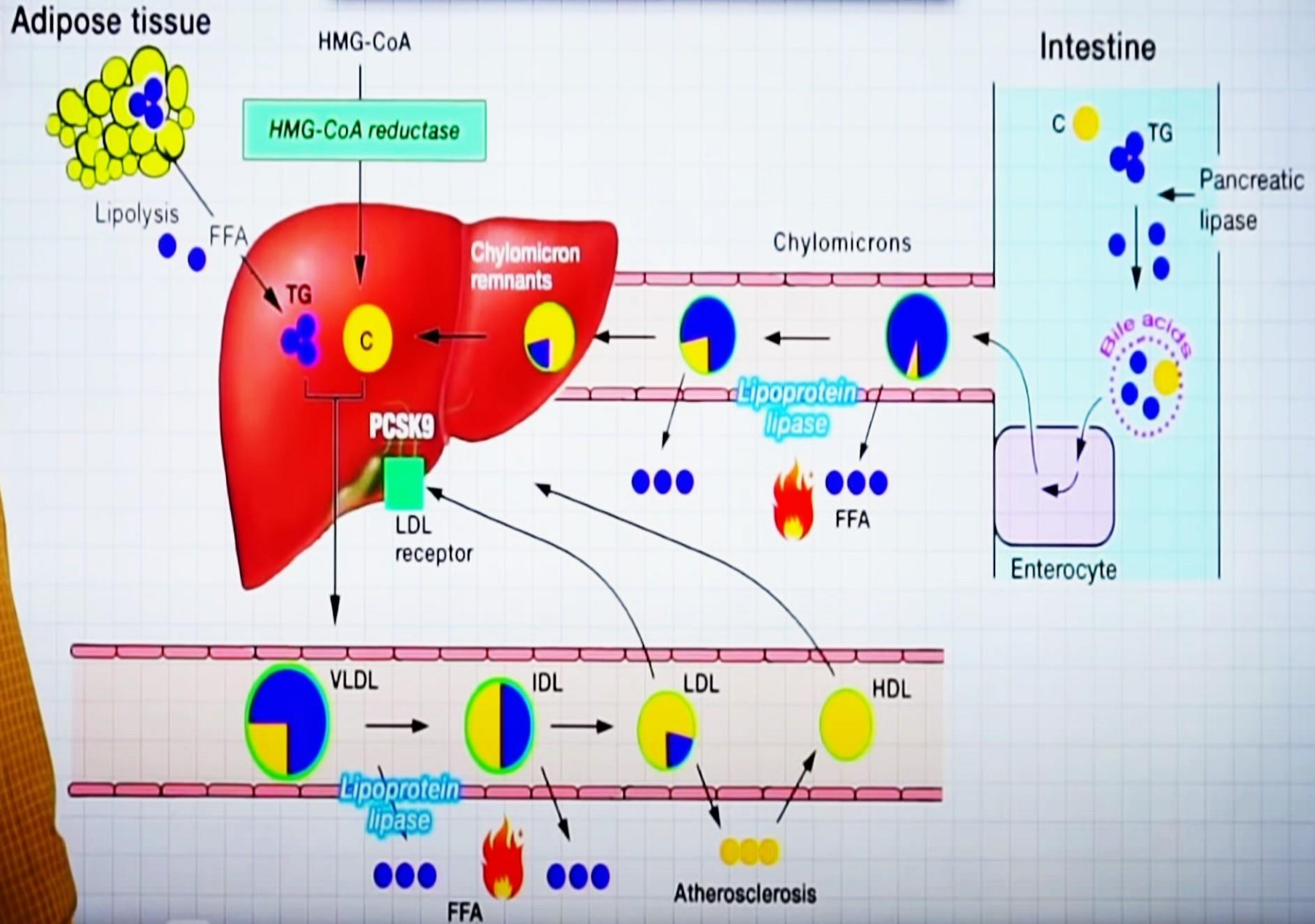
Class	Increased lipoprotein	Synonym
Type I	↑ chylomicrons	Familial chylomicronemia
Type IIa	↑ LDL	Familial hypercholesterolemia
IIb	↑ LDL and VLDL	Familial combined hyperlipidemia
Type III	↑ IDL	Familial dysbetalipoproteinemia
Type IV	↑ VLDL	Familial hypertriglyceridemia
Type V	↑ VLDL and chylomicrons	Familial mixed hyperlipedemia

2. Secondary (acquired) hyperlipidemia:

- Hypercholesterolemia: hypothyroidism, nephrotic syndrome, and drugs **e.g. thiazide**.
- Hypertriglyceridemia: **DM, alcohol, gout, renal failure**.

بسم الله الرحمن الرحيم

Lipoprotein Metabolism



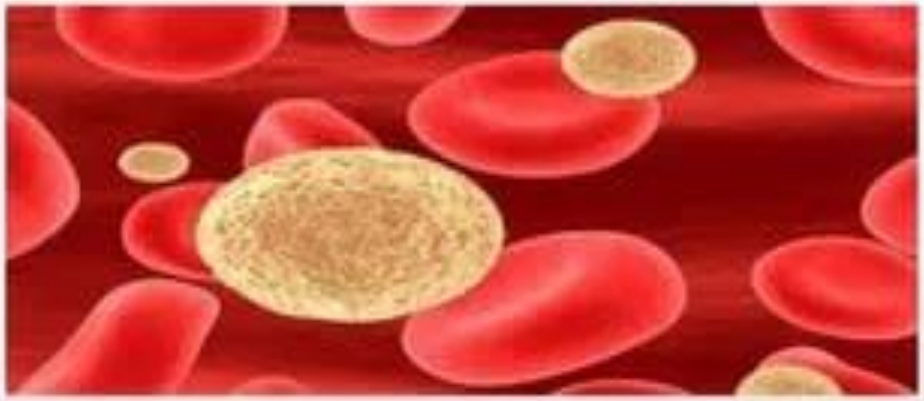
CAUSES OF HYPERLIPIDEMIAS

- Diet & Hereditary factors
- Hypothyroidism
- Not exercising
- kidney disease
- Inherit hyperlipidemia
- Obesity,Alcohol consumption & smoking
- Diabetes
- Pregnancy
- Obstructive liver disease, Acute hepatitis

SYMPTOMS OF HYPERLIPIDMIA

ANTIHYPERLIPIDEMICS

- The clinically important lipoproteins are HDL,LDL and VLDL .
- Antihyperlipidemics are the drugs used to reduce the deposited levels of cholesterol and other lipoproteins from the blood plasma .



Treatment of hyperlipidemia

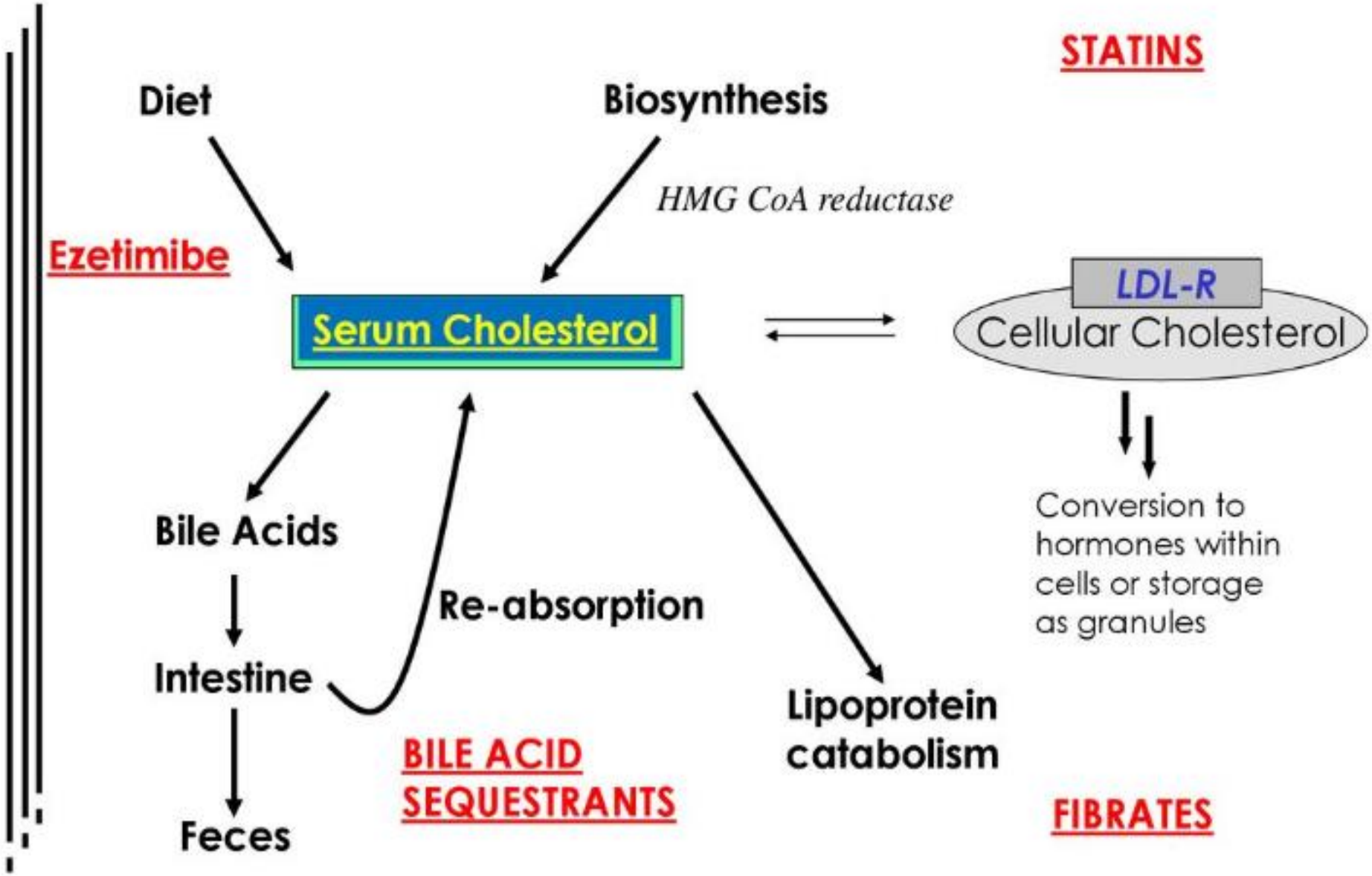
- Non-Pharmacological Therapy – first line treatment
  - **Diet modification**
    - Decrease intake of total fat and especially saturated fat
    - Increase fiber intake
    - Increase Omega-3-fatty acids (found in fish)
    - ↑ fruits and vegetables (antioxidants)
    - ↓ simple sugars (sucrose)
  - **Exercise (↑ HDL levels)**
- Pharmacological Therapy

Classification of Lipid-Lowering Drugs

بسم الله الرحمن الرحيم

1.	Inhibitors of intestinal cholesterol absorption:	- Bile acid binding resins - Ezetimibe
2.	Activators of plasma lipoprotein lipase:	- Fibric acid derivatives
3.	HMG-CoA reductase inhibitors:	- Statins
4.	Inhibitors of lipolysis and hepatic lipid production:	- Nicotinic acid - acipimox
5.	PCSK9 inhibitors:	- Evolocumab - alirocumab

Strategy For Controlling Hyperlipidemia

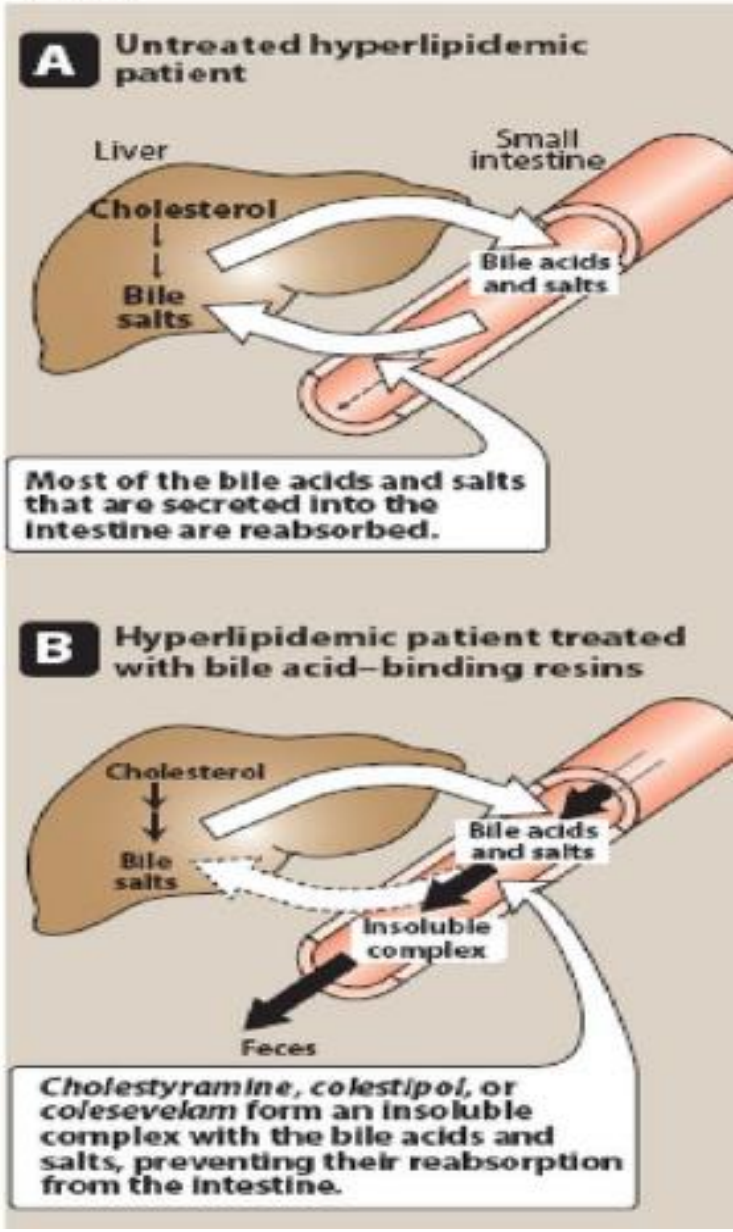


Cholesterol absorption inhibitors

Bile acid–binding resins

- Bile acid sequestrants (resins) have significant LDL cholesterol–lowering effects, although the benefits are less than those observed with statins.
- **Cholestyramine** , **Colestipol**, and **Colesevelam.**

✓ Anion-exchange resins that bind negatively charged bile acids and bile salts in the small intestine .



✓ The resin/bile acid complex is excreted in the feces, thus lowering the bile acid concentration.

- This causes hepatocytes to increase conversion of cholesterol to bile acids, which are essential components of the bile.
- Intracellular cholesterol concentrations decrease, Which activates an increased hepatic uptake of cholesterol-containing LDL particles, leading to a fall in plasma LDL-C.

✓ This increased uptake is mediated by an up-regulation of cell surface LDL receptors.

Pharmacokinetics

- ✓ Bile acid sequestrants are insoluble in water and have large molecular weights.
- ✓ After oral administration, they are neither absorbed nor metabolically altered by the intestine.
- ✓ Instead, they are totally excreted in feces.

Adverse effects:

1. GIT upset (the most common): nausea, vomiting and steatorrhea (due to ↓ fat absorption)
2. ↓absorption of fat-soluble vitamins.
3. ↓ absorption of anionic drugs e.g. **digitalis and warfarin**.

1. Inhibitors of Intestinal Lipid Absorption

بسم الله الرحمن الرحيم

1. Bile acid sequetrants: Cholestyramine & Colestipol

Mechanism	Ther Uses	Adverse effects
They bind to bile acids in the intestine and ↓ absorption of cholesterol.	1. Hypercholesterolemia (type IIa): Bile acid sequestrants are effective in reducing plasma cholesterol (10%-20%). 2. Diarrhea due to bile acid malabsorption. 3. Pruritus due to obstructive jaundice.	- GIT upset (the most common): nausea, vomiting and steatorrhea (due to ↓ fat absorption). - ↓ absorption of fat-soluble vitamins and some drugs (digitalis, warfarin, etc).

Ezetimibe:

Mechanism of action:

Ezetimibe is a selective inhibitor of intestinal cholesterol absorption. It is effective even in the absence of dietary cholesterol because it inhibits reabsorption of cholesterol excreted in the bile.

Therapeutic uses:

Hypercholesterolemia: Ezetimibe is synergistic with HMG-CoA reductase inhibitors, producing decrease of 25% in LDL cholesterol.

Adverse effects:

Reversible hepatic dysfunction: liver function tests should be done at regular intervals.

1. Inhibitors of Intestinal Lipid Absorption

بسم الله الرحمن الرحيم

2. Ezetimibe

Mechanism	Ther Uses	Adverse effects
Ezetimibe is a selective inhibitor of cholesterol absorption. It is effective even in the absence of dietary cholesterol because it inhibits reabsorption of cholesterol excreted in the bile.	Hypercholesterolemia (type IIa): alone, it can reduce plasma cholesterol level by 18%.	- Reversible hepatic dysfunction: liver function tests should be done at regular intervals

Fibric acid derivatives (Fibrates):

Fibrates: (Clofibrate, Fenofibrate, Bezafibrate, Gemfibrozil)

- **Fenofibrate and Gemfibrozil are derivatives of fibric acid that lower serum triglycerides and increase HDL levels.**
- **The fibrates are used in the treatment of hypertriglyceridemia, Leads to decreased triglyceride concentrations.**
- **Fenofibrate is more effective than gemfibrozil in lowering triglyceride levels.**
- Gemfibrozil and fenofibrate are completely absorbed after oral administration.
- Both drugs undergo extensive biotransformation, Excreted in the urine as glucuronide conjugates.

Mechanism of action:

Fibrates act on nuclear receptors called peroxisome proliferator activated receptors-α (PPAR-α) leading to ↑ synthesis of lipoprotein lipase → ↑ peripheral catabolism of VLDL and chylomicrons (TGs)

:Adverse effects

1. GIT upsets: nausea, vomiting (the most common.(
2. Increase formation of cholesterol gallstones.
3. Hepatic dysfunction and elevation of serum transaminases.
4. Fibrates increase the risk of myopathy if used in combination with statins.
5. Skin rash and dermatologic reactions.

بسم الله الرحمن الرحيم

3. Fibric acid derivatives (Fibrates)

Clofibrate, Fenofibrate, Bezafibrate, Gemfibrozil

Mechanism	Ther Uses	Adverse effects
Fibrates act on nuclear receptors called peroxisome proliferator activated receptors-α (PPAR-α) leading to ↑ synthesis of lipoprotein lipase → ↑ catabolism of VLDL and chylomicrons (i.e.TGs).	1. Hypertriglyceridemia (types IIb, III, IV and V). 2. Fenofibrate has antidiuretic action in individuals with mild diabetes insipidus. 3. Fenofibrate has mild uricosuric action	- GIT upsets: nausea, vomiting (the most common). - Increase formation of cholesterol gallstones. - Hepatic dysfunction and elevation of serum transaminases. - Fibrates increase the risk of myopathy if used in combination with statins.

HMG CoA reductase inhibitors (Statins)

- Competitive inhibitors of HMG CoA reductase, the rate-limiting step in cholesterol synthesis.

- **Pitavastatin**, **rosuvastatin**, and **atorvastatin** are the most potent LDL cholesterol–lowering statins, followed by **simvastatin, pravastatin, lovastatin and fluvastatin.**
- Also it ↓ triglyceride (TG) levels and may ↑ HDL cholesterol levels

- Statins drugs are effective in lowering cholesterol levels in all types of hyperlipidemia.
- All statins are metabolized in the liver
- Excretion occurs through bile and feces, but some in urine

Therapeutic uses: **Hypercholesterolemia (type II).**

- With other drugs for **combined hyperlipidemia**.

HMG-CoA reductase inhibitors (Statins)

(Lovastatin, Pravastatin, Mevastatin, Atorvastatin)

Mechanism of action:

Competitive inhibition of hydroxy-methyl-glutaryl coenzyme-A (HMG-CoA) reductase → ↓ cholesterol synthesis and ↑ hepatic uptake of LDL

.

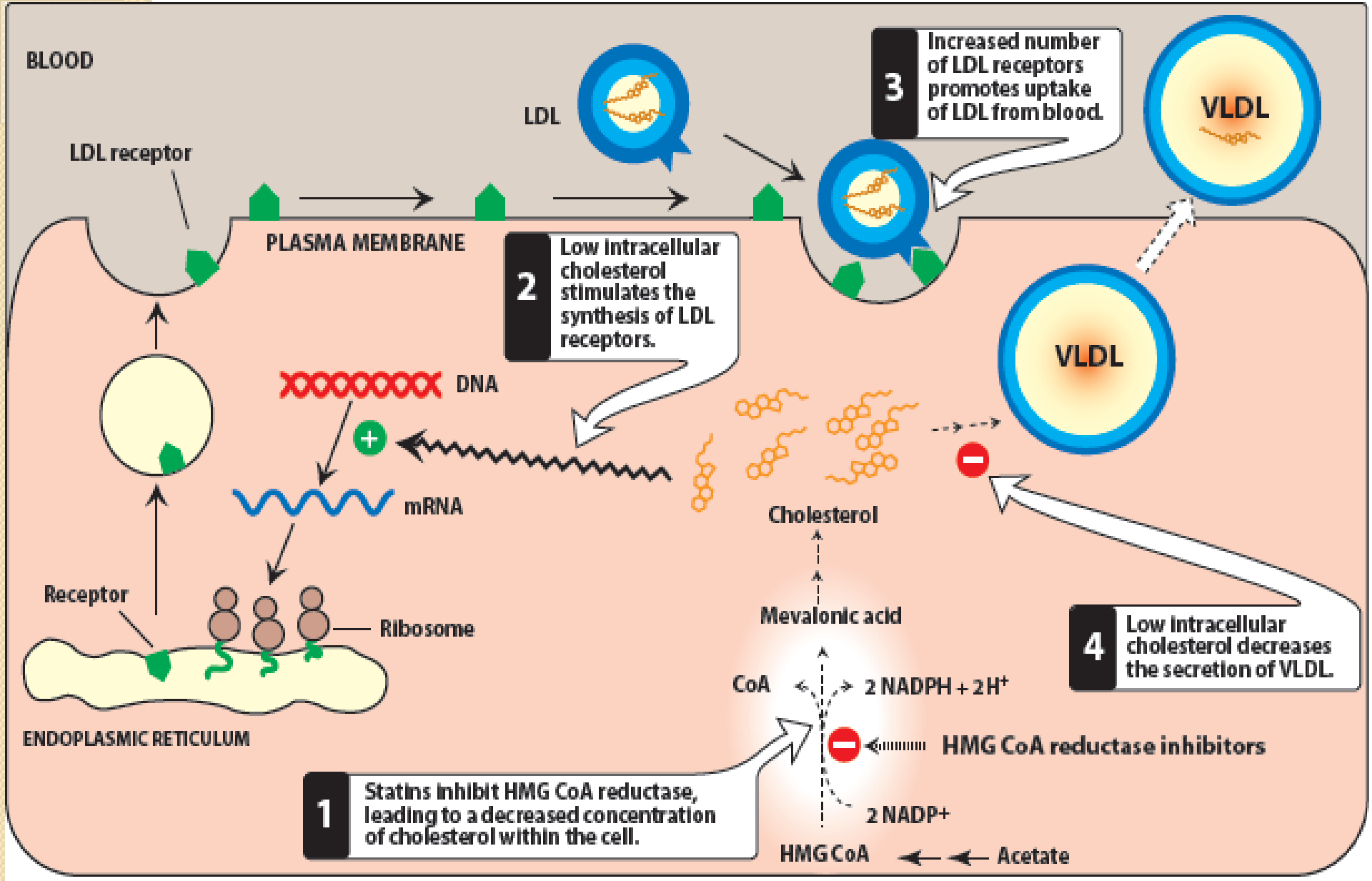
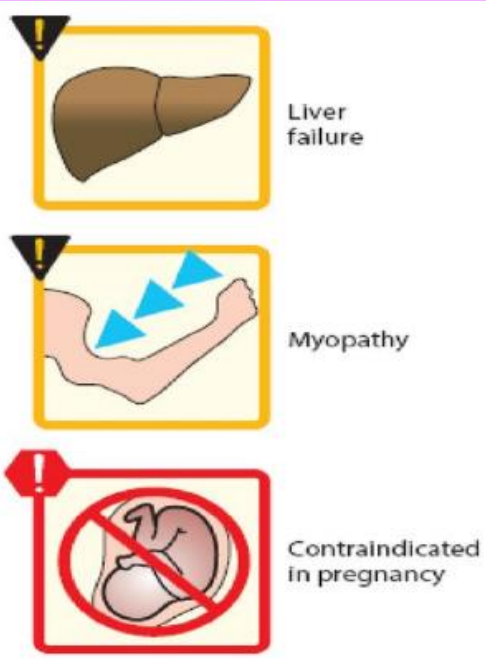


Figure 21.5
Inhibition of HMG CoA reductase by the statin drugs. HMG CoA = 3-hydroxy-3-methylglutaryl coenzyme A; LDL = low-density lipoprotein; VLDL = very–low-density lipoprotein.

Adverse effects

- Mild, transient GI disturbances
- Rash
- Headache
- Myopathy (muscle pain), possibly leading to the serious condition rhabdomyolysis
- Elevations in liver enzymes or liver disease

The increase in liver enzymes may occur with statin therapy, therefore liver function should be evaluated prior to treatment.



بسم الله الرحمن الرحيم

2. HMG-CoA reductase inhibitors (Statins)

Lovastatin, Pravastatin, Mevastatin, Semvastatin, Atorvastatin

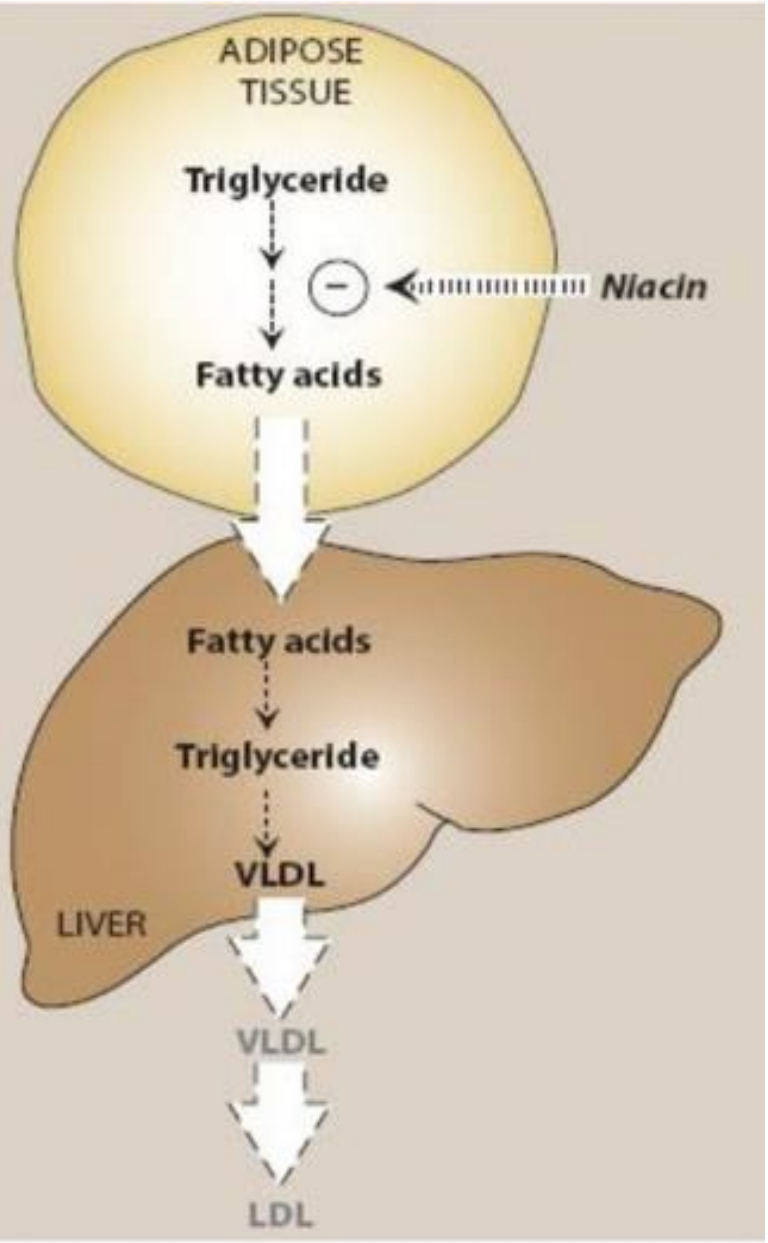
Mechanism	Ther Uses	Adverse effects
Competitive inhibition of HMG-CoA reductase → ↓ cholesterol synthesis and ↑ hepatic uptake of LDL.	1. Hypercholesterolemia (type II). 2. With other drugs for combined hyperlipidemia.	**H:** Hepatic dysfunction leading to elevation of serum transaminases. Therapy should be stopped if liver enzymes rise > 3-folds the upper normal value. **M:** Myopathy, myositis and rhabdomyolysis in both sk & cardiac muscle leading to ↑ of CPK enzyme. **G:** GIT upsets: nausea, vomiting (the most common). **Co-A:** Cataract (lenticular Opacity) in middle-Aged individuals. **R**eductase: Renal dysfunction (especially with lovastatin).

3. Nicotinic acid (Niacin; vitamin B3)

Mechanism of action:

- Niacin *(but not nicotinamide)* **inhibits lipolysis** in adipose tissue and inhibits fatty acid synthesis by the liver → ↓ hepatic VLDL and LDL synthesis.

- It can **reduce LDL-C** by 10% to 20%
- It is the most effective agent for **increasing HDL-C.**
- It **lowers triglycerides** by 20% to 35% at doses of 1.5-3 gm/day.
- **used in combination with statins**



Adverse effects:

1. **Skin flushing** and pruritis (the most common). It is harmless effect mediated by PGs and histamine release and can be diminished by taking aspirin 30 minutes before taking nicotinic acid.

.2 **Gastric irritation** (the drug should be avoided in peptic ulcer)

3. Niacin inhibits tubular secretion of uric acid and, thus, predisposes to **hyperuricemia and gout**.

4. The drug should be **avoided in hepatic disease due to** reversible increase in serum transaminases**.**

4. Nicotinic acid (Niacin; vitamin B3)

بسم الله الرحمن الرحيم

Mechanism	Ther Uses	Adverse effects
Niacin (but not nicotinamide) inhibits lipolysis in adipose tissue → ↓ FA synthesis by the liver → ↓ hepatic synthesis of VLDL & LDL This is distinct from the role of niacin as a vitamin, in which it is converted to nicotinamide and is used for the biosynthesis of the cofactors NAD and NADP.	In combination with other drugs for all types of hyperlipidemia (except type I which is mainly treated by diet control).	- Skin flushing and burning sensation (the most common). It is harmless effect mediated by PGs and histamine release and can be diminished by taking aspirin 30 minutes before taking nicotinic acid. - Gastric irritation. - Hyperglycemia, hyperuricemia.

Omega-3 fatty acids

- Omega-3 polyunsaturated fatty acids (PUFAs) are essential fatty acids that are predominately used for triglyceride lowering.
- Essential fatty acids inhibit VLDL and triglyceride synthesis in the liver.
- The omega-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are found in marine sources such as tuna and salmon.
- Approximately 4 g of marine-derived omega-3 PUFAs daily decreases serum triglyceride concentrations by 25% to 30%, with small increases in LDL-C and HDL-C.

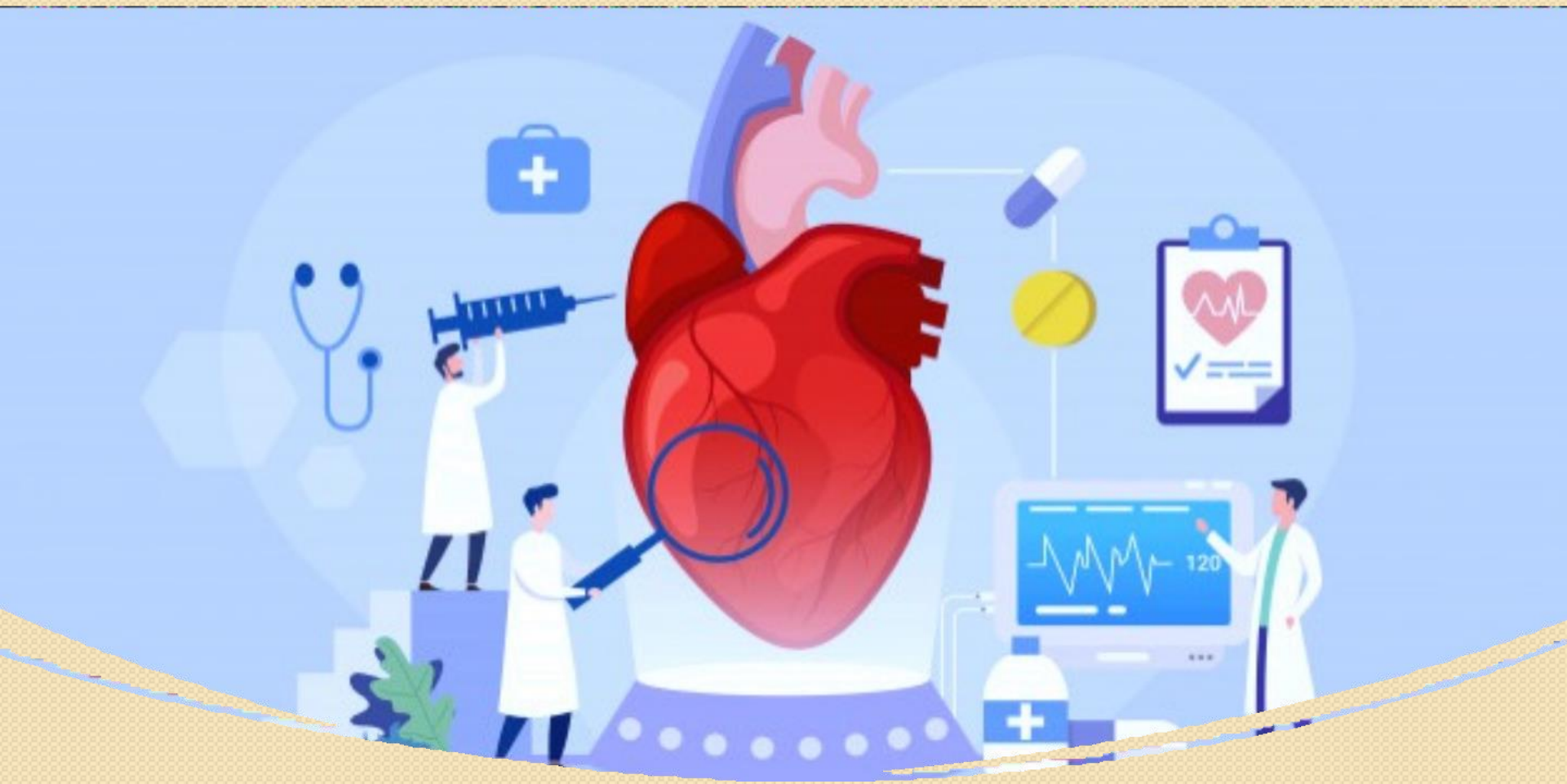
✓ Over-the-counter or prescription fish oil capsules (EPA/DHA) can be used for supplementation, as it is difficult to consume enough omega-3 PUFAs from dietary sources alone.

Summary

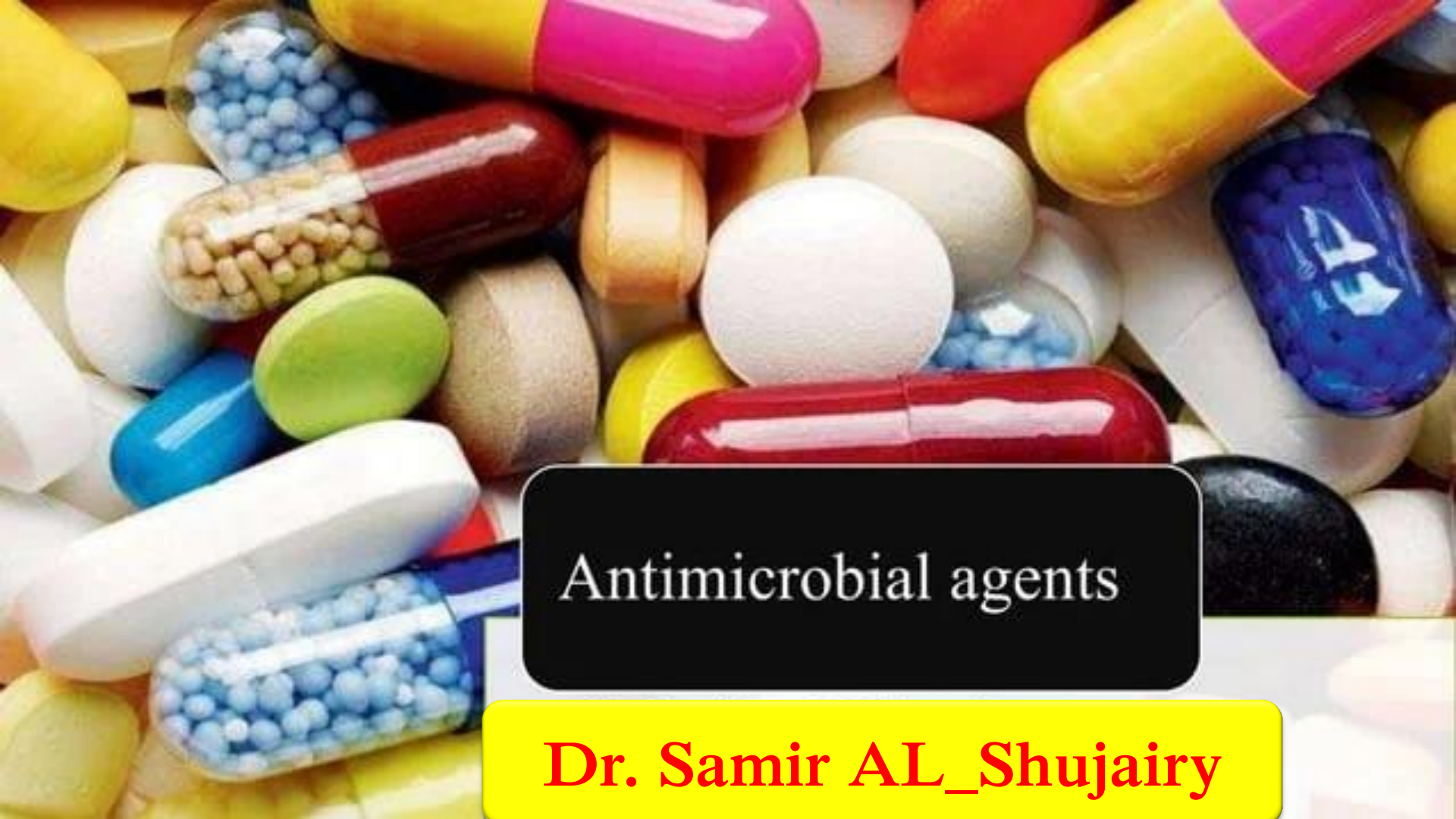
	Effect on LDL	Effect on HDL	Effect on TGs
Bile acid-binding resins	↓↓↓	↑	----
Reductase inhibitors	↓↓↓	↑	↓
Fibrates	↓	↑	↓↓↓
Niacin	↓	↑↑↑	↓↓

Treatment with drug combinations

Hypercholesterolemia	Cholestyramine + Reductase inhibitors
Hypertriglyceridemia	Niacin + Fibrates
Familial combined hyperlipidemia	Cholestyramine + Fibrates. Cholestyramine + Niacin. Statins + Fibrates *(this combination may ↑ risk of myopathy).*



Thank You


Antimicrobial agents
Dr. Samir AL_Shujairy

CONTENTS

- Introduction
- classification of antimicrobial agents
- Selection of antimicrobial agents
- Antibiotics
- Classification of antibiotics
- Antimicrobial resistance
- Factors involved in the usage of antibiotics rationally
- Ideal antibiotics
- antibiotics combination

Introduction

- An antimicrobial is an agent that kills or inhibits the growth of microorganisms without harming the cells of the host. The antimicrobial agent may be a chemical compounds and physical agents. These agents interfere with the growth and reproduction of causative organisms like bacteria, fungi, parasites , virus .

Classification of antimicrobial agents

- Drugs by susceptible organisms
  - Antibacterial
  - Antiviral
  - Antifungal
  - Antiprotozoal
  - Anthelmintic

Selection Of Antimicrobial Agents

- Organisms identity and its sensitivity to particular organism
- The site of infection
- The safety of the agent
- Patient factors
- The cost of the therapy

Empiric therapy prior to organism identification

- Acutely ill patient
- Selecting a drug

Identification and sensitivity of the organism

Laboratory methods of identification

- Disk diffusion method

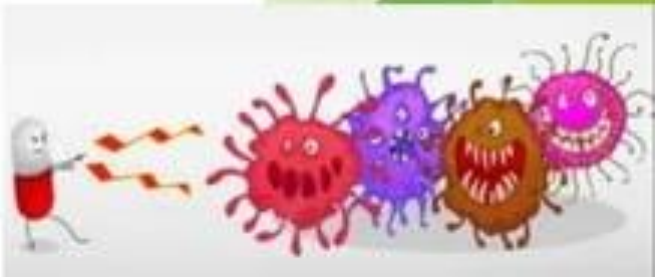
The effect of site of infection on therapy

- Blood brain barrier ,prostate

Status of the patient
1.Immune system
2.Renal dysfunction
3.Hepatic dysfunction
4.Poor Perfusion
5.Pregnancy
6.Lactation
7.age
Safety of the agent
Cost of therapy

Antibiotics

- A substance produced by which selectively suppress the growth of or kill other microorganisms at low concentrations and has the capacity to inhibit the growth of bacteria. It has a high chemotherapeutical index to reduce the active process in bacteria .



Classification of antibiotics

1. Based on chemical structures
2. Based on the sources
3. Based on mechanism of action
4. Based on spectrum of action / activity
5. Based on modes of action

1. Based on chemical structures

1. Groups of sulfonamides

- Sulfamethoxazole, sulfadiazine

2. Groups of Penicillin

- Penicillin G (Benzyl penicillin), Penicillin V, Ampicillin, amoxicillin, nafcillin

3. Groups of cephalosporin's

- cefalotin, cefazolin, cefamandole, cefuroxime,cefotaxime, ceftriaxone.

4. Groups of aminoglycosides

- streptomycin,neomycin, kanamycin, gentamycin, tobramycin

5. Groups of chloramphenicol

- chloramphenicol, tiamphenicol

6. Groups of tetracyclines

- chlortetracycline,oxytetracycline, doxycycline, minocycline

7. Groups of macrolides

- erythromycin,roxithromycin, spiramycin, azithromycin

8. Groups of polyenes

- amphotericin B, nystatin

9. Groups of Lincomycins

- lincomycin, clindamycin

10. Groups of polymixins

- Polymyxin B, Polymyxin E

II. *Based on the sources*

a. Antibiotic from microbes

- A.B. from fungi - Penicillin from P. notatum
- A.B. from bacteria
  - A.B. from eubacteria - polymyxin from bacillus polymyxa
  - A.B. from micromonosporaceae - gentamyicin from micromonospora purpurea

b. Antibiotics from algae - Usnat Acid

c. Antibiotics from higher plants - Garlisina from Allium sativum

d. Antibiotics from animals - Eritrina from hemoglobin of cow

III. *Based on mechanism of action*

A. Inhibition of cell wall synthesis leads to the death of the bacteria lysis (bactericidal effect)

- penicillin, cycloserine, vancomycin, bacitracin

B. Disruption of cell membrane function

- polymyxin (polymyxin B, polymyxin E), polyenes, nystatin

C. Inhibition of protein synthesis:

- This antibiotics inhibit one of the reactions in the process of transcription

1. Inhibition of translation process of microbes

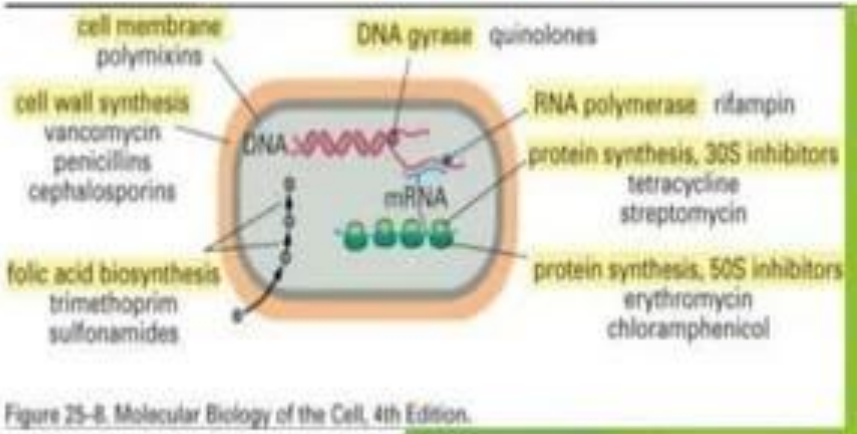


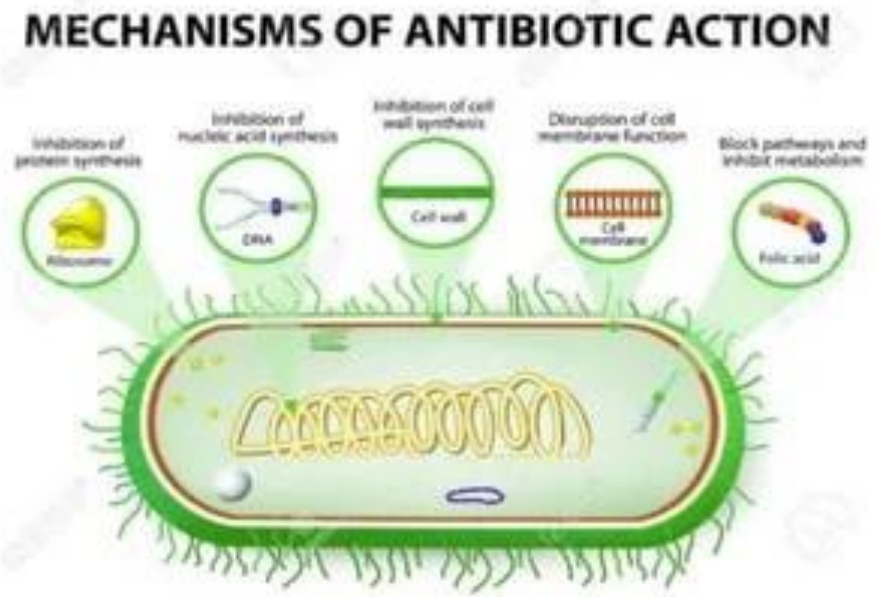
Figure 25-8. Molecular Biology of the Cell, 4th Edition.

- Inhibit ribosome on the 30 S subunit
  -streptomycin, tetracyclines, netilmycin, kanamycin
- Inhibit ribosome on the 50 S subunit
  -chloramphenicol, clindamycin, lincomycin
- Inhibits the transcription process of microbes
  -Rifampin, actinomycin

D. Inhibits specific metabolic reaction

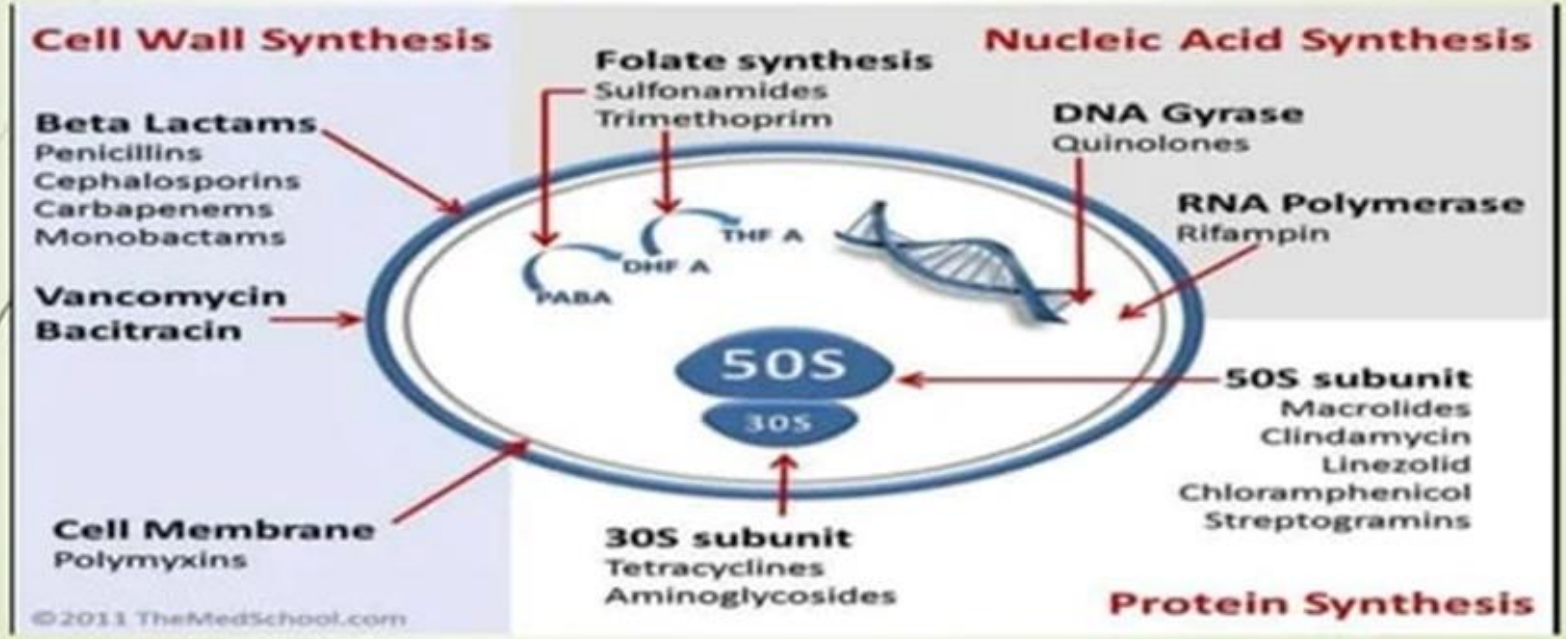
- Inhibits the enzymatic reactions

  -sulfonamides, INH, PAS,
  trimethoprim



Classification of AMAs

- *On the basis of mechanism of action*



IV. Based on spectrum of action

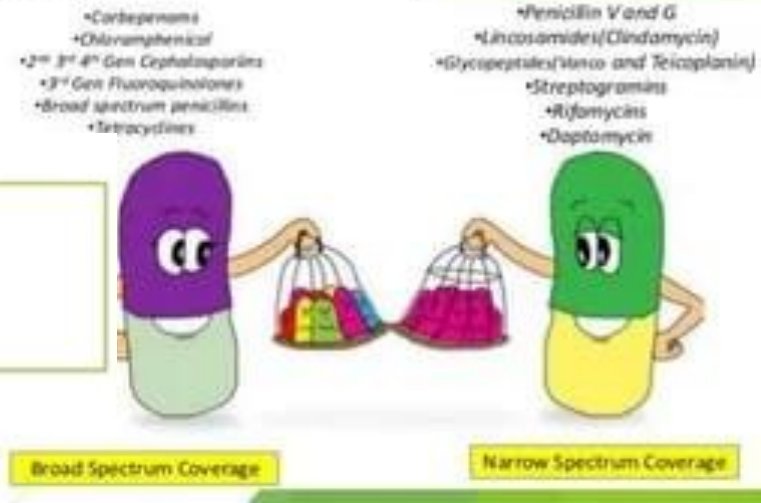
- **Broad spectrum:** Effective to Gram +, Gram - bacteria, mycoplasmas, chlamydiae, rickettsiae, sometimes protozoa

  -chloramphenicol, tetracyclines

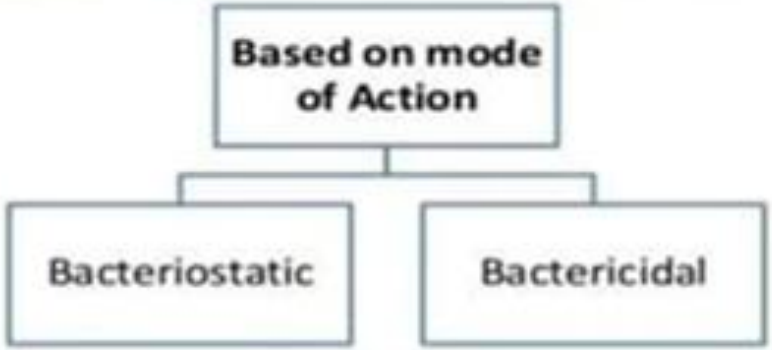
- **Narrow spectrum:** Effective to Gram +ve / Gram -ve bacteria only
  - penicillins, cephalosporins, erythromycins, polymyxins

Extended spectrum

- Active against gram+ve and significant number of gram-ve microorganims



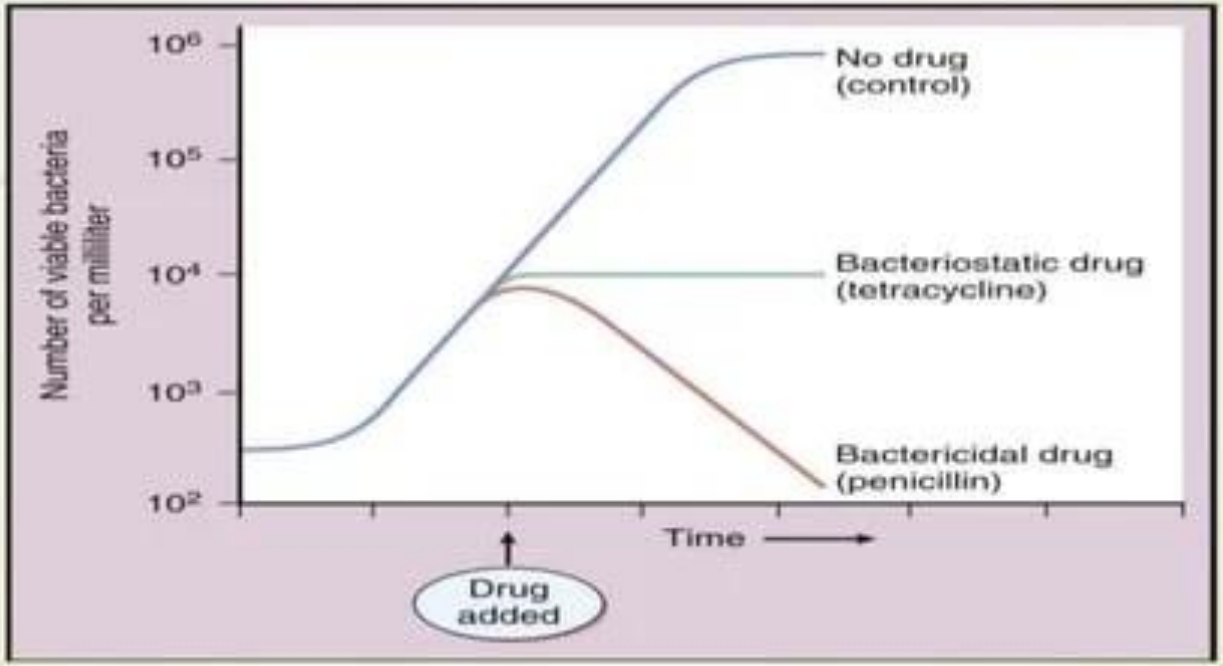
Classification of AMAs



Bacteriostatic: **Drugs arrest the growth and replication of bacteria at serum or urine levels, thus limiting the spread of infection until the immune system attacks and eliminates the pathogen.**

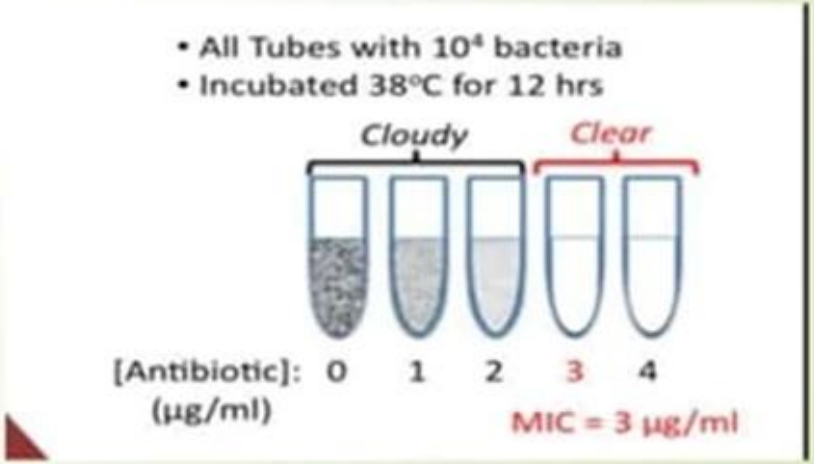
Bactericidal: **Drugs kill bacteria at drug serum levels. Because of their antimicrobial action, bactericidal agents are often the drugs of choice in seriously ill and immunocompromised patients.**

Bacteriostatic Vs Bactericidal



Minimum Inhibitory Concentration(**MIC**) and Minimum Bactericidal Concentration (**MBC**)

- **MIC**- Lowest antibiotic concentration that prevents the growth of microorganism after a 24 hr incubation period with a standard organism inoculation (10^4 to 10^5 cfu/ml)



Minimum Bactericidal Concentration **(MBC)**

- **MBC**- Lowest concentration of antibiotic that kills about 99.9% of organism

*

Principles of Antibiotic Dosing

A. Concentration-dependent killing

Certain antimicrobial agents, including **aminoglycosides** and ***daptomycin***, **show a significant increase in the rate of bacterial killing as the concentration of antibiotic increases from 4- to 64-fold the MIC of the drug for the infecting organism**

B. Time-dependent (concentration-independent) killing

β-lactams, glycopeptides, macrolides, clindamycin, and linezolid exhibit Time-dependent killing.

The clinical efficacy of these antimicrobials is predicted by **the percentage of time that blood concentrations of a drug remain above the MIC.**

Principles of Antibiotic Dosing- PAE

C. Post antibiotic effect (PAE)

is a persistent suppression of microbial growth that occurs after levels of antibiotic have fallen below the MIC.

Antimicrobial drugs exhibiting a long PAE (for example, **aminoglycosides** and **fluoroquinolones**) often require only one dose per day, particularly against gram negative bacteria.

combinations of antibiotics, such as β-lactams and aminoglycosides, show **synergism**; the combination is more effective than either of the drugs used separately.

A number of antibiotics act only when organisms are multiplying. Thus, co-administration of an **bacteriostasis** + **bactericidal** may result in the first drug interfering with the action of the second.

For example, bacteriostatic tetracycline drugs may interfere with the bactericidal effects of penicillins and cephalosporins.

combinations of antibiotics include

- **Reduces of super infections**
- **Decreases the emergence of resistant to monotherapy-as in Tuberculosis**

Antibiotic Combinations :

- The result may be addictive , potentiative or antagonistic
- **Addictive response :**one in which the antimicrobial effect of the combination is equal to the sum of the effects of the two drugs alone.
- **Potentiative interaction:** one in which the effect of the combination is GREATER than the sum of the effects of the individual agents.
- **Antagonistic response :** in certain cases the combination of two antibiotics may be less effective than one of the agents by itself .

Disadvantages of antibiotic combinations

- Increased risk of toxic and allergic reactions
- Possible antagonism of antimicrobial agents
- Increased risk of superinfection
- Selection of drug resistant bacteria
- Increased cost

Factors affecting the choice of an AMAs

- ***Age***

Chloramphenicol *in new born may cause* ***Grey Baby Syndrome***

Sulfonamides in *new born may cause* ***Kernicterus***

Tetracycline are C/I in children <6 years

- ***Pregnancy***

All antibiotics pose risk to the fetus when used in pregnancy except Pn, Cephalosporins and Macrolides

Factors affecting the choice of an AMAs

Impaired Host Defense

Bactericidal drugs are must in immunocompromised individual

Genetic Factors

Hemolysis in G-6PD deficiency

Chloroquine, Primaquine, Quinine, FQs etc

Factors affecting the choice of an AMAs

C/I In Renal failure	C/I in liver failure
Nitrofurantoin	Erythromycin estolate
Nalidixic acid	Tetracycline
Tc	Pyrazinamide
	Pefloxacin*

Problems with the use of AMAs

- ***Local Irritation***

- Gastric irritation on oral administration- Ampicillin
- Pain on i.m injection- Streptomycin, Tc

- ***Hypersensitivity/ Allergic Reaction***

Pn, Sulfonamides, Chloramphenicol

- ***Direct Systemic Toxicity***

Aminoglycoside causes Nephrotoxicity

Streptomycin causes Ototoxicity

Chloramphenicol causes Bone marrow depression

Problems with the use of AMAs

- ***Opportunistic Infection***
  - Pseudomembranous Colitis

- ***Nutritional Deficiency***
  - Vitamin B complex and Vitamin K deficiency

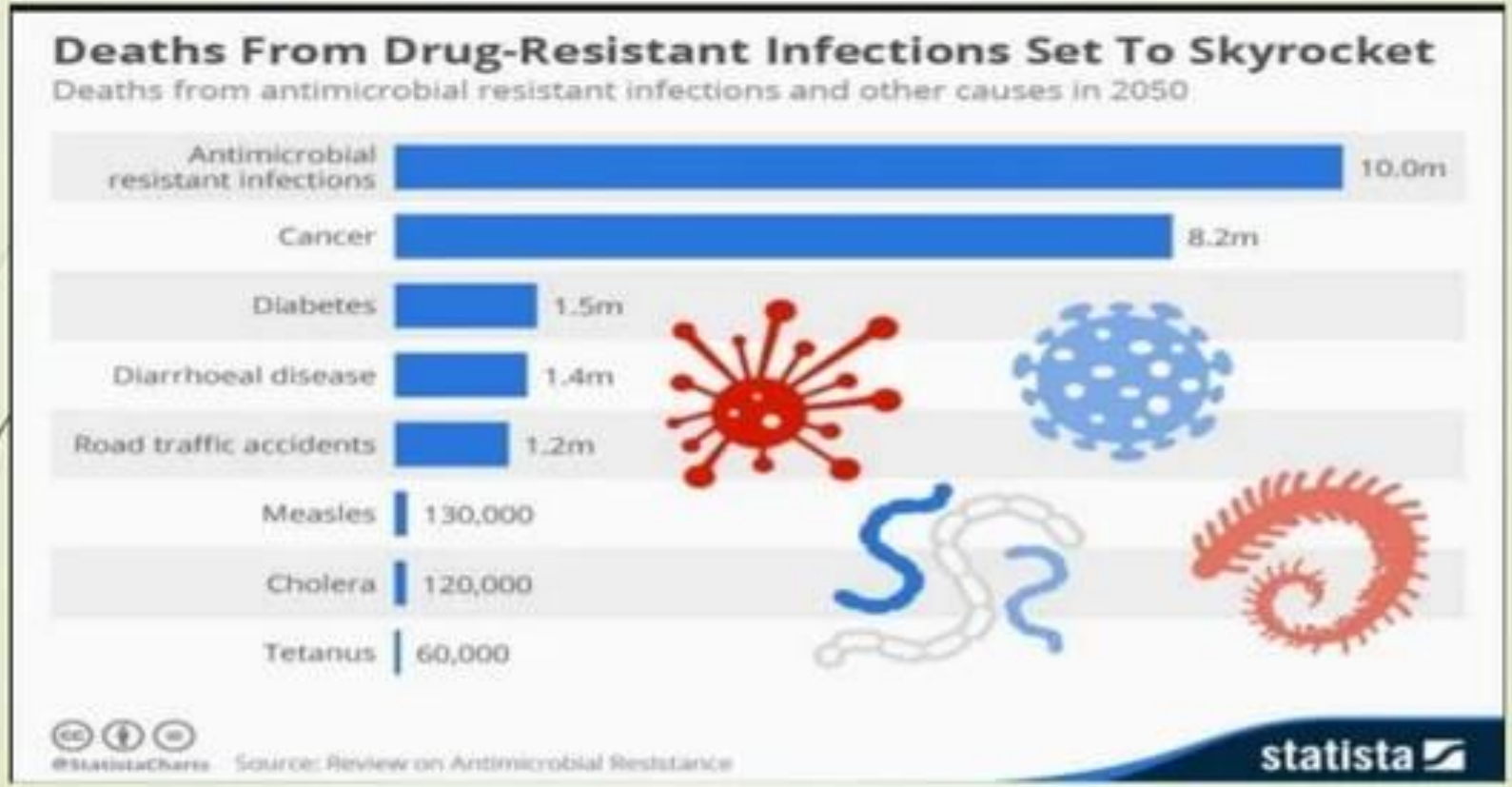
- ***Bacterial Resistance***

Antimicrobial Resistance

- It can be defined as insensitiveness of micro organism to a particular anti microbial drug

- Bacterial resistance is of great concern because if resistant strains are developed then a very useful antibiotic becomes useless

Antimicrobial Resistance

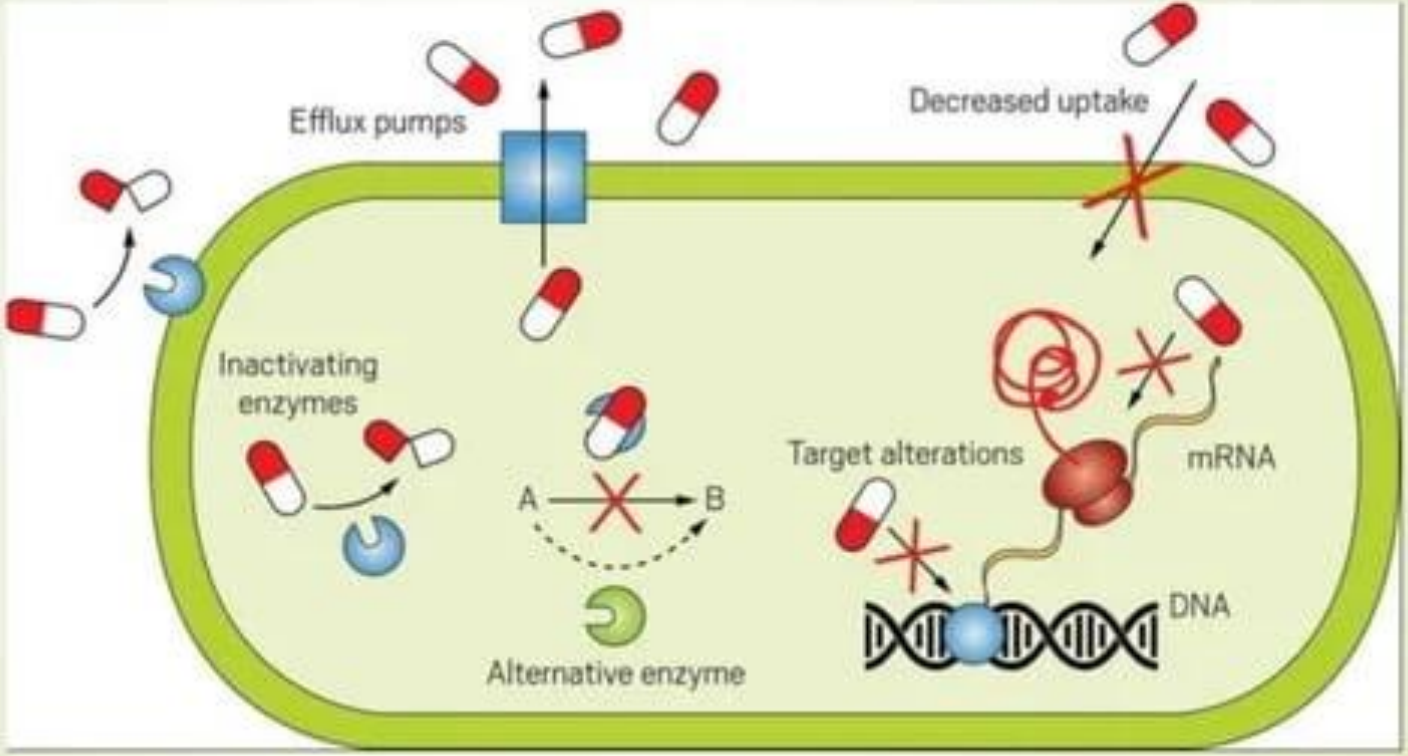


Mechanism of AMR

- Antimicrobial resistance can develop at any one or more of steps in the process by which a drug reaches and combines with its target. Thus resistance may develop due to

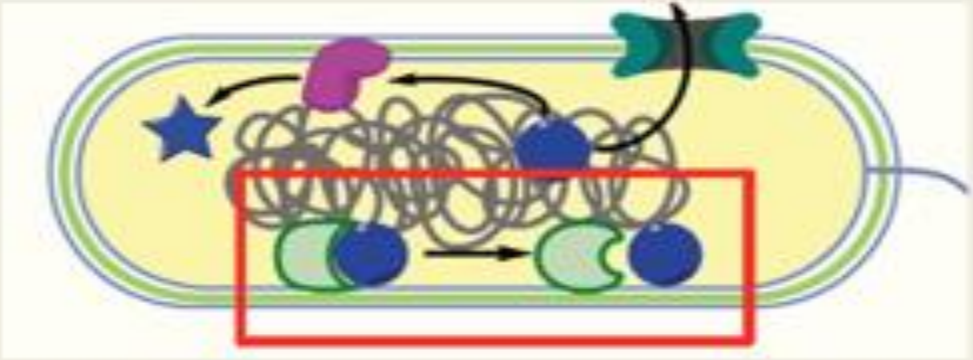
Mechanism of Resistance	Drugs
Decrease permeability	Aminoglycosides, Tetracyclines
Efflux pumps	Tetracyclines, Erythromycin, FQs
Inactivating enzymes	Aminoglycosides, Beta lactams Chloramphenicol
Alternative metabolic pathway	Sulfonamide
Decrease affinity for target	MRSA, Vancomycin

Mechanism of AMR



1. Modification of target sites:

Alteration of an antibiotic's target site through mutation can confer resistance to one or more related antibiotics. For example, *S. pneumoniae* resistance to β-lactam antibiotics involves alterations in one or more of the major bacterial penicillin-binding proteins, resulting in decreased binding of the antibiotic to its target.



2. Decreased accumulation:

Decreased uptake or increased efflux of an antibiotic can confer resistance because the drug is unable to attain access to the site of its action in sufficient concentrations to injure or kill the organism.

For example, gram-negative organisms can limit the penetration of certain agents, including β-lactam antibiotics, as a result of an alteration in the number and structure of porins (channels) in the outer membrane.

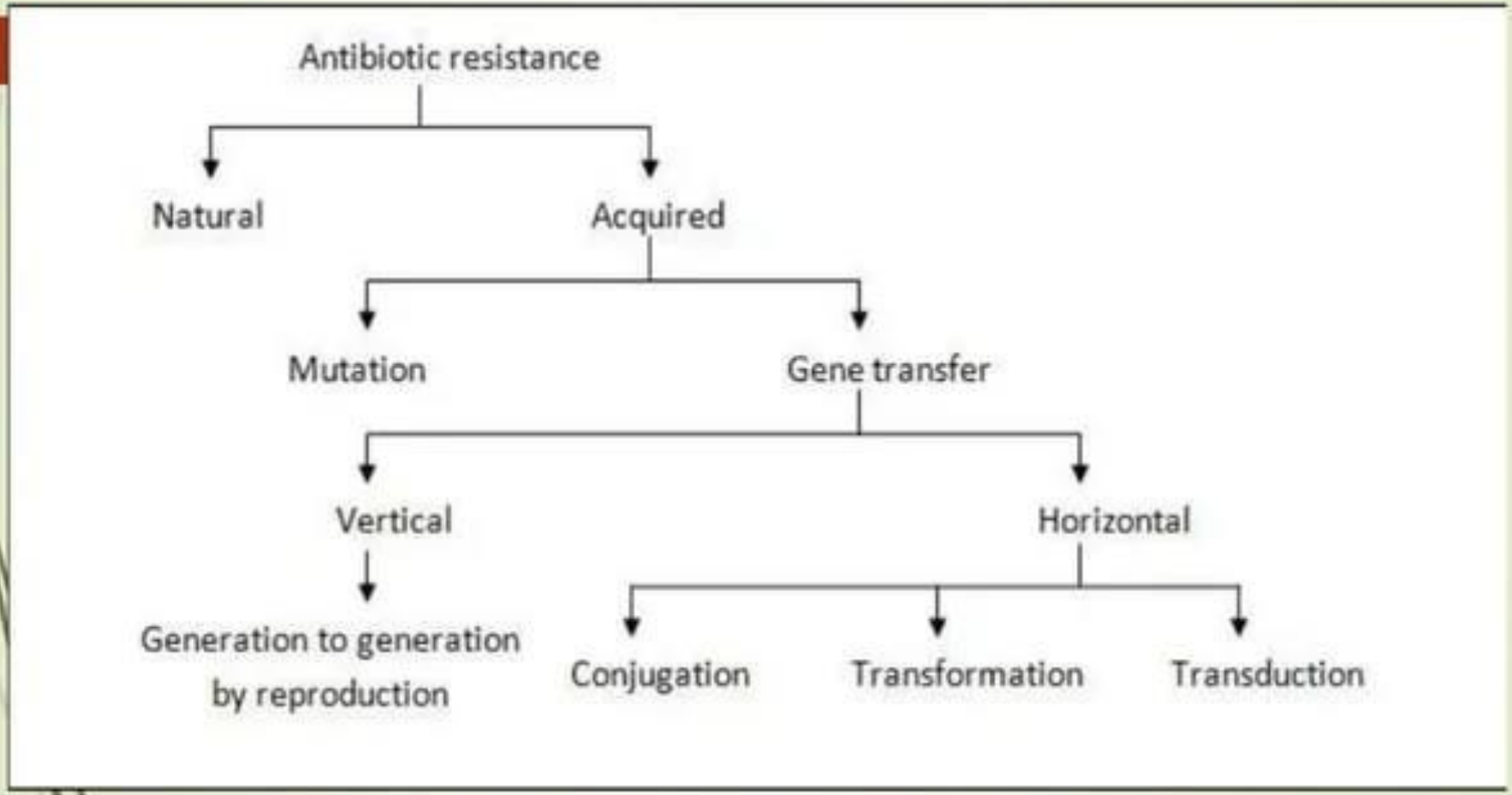
Also, the presence of an efflux pump can limit levels of a drug in an organism, as seen with tetracyclines.

3. Enzymatic inactivation:

The ability to **destroy or inactivate** the antimicrobial agent can also confer resistance on microorganisms.

Examples of antibiotic-inactivating enzymes include

- **β-lactamases (“penicillinases”) that hydrolytically inactivate the β-lactam ring of penicillins, cephalosporins, and related drugs**
- **acetyltransferases that transfer an acetyl group to the antibiotic, inactivating *chloramphenicol* or aminoglycosides**
- **esterases that hydrolyze the lactone ring of macrolides**.


Antibiotic resistance
Natural
Acquired
Mutation
Gene transfer
Vertical
Horizontal
Generation to generation by reproduction
Conjugation
Transformation
Transduction

Misuse of Antimicrobial Agents

- If use of AMAs is without justification and not following the principles of chemotherapy then all such use is considered as misuse of drugs

Examples of Misuse of Antimicrobial Agents

- Use of AMAs for non bacteriological infection
- Pyrexia of unknown origin
- Inadequate dose and duration of treatment
- Relying only on chemotherapy

Failure of Antimicrobial Therapy

- ***Clinician Factor***

- *R- Right Diagnosis*
- *R- Right Drug*
- *R- Right Dose*
- *R- Right Dosage*
- *R- Right duration*

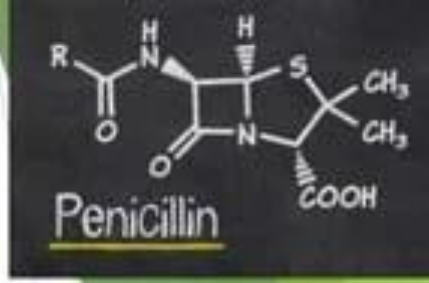
Failure of Antimicrobial Therapy

- ***Drug Factor***
  - *Drug Resistance*
  - *Use of bacteriostatic drug in immunocompromised states*
  - *Drug interactions with food*
- ***Patient Factor***
  - *Poor Compliance*
  - *Uncontrolled Diabetes, Immunocompromised states*

Ideal antibiotics :

- Effective even in the presence of body fluids exudate, protein or enzymes.
- Ability to reach the infected tissue, enough drug concentration during the span of a dosing interval in blood / infected area.
- Do not cause resistance
- Have a minimal toxic effects for the patient
- Safe for pregnancy and pediatric patients
- cost effective

Penicillin



- **Mechanism of action:** the drugs weaken the cell wall, causing the bacterium to take up excessive amounts of water and then rupture
- **Penicillinases (beta- lactamases)**
  enzymes that cleave the beta-lactam ring and thereby render penicillin and other beta-lactam antibiotics
- **Classification :**
- Narrow-spectrum (penicillinase sensitive)
- Narrow-spectrum that are penicillinase resistant (antistaphylococcal)
- Broad spectrum penicillin's (aminopenicillins)
- Extended spectrum penicillin's (antipseudomonal)

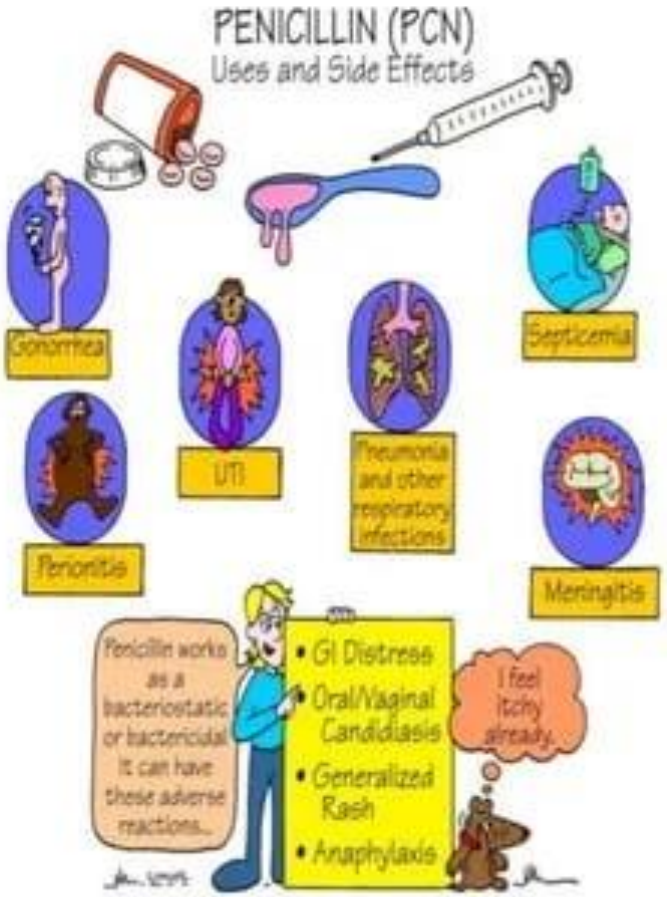
PENICILLIN G

- **ANTIMICROBIAL SPECTRUM :** active against most gram +ve bacteria, gram –ve cocci (Neisseria, meningitis) and spirochetes .
  With few exceptions gram –ve bacteria are resistance .
- **Therapeutic uses:**

- Pneumonia and meningitis caused by streptococcus pneumonia
- Pharyngitis caused by streptococcus pyogens
- Infectious endocarditis(streptococcus viridans)
- Gangrene , tetanus
- Syphilis (treponema pallidum)

- **Side effects and toxicities :**

- Pain at the site of infection , neurotoxicity with too high plasma levels.
  Inadvertent intra-arterial injection can produce severe reactions (gangrene,necrosis) and must be avoided .



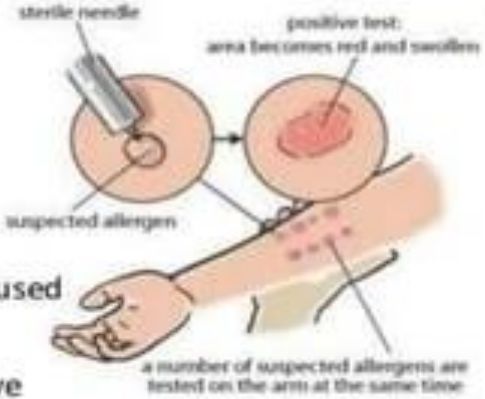
PENICILLIN ALLERGY

- Penicillin are the most common cause of drug allergy (1-10% of the patients will experience an allergic response) there is no direct relationship between size of dose and intensity of allergic response.
- Cross sensitivity :5-10% of patients allergic to penicillin's are also allergic to cephalosporin's
- **Types of allergic reactions:**
- Immediate (occurring 2-30 min after administration)
- Accelerated (occur within 1-72 hours)
- Late reactions (days or even weeks)
- Anaphylaxis (laryngeal edema, bronchoconstriction, severe hypotension) in 0.2% of patients ,treatment – epinephrine + respiratory support .

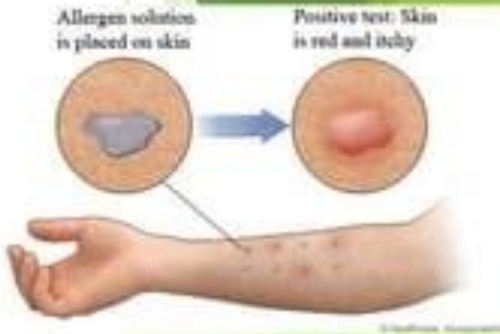
Skin tests for penicillin allergy

Test procedures

- **Skin prick test (SPT)**
  - Should be performed first
  - Both major and minor determinant are used
  - Read after 15-20 minutes
  - Positive: wheal size ≥ 3 mm than negative control



- **Intradermal skin test (IDT)**
  - Performed only if skin prick test is negative
  - May induce systemic reactions
  - More sensitive than skin prick test
  - Positive: wheal size ≥ 4 mm than control



Penicillin skin testing , Solensky, Franklin Adkinson Jr, Feb 2014

Management of patients with history of penicillin allergy

- Ask patients for previous history of allergy to penicillin
- If the patient refers to a positive history of allergy AVOID PENICILLIN entirely
- If the allergy is mild a CEPHALOSPORINE is appropriate as alternative.
- If the allergy is severe avoid CEPHALOSPHORINS
- For many infections VANCOMYCIN AND ERYTHROMYCIN are effective and safe .

Penicillinase-resistant Penicillin's

- Antistaphylococcol

Resistance to beta lactamases .

Acid labile : Methicillin, nafcillin, cloxacillin, dicloxacillin

Acid resistant: flucloxacillin.

Broad spectrum penicillin's

- Aminopenicillins
- Ampicillin :(SPECTRUM: bordetella pertussis , E coli , salmonella , shigella)

  Adverse effects – rashes (4-10% with ampicillin)
  diarrhoea

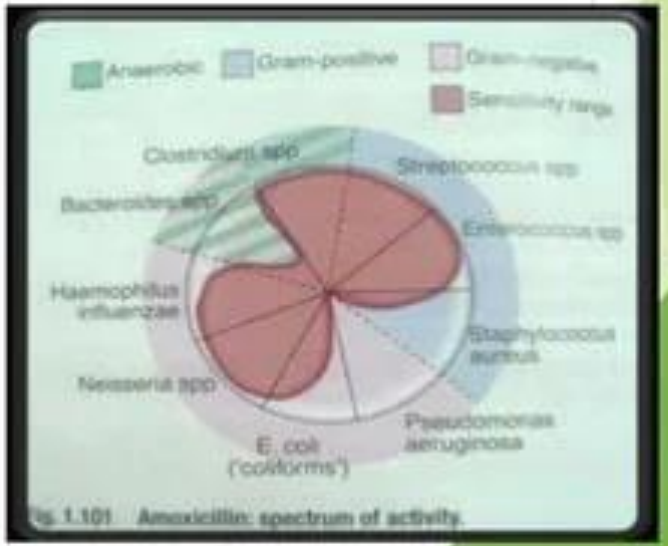
EXTENDED SPECTRUM PENICILLINS

- Used to treat infections with Pseudomonas Aeruginosa (ie Ticarcillin)
- Penicillins combined with beta lactamase inhibitor
  ie Amoxicillin + clavulanic acid = Augmentin

a.Carboxypenicillins : Carbenicillin, ticarcillin,

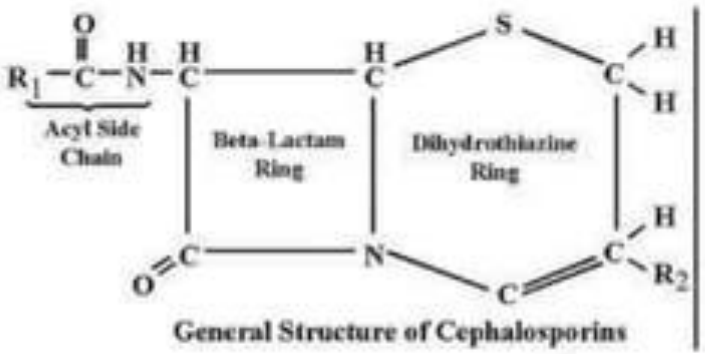
b. Aminopenicillin : Amipicillin, amoxicilllin.

c. Ureidopenicillin : Mezlocillin, piperacillin.



CEPHALOSPORINS

- Broad spectrum antibiotics with low toxicity
- mechanism of action : disruption of cell wall synthesis and consequent lysis of cell .



General Structure of Cephalosporins

CEPHALOSPORINS

First generation- More active	Second generation-	Third generation	Forth generation
More active against gram positive organism	more selective against gram positive and gram negative organisms	Highly active against gram negative organisms	similar antibacterial activity as that Of third generation but highly resistant to beta lactamases
Parenteral- Cephalothin Cefazolin Cephaloridine Oral- Cephalexin Cephadine Cefadroxil	Parenteral Cefuroxime Cefoxitin Oral Cefaclor Cefuroxime acetyl	Parenteral- Cefotaxim Ceftizoxime Ceftriaxone Cefoperazone Oral cefexim	Parenteral- Cefepime Cefiperome

Adverse effects

- **Allergic reactions** : rash that develops after days of treatment
  severe immediate reactions are rare.
- **Bleeding** : five cephalosporins cause bleeding tendencies
  (cefamandole , cefmentazole, cefoperazone , cefotetan and moxalactam)
  2 mechanism involved :
  -reduction in prothrombin levels and
  - impairment of platelet aggregation .
  (only with moxalactam)
- **Thrombophlebitis** : it may develop during IV infusion (>change in infusion site)
- **Pain at site of IV infusion**

IMIPENEM

- Relatively new beta-lactam antibiotic with very broad spectrum.
- Antimicrobial spectrum : highly active against gram +ve and gram-ve cocci .
- It is also the most effective beta-lactam antibiotic against anaerobic bacteria.

- **Pharmacokinetics**

  it is not absorbed from the GI tract .

  IV or IM administration .

- **Adverse effects**

  (generally well tolerated)

- GI effects (nausea, vomiting , diarrhoea)
- Hypersensitivity reactions (rashes ,pruritus)
- Superinfections with bacteria or fungi develop in about 4%of patients .
- Rarely seizures have occurred

Common Antibiotic Regimens Used to Treat Periodontal Diseases

Single Agent

Amoxicillin	500 mg Three times daily for 8 days
Azithromycin	500 mg Once daily for 3–7 days
Ciprofloxacin	500 mg Twice daily for 8 days
Clindamycin	300 mg Three times daily 10 days
Doxycycline	100–200 mg Once daily for 21 days
Metronidazole	500 mg Three times daily for 8 days

Combination Therapy*

Amoxicillin-metronidazole (250 mg amoxicillin-375 mg metronidazole, 3 times daily for 8 days) is the most common antibiotic combination in periodontics.

Ciprofloxacin-metronidazole (500 mg of each, twice daily for 8 days)

Thank You!!!

CEPHALOSPORINS

Cephalosporins: β-lactam antibiotics

1. Related structurally and functionally to the penicillins.
2. Most cephalosporins are produced semisynthetically by the chemical attachment of side chains to 7-aminocephalosporanic acid.
3. Cephalosporins have the same mode of action as penicillins, and they are affected by the same resistance mechanisms.

Generation of Cephalosporins

Cephalosporins have been classified as first, second, third, fourth, and advanced generation,

1. **First generation: act as *penicillin G* substitutes. They are resistant to the staphylococcal penicillinase and also have activity against *Proteus mirabilis, E. coli, and K. pneumoniae.***

2. Second generation: greater activity against gr-ve organisms: *H. influenzae, Enterobacter aerogenes*, and some Neisseria species,

- whereas activity against gram-positive organisms is weaker. Antimicrobial coverage of the cephamycins (*cefotetan* **and *cefoxitin)***

3. Third generation: third-generation cephalosporins have enhanced activity against gram-negative bacilli

Ceftriaxone and ***cefotaxime*** have become agents of choice in the treatment of meningitis.

Ceftazidime has activity against *P. aeruginosa*

Third-generation cephalosporins must be used with caution, as they are associated with significant “collateral damage,” essentially meaning the induction and spread of antimicrobial resistance.

4. Fourth generation: *Cefepime*, must be administered parenterally.

***Cefepime* has a wide antibacterial spectrum, with activity against streptococci and staphylococci (but only those that are *methicillin* susceptible).**

***Cefepime* is also effective against aerobic gram-negative organisms, such as Enterobacter species, *E. coli*, *K. pneumoniae*, *P. mirabilis*, and *P. aeruginosa*.**

5. Advanced generation: *Ceftaroline*,

- broad spectrum, administered IV. activity against MRSA and is indicated for the treatment of complicated skin and skin structure infections and community-acquired pneumonia.
- The unique structure allows *ceftaroline* to bind to PBP2a found with MRSA and PBP2x found with *Streptococcus pneumoniae*.
- In addition to its broad gram-positive activity, it also has similar gram negative activity to the third-generation cephalosporin *ceftriaxone*.

Pharmacokinetics

1. Administration: Many of the cephalosporins must be administered IV or IM because of their poor oral absorption.

Exceptions *Cephalexin, Cefdinir, Cefixime.*

2. Distribution:

All cephalosporins distribute very well into body fluids. However, adequate therapeutic levels in the CSF, regardless of inflammation, a few cephalosporins. For example, *ceftriaxone* and *cefotaxime* are effective in the treatment of neonatal and childhood meningitis caused by *H. influenzae*.

Cefazolin **is commonly used as a single prophylaxis dose prior to surgery because of its 1.8-hour half-life and its activity against penicillinase-producing *S. aureus*.**

Cefazolin **is effective for most surgical procedures, including orthopedic surgery because of its ability to penetrate bone.**

All cephalosporins cross the placenta.

3. Elimination:

Cephalosporins are eliminated through tubular secretion and/or glomerular filtration. Therefore, doses must be adjusted in cases of renal dysfunction to guard against accumulation and toxicity.

One exception is *ceftriaxone*, which is excreted through the bile into the feces and, therefore, is frequently employed in patients with renal insufficiency.

Resistance

Mechanisms of bacterial resistance to the cephalosporins are essentially the same for the penicillins.

cephalosporins are not susceptible to hydrolysis by the staphylococcal penicillinase,

cephalosporins may be susceptible to ESBLs. Organisms such as *E. coli and K. pneumoniae*

Extended Spectrum Beta-Lactamases

Adverse effects: Like the penicillins, the cephalosporins are generally well tolerated. allergic reactions, anaphylactic response, Stevens-Johnson syndrome, or toxic epidermal necrolysis to penicillins should not receive cephalosporins.

Cephalosporins should be avoided or used with caution in individuals with penicillin allergy.

Current data suggest that the cross-reactivity between penicillin and cephalosporins is around 3% to 5% and is determined by the similarity in the side chain, not the β-lactam structure.

The highest rate of allergic cross-sensitivity is between penicillin and first-generation cephalosporins.

OTHER β-LACTAM ANTIBIOTICS

A. Carbapenems

Carbapenems are synthetic β-lactam antibiotics that differ in structure from the penicillins in that the sulfur atom of the thiazolidine ring. has been replaced by a carbon atom.

Imipenem , meropenem, doripenem, and *ertapenem* are the drugs of this group currently available.

Imipenem is compounded with *cilastatin* to protect it from metabolism by renal dehydropeptidase.

Antibacterial spectrum:

Imipenem **resists hydrolysis by most β-lactamases. This drug plays a role in empiric therapy because it is active against β-lactamase–producing gram-positive and gram-negative organisms, anaerobes, and *P. aeruginosa***

Pharmacokinetics:

Imipenem, cilastatin and *meropenem* are administered IV and penetrate well into body tissues and fluids, including the CSF when the meninges are inflamed. *Meropenem* reach therapeutic levels in bacterial meningitis even without inflammation.

Excreted by glomerular filtration.

Imipenem undergoes cleavage by a dehydropeptidase found in the brush border of the proximal renal tubule. This enzyme forms an inactive metabolite that is potentially nephrotoxic.

Ertapenem can be administered via IV or IM injection once daily. Doses of these agents must be adjusted in patients with renal insufficiency

B. Monobactams:

The monobactams, which also disrupt bacterial cell wall synthesis, are unique because the β-lactam ring is not fused to another ring. ***Aztreonam***, which is the only commercially available monobactam, has antimicrobial activity directed primarily against gram-negative pathogens, including the Enterobacteriaceae and P. aeruginosa. It lacks activity against gram positive organisms and anaerobes. *Aztreonam* is resistant to the action of most β-lactamases, with the exception of the ESBLs. It is administered either IV or IM and can accumulate in patients with renal failure.

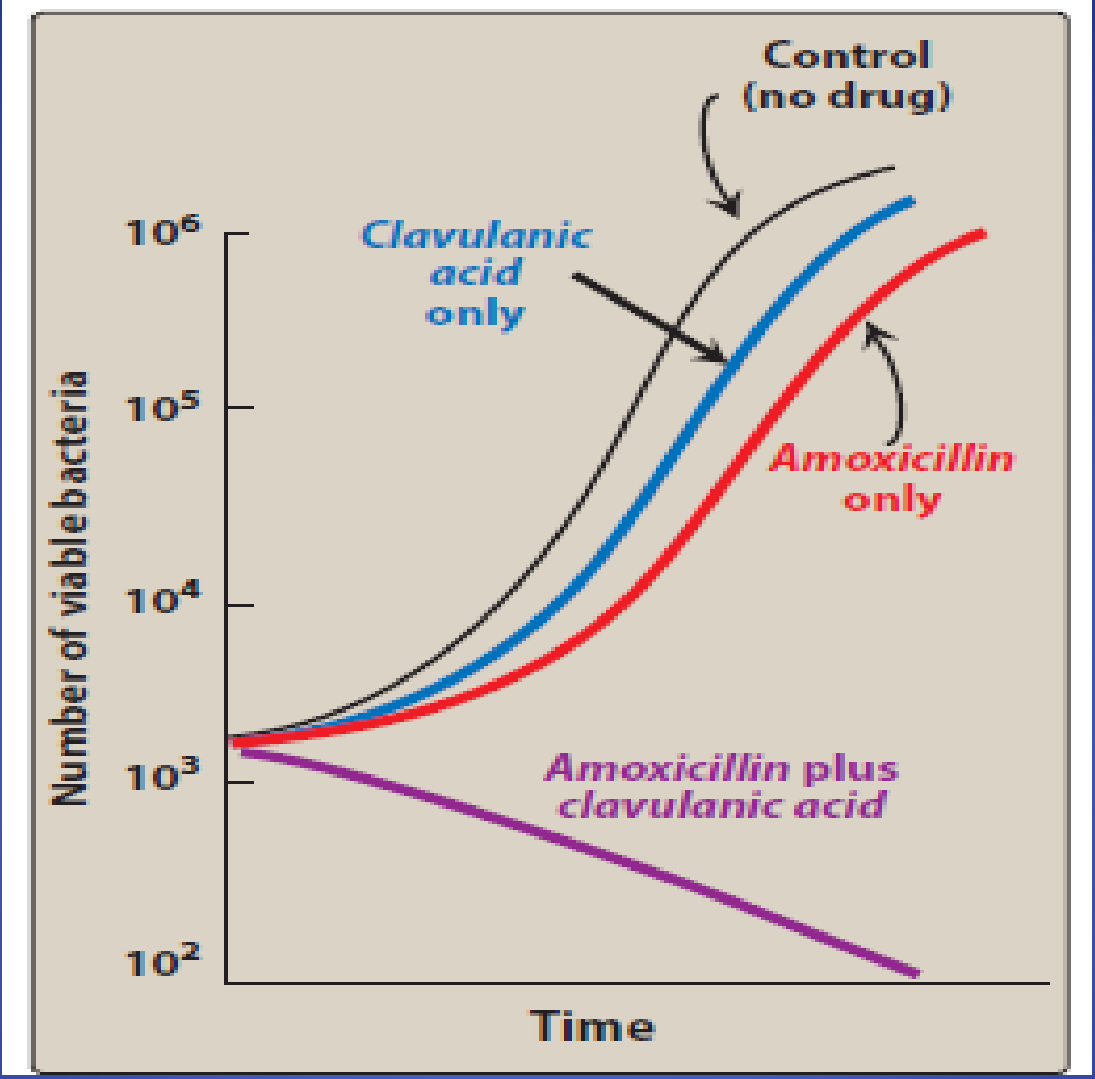
β-LACTAMASE INHIBITORS

Hydrolysis of the β-lactam ring, either by enzymatic cleavage with a β-lactamase or by acid, destroys the antimicrobial activity of a β-lactam antibiotic.

β-Lactamase inhibitors, such as *clavulanic acid, sulbactam*, and *tazobactam*, contain a β-lactam ring , The β-lactamase inhibitors are therefore formulated in combination with β-lactamase–sensitive antibiotics.

For example, the effect of *clavulanic acid* and *amoxicillin* on the growth of β-lactamase–producing E. coli.

***Clavulanic acid* alone is nearly devoid of any antibacterial Activity.**



The in vitro growth of Escherichia coli in the presence of *amoxicillin,* with and without *clavulanic acid*

VANCOMYCIN

Vancomycin is a tricyclic glycopeptide, increasingly important in the treatment of life-threatening MRSA and methicillin-resistant Staphylococcus epidermidis (MRSE) infections, as well as enterococcal infections

by restricting the use of *vancomycin* to the treatment of serious infections caused by β-lactam resistant, gram-positive microorganisms or gram-positive infections in patients who have a serious allergy to the β-lactams.

Serum drug concentrations are commonly measured to monitor and adjust dosages for safety and efficacy. *Vancomycin* is not absorbed after oral administration, so the use of the oral formulation is limited to the treatment of severe antibioticassociated *C. difficile* colitis.

DAPTOMYCIN

Daptomycin **is a bactericidal concentration-dependent cyclic lipopeptide antibiotic that is an alternative to other agents, such as** ***linezolid*** **and** ***quinupristin / dalfopristin,*** **for treating infections caused by resistant gram-positive organisms, including MRSA and** ***vancomycin*** **resistant enterococci (VRE).**

Daptomycin **use for treatment of complicated skin and skin structure infections and bacteremia caused by** ***S. aureus*****, including those with right-sided infective endocarditis. Efficacy of treatment with** ***daptomycin*** **in left-sided endocarditis has not been demonstrated.** ***daptomycin*** **is inactivated by pulmonary surfactants; thus, it should** ***never*** **be used in the treatment of pneumonia.**

TELAVANCIN

Telavancin **is a bactericidal concentration-dependent semisynthetic lipoglycopeptide antibiotic that is a synthetic derivative of** ***vancomycin.***

Like ***vancomycin, telavancin*** **inhibits bacterial cell wall synthesis. Moreover,** ***telavancin*** **exhibits an additional mechanism of action similar to that of** ***daptomycin,*** **which involves disruption of the bacterial cell membrane due to the presence of a lipophilic side chain moiety.**

It is an alternative to ***vancomycin, daptomycin,*** **and** ***linezolid,*** **in treating complicated skin and skin structure infections caused by**

resistant gram- positive organisms (including MRSA). It is also an agent of last choice for hospital-acquired and ventilator-associated bacterial pneumonia when alternative treatments are not suitable. *telavancin* in clinical practice is limited by significant adverse effects

FOSFOMYCIN

bactericidal synthetic derivative of phosphonic acid. It blocks cell wall synthesis by inhibiting the enzyme UDP-*N*-acetylglucosamine enolpyruvyl transferase, which catalyzes the first step in peptidoglycan synthesis. It is indicated for urinary tract infections caused by *E. coli or E. faecalis*. Due to its unique structure and mechanism of action, cross resistance with other antimicrobial agents is unlikely. *Fosfomycin* is rapidly absorbed after oral administration and distributes well to the kidneys, bladder, and prostate. The drug is excreted in its active form in the urine and feces.

POLYMYXINS

The polymyxins are cation polypeptides that bind to phospholipids on the bacterial cell membrane of gram-negative bacteria. They have a detergent-like effect that disrupts cell membrane integrity, leading to leakage of cellular components and ultimately cell death.

Polymyxins are concentration-dependent bactericidal agents with activity against most clinically important gram-negative bacteria, including *P. aeruginosa, E. coli, K. pneumoniae, Acinetobacter* species, and Enterobacter species.

However, alterations in the cell membrane lipid polysaccharides allow many species of Proteus and Serratia to be intrinsically resistant.

Only two forms of polymyxin are in clinical use today, *polymyxin B* and *colistin* (*polymyxin E*).

***Polymyxin B* is available in parenteral, ophthalmic, otic, and topical preparations.**

The use of these drugs has been limited for a long time, due to the increased risk of nephrotoxicity and neurotoxicity

Pharmacology

Lec 7+8
Dr Maha Mohsin Khalaf

College of Dentistry
University of Baghdad

Respiratory System

Asthma, chronic obstructive pulmonary disease (COPD), and allergic rhinitis are commonly encountered respiratory disorders. Each of these conditions may be associated with a troublesome cough, which may be the only presenting complaint. Asthma is a chronic disease characterized by hyperresponsive airways and episodes of acute bronchoconstriction causing shortness of breath, Allergic rhinitis characterized by itchy, watery eyes, runny nose, and a nonproductive cough that can significantly decrease quality of life. Whereas asthma is characterised by reversible airways obstruction and bronchial hyperreactivity, COPD is characterised by incompletely reversible airways obstruction and mucus hypersecretion; it is predominantly a disease of the smaller airways. Nevertheless, distinguishing the two can be difficult in some patients. Drugs used to treat respiratory conditions can be delivered topically to the nasal mucosa, inhaled into the lungs, or given orally or parenterally for systemic absorption. Local delivery methods, such as nasal sprays or inhalers, are preferred to target affected tissues while minimizing systemic side effects.

ASTHMA

The bronchi become hyperreactive (Figure 1) as a result of a persistent inflammatory process in response to a number of stimuli that include biological agents, e.g. allergens, viruses, and environmental chemicals such as ozone and glutaraldehyde. Inflammatory mediators are liberated from mast cells, eosinophils, neutrophils, monocytes and macrophages. Some mediators such as histamine are preformed and their release causes an immediate bronchial reaction. Others are formed after activation of cells and produce more sustained bronchoconstriction;

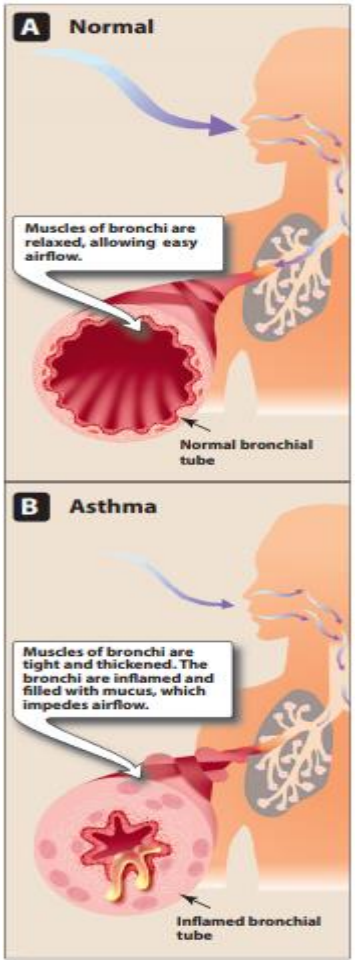


Figure 1: difference between normal and asthmatic airways

Preferred drugs used to treat asthma:

β2 -Adrenergic agonists

Inhaled β2 -adrenergic agonists directly relax airway smooth muscle. They are used for the quick relief of asthma symptoms, as well as adjunctive therapy for long-term control of the disease.

1. **Quick relief: Short-acting β2 agonists** (SABAs) have a rapid onset of action (5 to 30 minutes) and provide relief for 4 to 6 hours. They are used for symptomatic treatment of bronchospasm, providing quick relief of acute bronchoconstriction. All patients with asthma should be prescribed a SABA inhaler. β2 agonists have no anti-inflammatory effects, and they should never be used as the sole therapeutic agents for patients with persistent asthma. However, monotherapy with SABAs may be appropriate for patients with intermittent asthma or exercise-induced bronchospasm. Direct acting β2 -selective agonists

include **albuterol** and **levalbuterol.** These agents provide significant bronchodilation with little of the undesired effect of α or β1 stimulation. **Adverse effects**, such as tachycardia, hyperglycemia, hypokalemia, and hypomagnesemia, are minimized with inhaled delivery versus systemic administration. These agents can cause β2 -mediated skeletal muscle tremors.

2. **Long-term control**: **Salmeterol** and **formoterol** are long-acting β2 agonists (LABAs) and chemical analogs of albuterol. Salmeterol and formoterol have a long duration of action, providing bronchodilation for at least 12 hours. Neither salmeterol nor formoterol should be used for quick relief of an acute asthma attack. Use of LABA monotherapy is contraindicated, and LABAs should be used only in combination with an asthma controller medication. Inhaled corticosteroids remain the long-term controllers of choice in asthma, and LABAs are considered to be useful adjunctive therapy for attaining asthma control. Some LABAs are available as a combination product with an ICS. **Adverse effects** of LABAs are similar to quick-relief β2 agonists.

Corticosteroids

ICS are the drugs of choice for long-term control in patients with any degree of persistent asthma. Corticosteroids inhibit the release of arachidonic acid through phospholipase A2 inhibition, thereby producing direct anti-inflammatory properties in the airways. No other medications are as effective as ICS in the long-term control of asthma in children and adults. To be effective in controlling inflammation, glucocorticoids must be used regularly. Severe persistent asthma may require the addition of a short course of oral glucocorticoid treatment.

1. Actions on lung: ICS do not directly affect the airway smooth muscle. Instead, ICS therapy directly targets underlying airway inflammation by decreasing the inflammatory cascade (eosinophils, macrophages, and T lymphocytes), reversing mucosal edema, decreasing the permeability of capillaries, and inhibiting the release of leukotrienes (Figure 2). After several months of regular use, ICS reduce the hyperresponsiveness of the airway smooth muscle to a variety of bronchoconstrictor stimuli, such as allergens, irritants, cold air, and exercise.

2. Routes of administration a. Inhalation: The development of ICS has markedly reduced the need for systemic corticosteroid treatment to achieve asthma control. However, as with all inhaled medications, appropriate inhalation technique is critical to the success of therapy. **b. Oral/systemic**: Patients with a severe exacerbation of asthma (status asthmaticus) may require intravenous methylprednisolone or oral prednisone to reduce airway inflammation. In most cases, suppression of the hypothalamic–pituitary–adrenal cortex axis will not occur

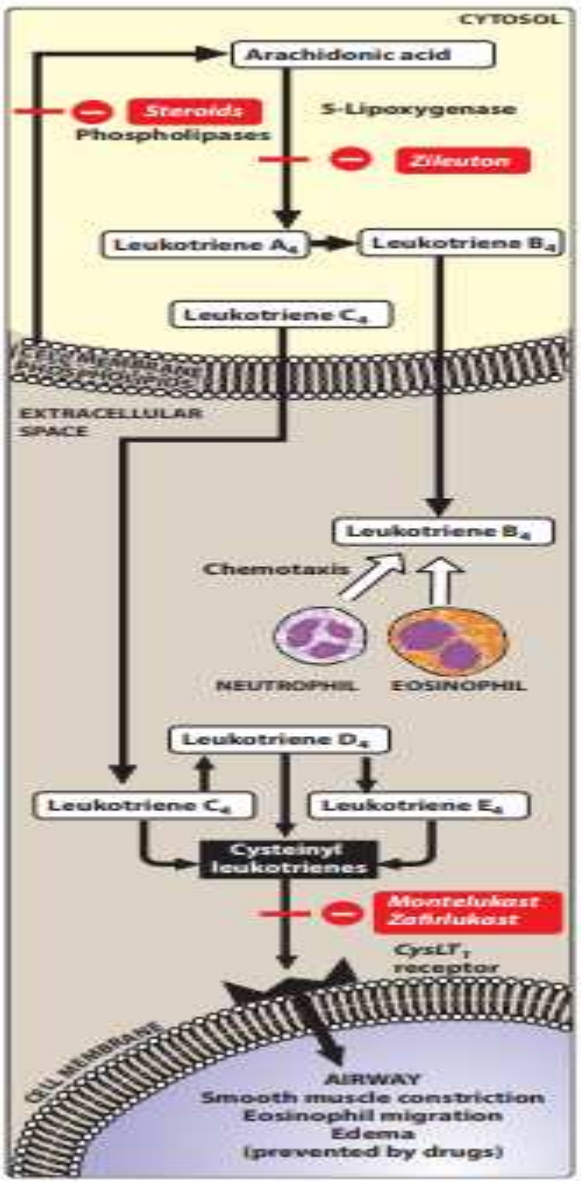
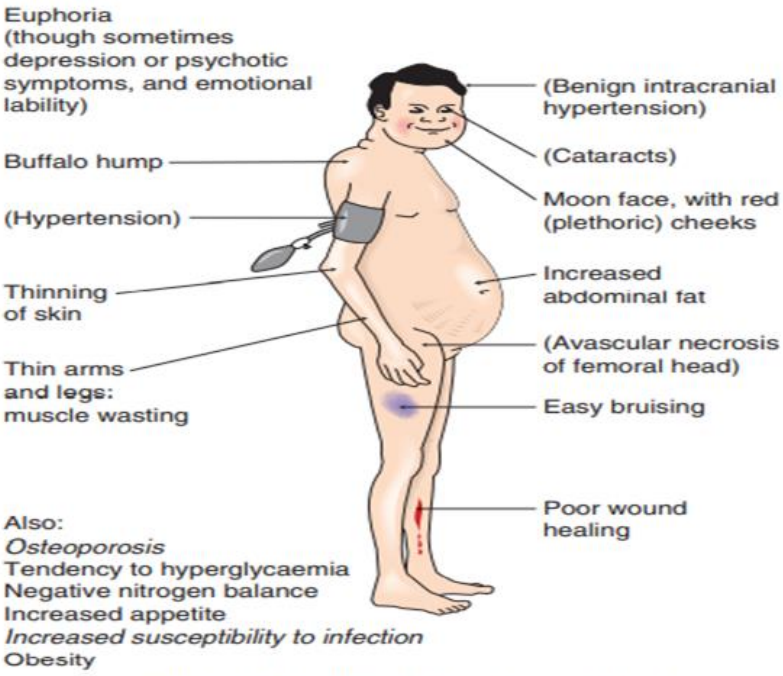


Figure 2: Mechanism of action of Corticosteroids

during the short course of oral prednisone "burst" typically prescribed for an asthma exacerbation.

Therefore, prednisone dose taper is unnecessary prior to discontinuation. Due to the increased incidence of adverse effects with oral therapy, chronic maintenance with systemic administration of corticosteroids should be reserved for patients who are not controlled on an ICS.

3. Adverse effects: Oral or parenteral glucocorticoids have a variety of potentially serious side effects (Figure 3), whereas ICS, particularly if used with a spacer, have few systemic effects. ICS deposition on the oral and laryngeal mucosa can cause adverse effects, such as oropharyngeal candidiasis (due to local immune suppression) and hoarseness. Patients should be instructed to rinse the mouth in a "swish-and-spit" method with water following use of the inhaler to decrease the chance of these adverse events.



Cushing's syndrome. This is caused by excessive exposure to glucocorticoids, and may be caused by disease (e.g. an adrenocorticotrophic hormone-secreting tumour) or by prolonged administration of glucocorticoid drugs (iatrogenic Cushing's). Italicised effects are particularly common. Less frequent effects, related to dose and duration of therapy, are shown in parentheses.

Figure 3: ICS side effects

Alternative drugs used to treat asthma

These drugs are useful for treatment of asthma in patients who are poorly controlled by conventional therapy or experience adverse effects secondary to corticosteroid treatment. These drugs should be used in conjunction with ICS therapy for most patients, not as monotherapy.

A. Leukotriene modifiers Leukotrienes (LT) B4 and the cysteinyl leukotrienes, LTC4, LTD4, and LTE4, are products of the 5-lipoxygenase pathway of arachidonic acid metabolism and part of the inflammatory cascade. 5-Lipoxygenase is found in cells of myeloid origin, such as mast cells, basophils, eosinophils, and

neutrophils. LTB4 is a potent chemoattractant for neutrophils and eosinophils, whereas the cysteinyl leukotrienes constrict bronchiolar smooth muscle, increase endothelial permeability, and promote mucus secretion. **Zileuton** is a selective and specific inhibitor of 5-lipoxygenase, preventing the formation of both LTB4 and the cysteinyl leukotrienes. Because **zafirlukast** and **montelukast** are selective antagonists of the cysteinyl leukotriene-1 receptor, they block the effects of cysteinyl leukotrienes (Figure 2). All three drugs are approved for the prevention of asthma symptoms. They should not be used in situations where immediate bronchodilation is required. Leukotriene receptor antagonists have also shown efficacy for the prevention of exercise induced bronchospasm.

Pharmacokinetics: All three drugs are orally active and highly protein bound. Food impairs the absorption of zafirlukast. The drugs are metabolized extensively by the liver. Zileuton and its metabolites are excreted in urine, whereas zafirlukast, montelukast, and their metabolites undergo biliary excretion.

Adverse effects: Elevations in serum hepatic enzymes have occurred with all three agents, requiring periodic monitoring and discontinuation when enzymes exceed three to five times the upper limit of normal. Other effects include headache and dyspepsia.

B. Cromolyn is a prophylactic anti-inflammatory agent that inhibits mast cell degranulation and release of histamine. It is an alternative therapy for mild persistent asthma. However, it is not useful in managing an acute asthma attack, because it is not a bronchodilator. Cromolyn is available as a nebulized solution for use in asthma. Due to its short duration of action, this agent requires dosing three or four times daily, which affects adherence and limits its use. Adverse effects are minor and include cough, irritation, and unpleasant taste.

C. Cholinergic antagonists The anticholinergic agents block vagally mediated contraction of airway smooth muscle and mucus secretion. Inhaled **ipratropium**, a quaternary derivative of atropine, is not recommended for the routine treatment of acute bronchospasm in asthma, as its onset is much slower than inhaled SABAs. However, it may be useful in patients who are unable to tolerate a SABA or patients with concomitant COPD. Ipratropium also offers additional benefit when used with a SABA for the treatment of acute asthma exacerbations in the emergency department. **Adverse effects** such as xerostomia and bitter taste are related to local anticholinergic effects.

D. Theophylline is a bronchodilator that relieves airflow obstruction in chronic asthma and decreases its symptoms. It may also possess anti-inflammatory activity, **Theophylline** competitively inhibits type III and type IV phosphodiesterase (PDE), the enzyme responsible for breaking down cyclic AMP in smooth muscle cells, possibly resulting in bronchodilation. **Theophylline** also binds to the adenosine A2B receptor and blocks adenosine mediated bronchoconstriction. Previously, the mainstay of asthma therapy, theophylline has been largely replaced with β2 agonists and corticosteroids due to its narrow therapeutic window, adverse effect profile, and potential for drug interactions. Overdose may cause seizures or potentially fatal arrhythmias. Theophylline is metabolized in the liver. It is subject to numerous drug interactions. Serum concentration monitoring should be performed when theophylline is used chronically.

E. Omalizumab is a recombinant DNA-derived monoclonal antibody that selectively binds to human immunoglobulin E (IgE). This leads to decreased binding of IgE to its receptor on the surface of mast cells and basophils. Reduction in surface-bound IgE limits the release of mediators of the allergic response. Omalizumab is indicated for the treatment of moderate to severe persistent asthma in patients who are poorly controlled with conventional therapy. Its use is limited by the high cost, route of administration (subcutaneous), and adverse effect profile. Adverse effects include serious anaphylactic reaction (rare), arthralgias, fever, and rash. Secondary malignancies have been reported.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is a chronic, irreversible obstruction of airflow that is usually progressive. Symptoms include cough, excess mucus production, chest tightness, breathlessness, difficulty sleeping, and fatigue. Although symptoms are similar to asthma, the characteristic irreversible airflow obstruction of COPD is one of the most significant differences between the diseases. Smoking is the greatest risk factor for COPD and is directly linked to the progressive decline of lung function as demonstrated by forced expiratory volume in one second (FEV1). Smoking cessation and/or continued avoidance should be recommended regardless of stage/ severity of COPD and age of patient. Drug therapy for COPD is aimed at relief of symptoms and prevention of disease progression.

A. Bronchodilators Inhaled bronchodilators, including the β2 -adrenergic agonists and anticholinergic agents (**ipratropium** and **tiotropium**), are the foundation of therapy for COPD. These drugs increase airflow, alleviate symptoms, and decrease exacerbation rates. The long-acting agents, LABAs and tiotropium, are preferred as first-line treatment of COPD for all patients except those who are at low risk with less symptoms. Combination of both an anticholinergic and a β2 agonist may be helpful in patients who have inadequate response to a single inhaled bronchodilators.

B. Corticosteroids The addition of an ICS to a long-acting bronchodilator may improve symptoms, lung function and quality of life in COPD patients. However, the use of an ICS is associated with an increased risk of pneumonia, and therefore, use should be restricted to these patients. Although often used for acute exacerbations, oral corticosteroids are not recommended for long-term treatment.

C. Other agents: Roflumilast is an oral phosphodiesterase-4 inhibitor used to reduce exacerbations in patients with severe chronic bronchitis. Although its activity is not well defined in COPD, it is theorized to reduce inflammation by increasing levels of intracellular cAMP in lung cells. Roflumilast is not a bronchodilator and is not indicated for the relief of acute bronchospasm. Its use is limited by common side effects including nausea, vomiting, diarrhea, and headache. As in asthma, the use of theophylline has largely been replaced by the more effective and tolerable long-acting bronchodilators.

DRUGS USED TO TREAT ALLERGIC RHINITIS

Rhinitis is an inflammation of the mucous membranes of the nose and is characterized by sneezing, itchy nose/eyes, watery rhinorrhea, nasal congestion, and sometimes, a nonproductive cough. An attack may be precipitated by inhalation of an allergen (such as dust, pollen, or animal dander). The foreign material interacts with mast cells coated with IgE generated in response to a previous allergen exposure. The mast cells release mediators, such as histamine, leukotrienes, and chemotactic factors that promote bronchiolar spasm and mucosal thickening from edema and cellular infiltration. Antihistamines and/or intranasal corticosteroids are preferred therapies for allergic rhinitis.

A. Antihistamines (H1 -receptor blockers) Antihistamines are useful for the management of symptoms of allergic rhinitis caused by histamine release (sneezing, watery rhinorrhea, itchy eyes/nose). However, they are more effective for prevention of symptoms, rather than treatment once symptoms have begun. Ophthalmic and nasal antihistamine delivery devices are available for more targeted tissue delivery. First-generation antihistamines, such as **diphenhydramine** and **chlorpheniramine**, are usually not preferred due to adverse effects, such as sedation, performance impairment, and other anticholinergic effects. The second

generation antihistamines (for example, **fexofenadine, loratadine, desloratadine, cetirizine**, and intranasal **azelastine**) are generally better tolerated. Combinations of antihistamines with decongestants are effective when congestion is a feature of rhinitis.

B. Corticosteroids Intranasal corticosteroids, such as **beclomethasone, budesonide, fluticasone, ciclesonide, mometasone,** and **triamcinolone,** are the most effective medications for treatment of allergic rhinitis. They improve sneezing, itching, rhinorrhea, and nasal congestion. Systemic absorption is minimal, and side effects of intranasal corticosteroid treatment are localized. These include nasal irritation, nosebleed, sore throat, and, rarely, candidiasis. To avoid systemic absorption, patients should be instructed not to inhale deeply while administering these drugs because the target tissue is the nose, not the lungs or the throat. For patients with chronic rhinitis, improvement may not be seen until 1 to 2 weeks after starting therapy.

C. α-Adrenergic agonists Short-acting α-adrenergic agonists ("nasal decongestants"), such as **phenylephrine**, constrict dilated arterioles in the nasal mucosa and reduce airway resistance. Longer-acting **oxymetazoline** is also available. When administered as an aerosol, these drugs have a rapid onset of action and show few systemic effects. Unfortunately, the α-adrenergic agonist intranasal formulations should be used no longer than 3 days due to the risk of rebound nasal congestion (rhinitis medicamentosa). For this reason, the α-adrenergic agents have no place in the long-term treatment of allergic rhinitis. Administration of oral α-adrenergic agonist formulations results in a longer duration of action but also increased systemic effects.

As with intranasal formulations, regular use of oral α-adrenergic agonists (phenylephrine and pseudoephedrine) alone or in combination with antihistamines is not recommended.

D. Other agents Intranasal **cromolyn** may be useful in allergic rhinitis, particularly when administered before contact with an allergen. To optimize the therapeutic effect, dosing should begin at least 1 to 2 weeks prior to allergen exposure. A nonprescription (over-the-counter) nasal formulation of cromolyn is available.

DRUGS USED TO TREAT COUGH

Coughing is an important defense mechanism of the respiratory system to irritants and is a common reason for patients to seek medical care. A troublesome cough may represent several etiologies, such as the common cold, sinusitis, and/or an underlying chronic respiratory disease. In some cases, cough may be an effective defense reflex against an underlying bacterial infection and should not be suppressed. Before treating cough, identification of its cause is important to ensure that antitussive treatment is appropriate. The priority should always be to treat the underlying cause of cough when possible.

A. Opioids: Codeine, an opioid, decreases the sensitivity of cough centers in the central nervous system to peripheral stimuli and decreases mucosal secretion. These therapeutic effects occur at doses lower than those required for analgesia. However, common side effects, such as constipation, dysphoria, and fatigue, still occur. In addition, it has addictive potential. **Dextromethorphan** is a synthetic derivative of morphine that has no analgesic effects in antitussive doses. In low doses, it has a low addictive profile. However, it is a potential drug of abuse, since it may cause dysphoria at high doses. Dextromethorphan has a significantly safer side effect profile than codeine and is equally effective for cough suppression. **Guaifenesin**, an expectorant, is available as a single-ingredient formulation and is also a common ingredient in combination products with codeine or dextromethorphan.

B. Benzonatate Unlike the opioids, benzonatate suppresses the cough reflex through peripheral action. It anesthetizes the stretch receptors located in the respiratory passages, lungs, and pleura. Side effects include dizziness, numbness of the tongue, mouth, and throat. These localized side effects may be particularly problematic if the capsules are broken or chewed and the medication comes in direct contact with the oral mucosa.

Table 1 summarize all the drugs used in respiratory system diseases treatment

MEDICATION	INDICATION
SHORT-ACTING β_2 ADRENERGIC AGONISTS	
Albuterol PROAIR, PROVENTIL, VENTOLIN	Asthma, COPD
Levalbuterol XOPENEX	Asthma, COPD
LONG-ACTING β_2 ADRENERGIC AGONISTS	
Arformoterol BROVANA	COPD
Formoterol FORADIL, PERFOROMIST	Asthma, COPD
Indacaterol ARCAPTA	COPD
Salmeterol SEREVENT	Asthma, COPD
INHALED CORTICOSTEROIDS	
Beclomethasone BECONASE AQ, QVAR	Allergic rhinitis, Asthma, COPD
Budesonide PULMICORT, RHINOCORT	Allergic rhinitis, Asthma, COPD
Ciclesonide ALVESCO, OMNARIS, ZETONNA	Allergic rhinitis
Fluticasone FLONASE, FLOVENT	Allergic rhinitis, Asthma, COPD
Mometasone ASMANEX, NASONEX	Allergic rhinitis, Asthma
Triamcinolone NASACORT AQ	Allergic rhinitis
LONG-ACTING β_2 ADRENERGIC AGONIST/CORTICOSTEROID COMBINATION	
Formoterol/budesonide SYMBICORT	Asthma, COPD
Formoterol/mometasone DULERA	Asthma, COPD
Salmeterol/fluticasone ADVAIR	Asthma, COPD
Vilanterol/fluticasone BREO ELLIPTA	COPD
SHORT-ACTING ANTICHOLINERGIC	
Ipratropium ATROVENT	Allergic rhinitis, COPD
LONG-ACTING ANTICHOLINERGIC	
Aclidinium bromide TUDORZA PRESSAIR	COPD
Tiotropium SPIRIVA	COPD
LEUKOTRIENE MODIFIERS	
Montelukast SINGULAIR	Asthma, Allergic rhinitis
Zafirlukast ACCOLATE	Asthma
Zileuton ZYFLO CR	Asthma
ANTIHISTAMINES (H_1-RECEPTOR BLOCKERS)	
Azelastine ASTELIN, ASTEPRO	Allergic rhinitis
Cetirizine ZYRTEC	Allergic rhinitis
Desloratadine CLARINEX	Allergic rhinitis
Fexofenadine ALLEGRA	Allergic rhinitis
Loratadine CLARITIN	Allergic rhinitis
α-ADRENERGIC AGONISTS	
Oxymetazoline AFRIN, ORISTAN	Allergic rhinitis
Phenylephrine NEOSYNEPHRINE, SUDAFED PE	Allergic rhinitis
Pseudoephedrine SUDAFED	Allergic rhinitis
AGENTS FOR COUGH	
Benzonatate TESSALON PERLES	Cough suppressant
Codeine (with guaifenesin) VARIOUS	Cough suppressant/expectorant
Dextromethorphan VARIOUS	Cough suppressant
Dextromethorphan (with guaifenesin) VARIOUS	Cough suppressant/expectorant
Guaifenesin VARIOUS	Expectorant
OTHER AGENTS	
Cromolyn NASALCROM	Asthma, Allergic rhinitis
Omalizumab XOLAIR	Asthma
Roflumilast DALIRESP	COPD
Theophylline ELIXOPHYLLIN, THEO-24, UNIPHYL	Asthma

Table 1 drugs for respiratory system diseases

HISTAMINE AND ANTIHISTAMINE

Histamine is a naturally occurring amine that is found in most tissues in an inactive bound form, and pharmacologically active free histamine, released in response to stimuli such as physical trauma or immunoglobulin (Ig) E-mediated activation, is an important component of the acute inflammatory response. The physiological functions of histamine are suggested by its distribution in the body, in:

- Body epithelia (the gut, the respiratory tract and in the skin), where it is released in response to invasion by foreign substances
- Glands (gastric, intestinal, lachrymal, salivary), where it mediates part of the normal secretory process
- Mast cells near blood vessels, where it plays a role in regulating the microcirculation. \
- Histamine functions as a neurotransmitter in the brain.
- It also occurs as a component of venoms and in secretions from insect stings.

Release of histamine: Most often, histamine is just one of several chemical mediators released in response to stimuli. The stimuli for release of histamine from tissues may include destruction of cells as a result of cold, toxins from organisms, venoms from insects and spiders, and trauma. Allergies and anaphylaxis can also trigger significant release of histamine.

Actions Histamine acts as a local hormone (autacoid) similarly to serotonin or prostaglandins, i.e. it functions within the immediate vicinity of its site of release. With gastric secretion, for example, stimulation of receptors on the histamine containing cell causes release of histamine, which in turn acts on receptors on parietal cells which then secrete hydrogen ion.

Histamine receptors Histamine binds to H1, H2 and H3 receptors, all of which are G-protein coupled. The H1 receptor is largely responsible for mediating its pro-inflammatory effects, including the vasomotor changes, increased vascular permeability and upregulation of adhesion molecules on vascular endothelium, i.e. it mediates the oedema and vascular effects of histamine.

H2 receptors mediate release of gastric acid. Blockade of histamine H1 and H2 receptors has substantial therapeutic utility. H3 receptors are expressed in a wide range of tissues including brain and nerve endings, and function as feedback inhibitors for histamine and other neurotransmitters. More recently identified is the H4 receptor, which is involved in leucocyte chemotaxis.

HISTAMINE ANTAGONISM AND H1- AND H2-RECEPTOR ANTAGONISTS

The effects of histamine can be opposed in three ways:

• By using a drug with opposing effects. Histamine constricts bronchi, causes vasodilatation and increases capillary permeability; adrenaline (epinephrine), by activating α and β2 adrenoceptors, produces opposite effects - referred to as physiological antagonism.

• By blocking histamine binding to its site of action (receptors), i.e. using competitive H1- and H2-receptor antagonists.

• By preventing the release of histamine from storage cells. **Glucocorticoids** and **sodium cromoglicate** can suppress IgE-induced release from mast cells; β2 agonists have a similar effect.

Drugs that competitively block H1-histamine receptors were the first to be introduced and are conventionally called the 'antihistamines'. They effectively inhibit the components of the triple response and partially prevent the hypotensive effect of histamine, but they have no effect on histamine-induced gastric secretion which is suppressed by blockade of histamine H2 receptors.

Thus, histamine antagonists are classified as:

- histamine H1-receptor antagonists
- histamine H2-receptor antagonists: **cimetidine, famotidine, nizatidine, ranitidine**

Histamine H1-receptor antagonists. The selectivity implied by the term 'antihistamine'is unsatisfactory because the older first-generation antagonists show considerable blocking activity against muscarinic receptors, and often serotonin and α-adrenergic receptors as well. These features are a disadvantage when H1 antihistamines are used specifically to antagonise the effects of histamine, e.g. for allergies. Hence the appearance of second-generation H1 antagonists that are more selective for H1 receptors and largely free of anti-muscarinic and sedative effects has been an important advance. Actions H1-receptor antihistamines oppose, to varying degrees, the effects of liberated histamine. They are generally competitive, surmountable inhibitors and strongly block all components of the triple response (a pure H1-receptor effect), but only partially counteract the hypotensive effect of high-dose histamine (a mixed H1- and H2-receptor effect). H1 antihistamines are of negligible use in asthma, in which non-histamine mediators, such as the cysteinyl leukotrienes, are the predominant constrictors. They are more effective if used before histamine has been liberated, and reversal of effects of free histamine is more readily achieved by physiological antagonism with adrenaline (epinephrine), which is used first in life-threatening allergic reactions. The older first-generation H1 antihistamines cause drowsiness and patients should be warned of this, e.g. about driving or operating machinery, and about additive effects with alcohol. Paradoxically, they can increase seizure activity in epileptics, especially children, and can cause seizures in non-epileptic subjects if taken in overdose. The newer second-generation H1 antihistamines penetrate the blood-brain barrier less readily and are largely devoid of such central effects. Antimuscarinic effects of first-generation H1 antihistamines are sometimes put to therapeutic advantage in parkinsonism and motion sickness.

Uses The H1 antihistamines are used for symptomatic relief of allergies such as hay fever and urticaria. They are of broadly similar therapeutic efficacy.

INDIVIDUAL H1-RECEPTOR ANTIHISTAMINES

Non-sedative second-generation drugs These newer drugs are relatively selective for H1 receptors, enter the brain less readily than do the earlier antihistamines, and lack the unwanted antimuscarinic effects. Differences lie principally in their duration of action. **Cetirizine** (t½ 7 h), **loratadine** (t½ 15 h) and **terfenadine** (t½ 20 h) are effective taken once daily and are suitable for general use. **Acrivastine** (t½ 2 h) is so short acting that it is best reserved for intermittent therapy, e.g. when breakthrough symptoms occur in a patient using topical therapy for hay fever. Other non-sedating antihistamines are **desloratadine, fexofenadine, levocetirizine** and **mizolastine.**

Adverse effects The second-generation antihistamines are well tolerated but a noteworthy effect occurs with **terfenadine**. This drug can cause ventricular tachycardia and probably explains the sudden deaths reported during early use of terfenadine. The event is prone to occur with high dose or when metabolism of terfenadine is inhibited, and inhibiting drugs include erythromycin, ketoconazole and even grapefruit juice. **Fexofenadine**, the active metabolite of terfenadine, appears to be safer regarding the effect on the heart.

Sedative first-generation agents

Chlorphenamine (t½ 20 h) is effective when urticaria is prominent, and its sedative effect is then useful. **Diphenhydramine** (t½ 32 h) is strongly sedative and has antimuscarinic effects; it is also used in parkinsonism and motion sickness. **Promethazine** (t½ 12 h) is so strongly sedative that it is used as an hypnotic in adults and children. **Alimemazine, azatadine, brompheniramine, clemastine, cyproheptadine**, **diphenylpyraline, doxylamine, hydroxyzine** and **triprolidine** are similar.

Adverse effects Apart from sedation, these include: dizziness, fatigue, insomnia, nervousness, tremors and antimuscarinic effects, e.g. dry mouth, blurred vision and gastrointestinal disturbance. Dermatitis and agranulocytosis can occur. Severe poisoning due to overdose results in coma and sometimes in convulsions.

Corticosteroids

The adrenal gland consists of the cortex and the medulla. The medulla secretes catecholamines, whereas the cortex, secretes two types of corticosteroids (glucocorticoids and mineralocorticoids) and the adrenal androgens. The adrenal cortex has three zones, and each zone synthesizes a different type of steroid hormone from cholesterol. The outer zona glomerulosa produces mineralocorticoids (for example, aldosterone) that are responsible for regulating salt and water metabolism. Production of aldosterone is regulated primarily by the renin–angiotensin system. The middle zona fasciculata synthesizes glucocorticoids (for example, cortisol) that are involved with metabolism and response to stress. The inner zona reticularis secretes adrenal androgens.

A. Glucocorticoids

Cortisol is the principal human glucocorticoid. Normally, its production is diurnal, with a peak early in the morning followed by a decline and then a secondary, smaller peak in the late afternoon. Factors such as stress and levels of the circulating steroid influence secretion. The effects of cortisol are many and diverse. In general, all glucocorticoids:

1. Promote normal intermediary metabolism: Glucocorticoids favor gluconeogenesis. They stimulate protein catabolism (except in the liver) and lipolysis, thereby providing the building blocks and energy that are needed for glucose synthesis.

2. Increase resistance to stress: By raising plasma glucose levels, glucocorticoids provide the body with energy to combat stress caused by trauma, fright, infection, bleeding, or debilitating disease.

3. Alter blood cell levels in plasma: Glucocorticoids cause a decrease in eosinophils, basophils, monocytes, and lymphocytes by redistributing them from the circulation to lymphoid tissue. Glucocorticoids also increase hemoglobin, erythrocytes, platelets, and polymorphonuclear leukocytes.

4. Anti-inflammatory effect They have powerful anti-inflammatory and immunosuppressant effects. They prevent or suppress the clinical features of inflammation such as redness, heat, pain and swelling. At tissue level, they suppress the early phenomena (capillary permeability, oedema, cellular infiltration and phagocytosis) and late responses like capillary proliferation, collagen deposition, fibroblast activity and scar formation (Figure 4).

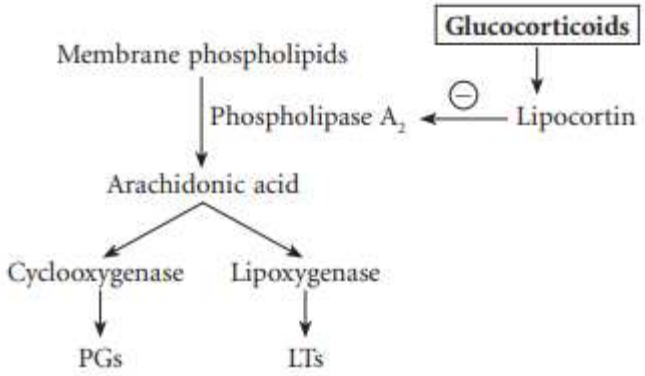


Figure 4: anti-inflammatory effect of glucocorticoids

a. Glucocorticoids induce a protein called lipocortin, which inhibits phospholipase A2, so prostaglandins (PGs), leukotrienes (LTs) and PAF are not formed.
b. Tumour necrosis factor-alpha (TNF-α- is inhibited by glucocorticoids, which is necessary for initiating infl ammatory process.

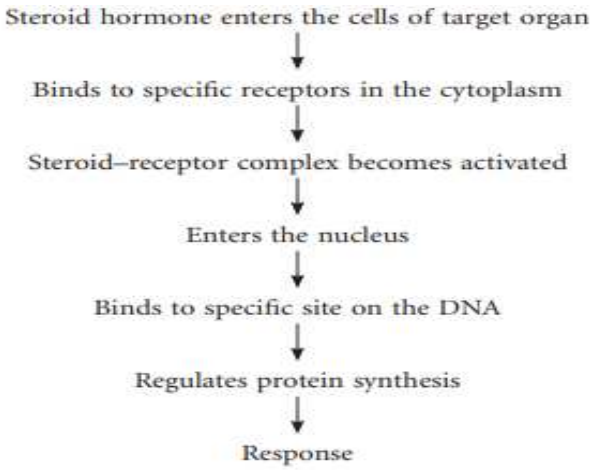


Figure 5: another mechanism of action of steroid

c. Glucocorticoids stabilize the lysosomal membrane and prevent the release of infl ammatory mediators.

B. Mineralocorticoids

Mineralocorticoids help to control fluid status and concentration of electrolytes, especially sodium and potassium. Aldosterone acts on distal tubules and collecting ducts in the kidney, causing reabsorption of sodium, bicarbonate, and water. Conversely, aldosterone decreases reabsorption of potassium, which, with H+, is then lost in the urine. Enhancement of sodium reabsorption by aldosterone also occurs in gastrointestinal mucosa and in sweat and salivary glands.

Therapeutic uses of the corticosteroids

Endocrinal uses:

1. Acute adrenal insufficiency: It is a medical emergency. It is treated with i.v. hydrocortisone and i.v. normal saline with 5% glucose to correct fluid and electrolyte imbalance. Precipitating causes such as trauma, infection or haemorrhage should be treated.

2. Chronic adrenal insufficiency: Treated with oral hydrocortisone (two-third of the daily dose is given in the morning and one-third in the evening) along with adequate salt and water.

Non-endocrinal uses

Corticosteroids are one of the most important groups of drugs used clinically in a variety of diseases. Because of their dramatic symptomatic relief, they are often misused. Non-endocrinal diseases require supra-physiological doses of steroid, which inevitably carries risk. The beneficial effects of glucocorticoids are mainly due to their anti-inflammatory and immunosuppressant effects.

1. In dentistry: Topical or systemic glucocorticoids are used in: a. Recurrent aphthous stomatitis b. Chronic ulcerative stomatitis c. Oral pemphigoid d. Erythema multiforme e. Temporomandibular joint pain: Intra-articular triamcinolone is used.

2. Rheumatoid arthritis: They produce an immediate and dramatic symptomatic relief in rheumatoid arthritis; but they do not halt the progression of the disease. Intra-articular injection is preferred only if one or two joints are involved.

3. Osteoarthritis: rarely used.

4. Rheumatic fever: They produce more rapid symptomatic relief than aspirin. **Prednisolone** is given along with aspirin and should be continued until the erythrocyte sedimentation rate (ESR) comes to normal and then the steroid is tapered off gradually.

5. Allergic diseases: The manifestations of allergic diseases, such as hay fever, reactions to drugs, urticaria, contact dermatitis, angioneurotic oedema and anaphylaxis, can be suppressed by glucocorticoids; but they have a slow onset of action. Hence, severe reactions such as anaphylaxis and angioneurotic oedema require immediate therapy with adrenaline. In hay fever, serum sickness and mild allergic reactions, antihistamines are the preferred drugs.

6. Bronchial asthma: They have anti-inflammatory and anti-allergic effects; hence they reduce mucosal oedema and bronchial hyperirritability. In acute severe asthma, i.v. hydrocortisone is given along with nebulized β2 -agonist and ipratropium bromide. If a chronic asthmatic needs steroid, it is better to give inhalational preparations like **beclomethasone, budesonide** or **fluticasone** because they cause minimal systemic adverse effects.

7. Collagen diseases: Collagen diseases such as polymyositis, polyarteritis nodosa, etc. can be controlled with large doses of glucocorticoids. Steroids with negligible salt and water retaining property is preferred.

8. Renal disease: Glucocorticoids are the first-line drugs in nephrotic syndrome.

9. Ocular diseases: They are frequently used to suppress inflammation in the eye; thus they prevent damage to vision. Agents may be administered topically, sub-conjunctivally, systemically or by retrobulbar

injection, depending upon the condition. Steroids are contraindicated in herpes simplex keratitis and ocular injuries.

10. Skin diseases: They dramatically relieve itching, pain, and inflammation in allergic and other dermatoses. To minimize systemic effects, topical steroids are preferred. Systemic steroid therapy is needed in severe conditions like exfoliative dermatitis, dermatomyositis, pemphigus, etc. Psoriasis, keloids and hypertrophic scar are sometimes treated by intralesional injection of steroids.

11. Haematological disorders: Autoimmune haemolytic anaemias usually respond to glucocorticoids. Because of their lympholytic action, glucocorticoids are used to treat certain malignancies, leukaemia, lymphomas, Hodgkin's disease, multiple myeloma, etc., usually in combination with antineoplastic drugs.

12. Cerebral oedema

13. Intestinal diseases

14. Shock

15. Organ transplantation

16. Hypercalcaemia

FLUOROQUINOLONES

By

Dr. Samir AL_Shujairy

Nalidixic acid is the predecessor to all fluoroquinolones, a class. Over 10,000 fluoroquinolone analogs have been Synthesized.

wide clinical applications.

1.Fluoroquinolones greater efficacy, a broader spectrum of antimicrobial activity,

2.abetter safety profile than their predecessors.

3. spread of antimicrobial resistance in many organisms

Fluoroquinolones may be classified into "generations"

The nonfluorinated quinolone *nalidixic acid* is first generation, with a narrow spectrum of susceptible organisms.

Ciprofloxacin and *norfloxacin* are second generation because of their activity against aerobic gram-negative and atypical bacteria.

exhibit significant intracellular penetration, allowing therapy for infections in which a bacterium spends part or all of its life cycle inside a host cell (chlamydia, mycoplasma, and mycobacteria).

Levofloxacin is third generation because of its increased activity against gram-positive bacteria.

Lastly, the fourth generation includes only *moxifloxacin* because of its activity against anaerobic and gram-positive organisms.

Mechanism of action

1. Fluoroquinolones enter bacteria through porin channels.
2. Exhibit antimicrobial effects on DNA gyrase
3. (bacterial topoisomerase II) and bacterial topoisomerase IV. Inhibition of DNA gyrase results:
4. Relaxation of supercoiled DNA, promoting DNA strand breakage Inhibition of topoisomerase IV impacts chromosomal stabilization during cell division.
5. interfering with the separation of newly replicated DNA.

In **gram-negative** organisms (*Pseudomonas aeruginosa*), inhibition of DNA gyrase is more significant than topoisomerase IV.

whereas in **gram-positive** organisms (*Streptococcus pneumoniae*), opposite is true.

(***ciprofloxacin***) higher affinity for topoisomerase IV should not be used for *S. pneumoniae* infections,

(***moxifloxacin***) more topoisomerase II activity should not be used for *P. aeruginosa* infections.

Antimicrobial spectrum

Fluoroquinolones :

1. bactericidal.
2. exhibit concentration -dependent killing.
3. Bactericidal activity is more pronounced as serum drug concentrations increase to approximately 30-fold the MIC of the bacteria.

fluoroquinolones are effective against gram-negative organisms (*Escherichia coli, P. aeruginosa, Haemophilus influenzae*),

atypical organisms (Legionellaceae, Chlamydiaceae),

gram-positive organisms (streptococci), and some mycobacteria (*Mycobacterium tuberculosis*). Fluoroquinolones are typically not used for the treatment of *Staphylococcus aureus* or enterococcal infections.

not effective against syphilis.

limited against *Neisseria gonorrhoeae* due to disseminated resistance worldwide.

Levofloxacin and *moxifloxacin* are referred to “respiratory fluoroquinolones,” because they have excellent activity against *S. pneumoniae,* a common cause of community-acquired pneumonia (CAP).

Moxifloxacin has activity against many anaerobes.

Fluoroquinolones are commonly considered alternatives for patients with severe β-lactam allergy.

clinically useful fluoroquinolones

Norfloxacin: Poor oral bioavailability and a short half-life. It is effective in treating nonsystemic infections, such as urinary tract infections (UTIs), prostatitis, and infectious diarrhea.

Ciprofloxacin: effective in the treatment of many systemic infections caused by gram-negative bacilli. Of the best activity against *P. aeruginosa* and in cystic fibrosis patients.

bioavailability 80% ,

intravenous and oral formulations are frequently interchanged.

Traveler's diarrhea caused by *E. coli* as well as typhoid fever caused by *Salmonella typhi* can be effectively treated with *ciprofloxacin*.

second-line agent in the treatment of tuberculosis.

Levofloxacin: broad spectrum, utilized in a wide range of infections, including prostatitis, skin infections, CAP, and nosocomial pneumonia.

Levofloxacin has 100% bioavailability and is dosed once daily..

Moxifloxacin: not only has enhanced activity against gram-positive organisms (*S. pneumoniae*) but also has excellent activity against many anaerobes, although resistance to *Bacteroides fragilis* has been reported.

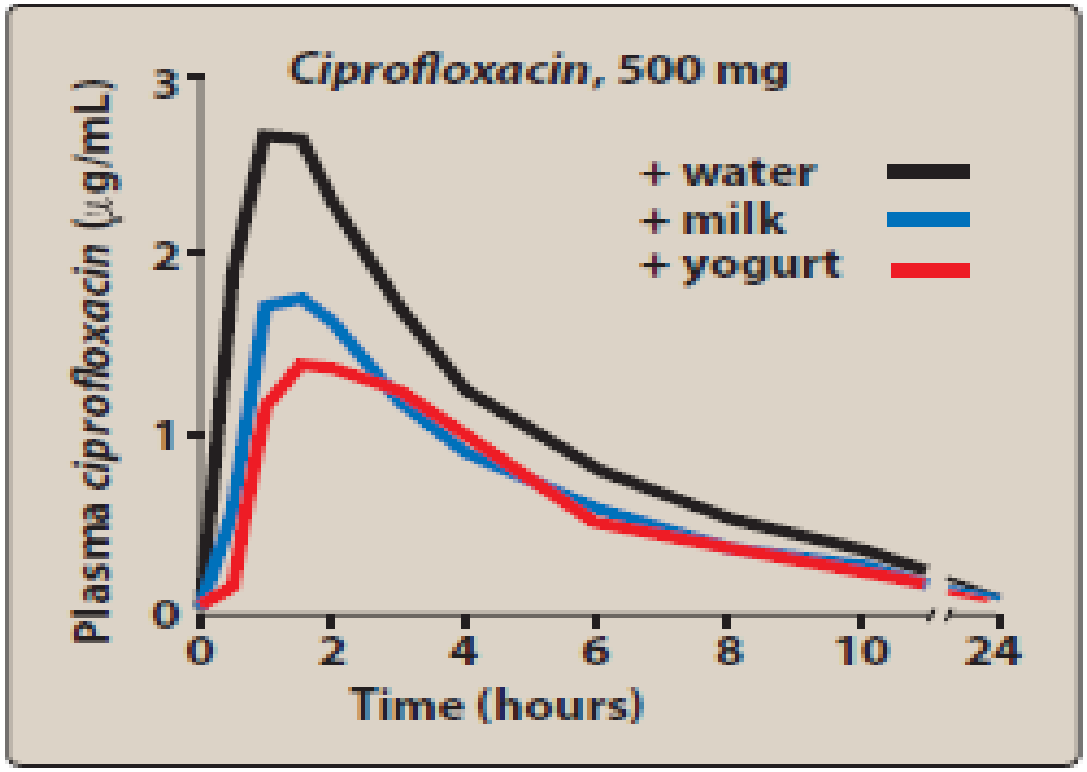
poor activity against *P. aeruginosa*.

Moxifloxacin does not concentrate in urine and is not indicated for the treatment of UTIs.

Pharmacokinetics

Absorption: *norfloxacin* 35% to 70% of orally administered is absorbed, compared with 80% to 99% of the other fluoroquinolones. Intravenous and ophthalmic preparations of *ciprofloxacin*, *levofloxacin*, and *moxifloxacin* are available.

Ingestion of fluoroquinolones with *sucralfate*, aluminum- or magnesium containing antacids, or dietary supplements containing iron or zinc, Calcium and other divalent cations can reduce the absorption.


Ciprofloxacin, 500 mg
+ water
+ milk
+ yogurt
Plasma ciprofloxacin (μg/mL)
3
2
1
0
0
2
4
6
8
10
24
Time (hours)

Distribution:

1. Binding to plasma proteins ranges from 10% to 40%.
2. distribute well into all tissues and body fluids,
3. Levels are high in bone, urine (except *moxifloxacin*), kidney, and prostatic tissue (but not prostatic fluid), and concentrations in the lungs exceed those in serum.
4. Penetration into cerebrospinal fluid low except *ofloxacin*.
5. Fluoroquinolones accumulate in macrophages & polymorphonuclear leukocytes, thus having activity against intracellular organisms.

Elimination: Most fluoroquinolones are excreted renally. Therefore, dosage adjustments are needed in renal dysfunction.

Moxifloxacin is excreted primarily by the liver, and no dose adjustment is required for renal impairment.

Resistance

chromosomal mutations.

Cross-resistance exists among the quinolones.

1. Altered target: Chromosomal mutations in bacterial genes (for example, gyrA or parC) have been associated with a decreased affinity for fluoroquinolones at their site of action.

Both topoisomerase IV and DNA gyrase may undergo mutations.

2.Decreased accumulation: Reduced intracellular concentration is linked to

1) porin channels and 2) efflux pumps.

The former involves a decreased number of porin proteins in the outer membrane of the resistant cell, thereby impairing access of the drugs to the intracellular topoisomerases.

The latter mechanism pumps drug out of the cell.

Adverse reactions

1. nausea, vomiting, and diarrhea. Headache and dizziness or lightheadedness may occur.

2. patients with central nervous system (CNS) disorders, such as epilepsy, should be treated cautiously with these drugs.

3. Articular cartilage erosion (arthropathy) has been observed in immature animals exposed to fluoroquinolones.

4.avoided in pregnancy & lactation and children under 18 yrs of age

5.should not be used in patients with predisposed to arrhythmias cause QT prolongation.

6.Ciprofloxacin increase serum levels of *theophylline* by inhibiting metabolism.

7.Quinolones may also raise the serum levels of *warfarin*, *caffeine*, and *cyclosporine*.

FOLATE ANTAGONISTS

Enzymes requiring folate-derived cofactors are essential for the synthesis of purines and pyrimidines (precursors of RNA and DNA) and other compounds necessary for cellular growth and replication. Therefore, in the absence of folate, cells cannot grow or divide.

To synthesize the critical folate derivative, tetrahydrofolic acid, humans must first obtain preformed folate in the form of folic acid from the diet.

In contrast, many bacteria are impermeable to folic acid and other folates and, therefore, must rely on their ability to synthesize folate

The sulfonamides are a family of antibiotics that inhibit synthesis of folate.

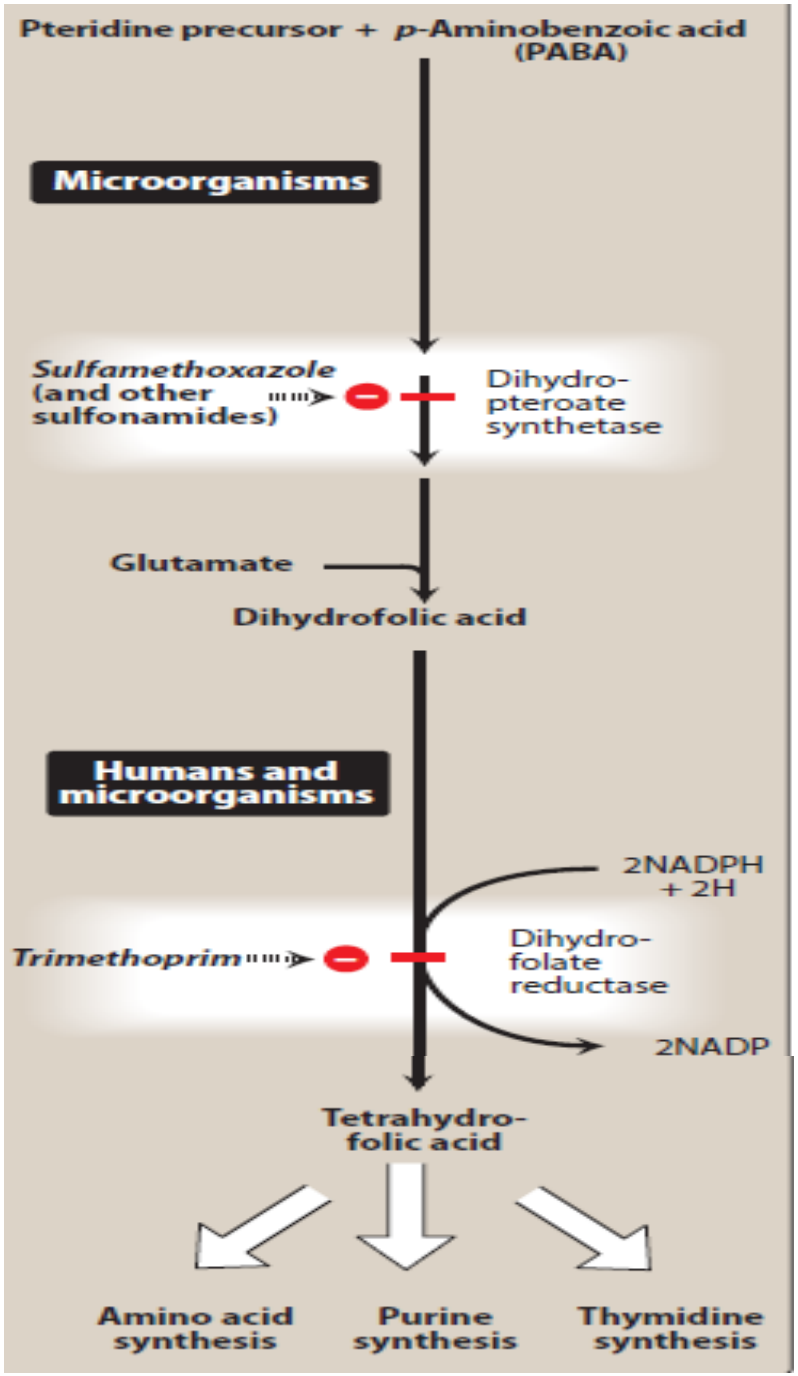
A second type of folate antagonist—*trimethoprim*—prevents microorganisms from converting dihydrofolic acid to tetrahydrofolic acid, with minimal effect on the ability of human cells to make this conversion.

Both sulfonamides and *trimethoprim* interfere with the ability of bacterium to perform DNA synthesis.

Combining sulfonamide *sulfamethoxazole* with *trimethoprim* (the generic name for the combination is ***cotrimoxazole***) provides a synergistic combination.

SULFONAMIDES

Mechanism of action



Antibacterial spectrum

Sulfa drugs are active against select Enterobacteriaceae in the urinary tract and Nocardia infections.

sulfadiazine in combination with the dihydrofolate reductase inhibitor *pyrimethamine* is the preferred treatment for toxoplasmosis.

Sulfadoxine in combination with *pyrimethamine* is used as an antimalarial drug.

Pharmacokinetics

Absorption: After oral administration, most sulfa drugs are well Absorbed. An exception is *sulfasalazine* . It is not absorbed when administered orally or as a suppository and, therefore, is reserved for treatment of chronic inflammatory bowel disease (for example, ulcerative colitis).

Absorption of sulfapyridine can lead to toxicity in patients who are slow acetylators.

burn, creams of *silver sulfadiazine* or *mafenide acetate* (α*-amino-p-toluenesulfonamide*) have been effective in reducing burn-associated sepsis because they prevent colonization of bacteria.

Distribution:

1.Sulfa drugs are bound to serum albumin in the circulation,

2. extent of binding depends on the ionization constant (pKa) of the drug.

3. smaller the pKa value, the greater the binding.

4.Sulfa drugs distribute throughout the bodily fluids and penetrate well into cerebrospinal fluid—even in the absence of inflammation.

5.pass the placental barrier and enter fetal tissues.

Metabolism:

1. The sulfa drugs are acetylated and conjugated primarily in the liver.
2. The acetylated product is devoid of antimicrobial activity but retains the toxic potential to precipitate at neutral or acidic pH.
3. causes crystalluria ("stone formation"; potential damage to the kidney.

Excretion: Sulfa drugs are eliminated by glomerular filtration and secretion and require dose adjustments for renal dysfunction. Sulfonamides may be eliminated in breast milk.

Resistance

Bacteria that can obtain folate from their environment are naturally resistant to these drugs.

Acquired bacterial resistance to the sulfa drugs can arise from plasmid transfers or random mutations.

Organisms resistant to one member of this drug family are resistant to all.

Resistance is generally irreversible and may be due to

1) an altered dihydropteroate synthetase,

2) decreased cellular permeability to sulfa drugs, or

3) enhanced production of the natural substrate, PABA.

Adverse effects

1. Crystalluria: Nephrotoxicity may develop as a result of crystalluria Adequate hydration and alkalinization of urine can prevent the problem by reducing the concentration of drug and promoting its ionization.

2. Hypersensitivity:

3. Hematopoietic disturbances: Hemolytic anemia is encountered in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Granulocytopenia and thrombocytopenia can also occur.

Fatal reactions have been reported from associated agranulocytosis, aplastic anemia

4. Kernicterus: This disorder may occur in newborns, because sulfa drugs displace bilirubin from binding sites on serum albumin. The bilirubin is then free to pass into the CNS, because the blood-brain barrier is not fully developed.

5. Drug potentiation: Transient potentiation of the anticoagulant effect of *warfarin* results from the displacement from binding sites on serum albumin. Serum *methotrexate* levels may also rise through its displacement.

TRIMETHOPRIM

Trimethoprim ,a potent inhibitor of bacterial dihydrofolate reductase, *Trimethoprim* is most often compounded with *sulfamethoxazole*, producing the combination called *cotrimoxazole*.

Mechanism of action

The active form of folate is the tetrahydro derivative that is formed through reduction of dihydrofolic acid by dihydrofolate reductase. This enzymatic reaction is inhibited by *trimethoprim*, leading to a decreased availability of the tetrahydrofolate cofactors required for purine, pyrimidine, and amino acid synthesis.

Antibacterial spectrum

The antibacterial spectrum of *trimethoprim* is similar to that of *sulfamethoxazole*.

trimethoprim is 20- to 50-fold more potent than the sulfonamides.

Trimethoprim may be used alone in the treatment of UTIs and in the treatment of bacterial prostatitis

Pharmacokinetics: *Trimethoprim* is rapidly absorbed following oral administration. Because the drug is a weak base, higher concentrations of *trimethoprim* are achieved in the relatively acidic prostatic and vaginal fluids. The drug is widely distributed into body tissues and fluids, including penetration into the cerebrospinal fluid. *Trimethoprim* undergoes some *O*-demethylation, but 60% to 80% is renally excreted unchanged.

Adverse effects

Trimethoprim can produce the effects of folic acid deficiency. These effects include megaloblastic anemia, leukopenia, and granulocytopenia,especially in pregnant patients and those having very poor diets.

These blood disorders may be reversed by the simultaneous administration of *folinic acid*, which does not enter bacteria.

COTRIMOXAZOLE

The combination of *trimethoprim* with *sulfamethoxazole*, called *cotrimoxazole,* shows greater antimicrobial activity than equivalent quantities of either drug used alone

Mechanism of action

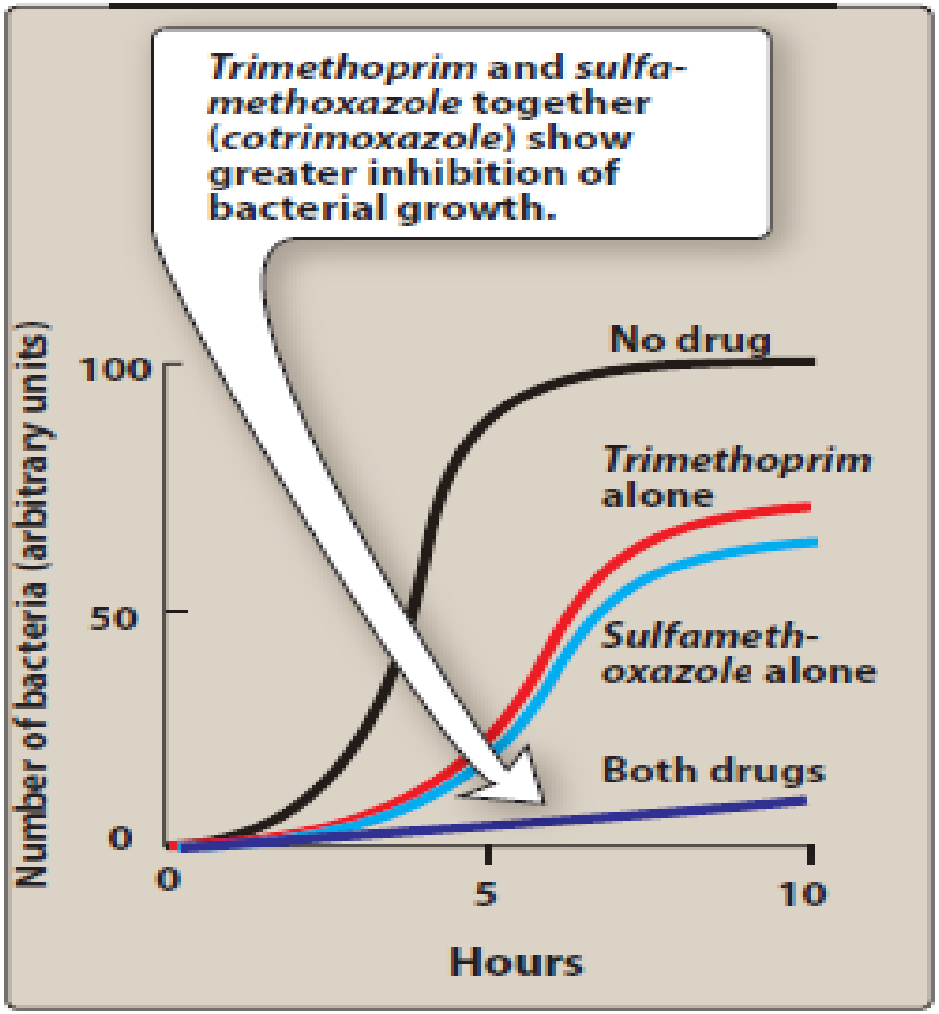
The synergistic antimicrobial activity of *cotrimoxazole* results from its inhibition of two sequential steps in the synthesis of tetrahydrofolic acid.

Sulfamethoxazole inhibits the incorporation of PABA into dihydrofolic acid precursors, and *trimethoprim* prevents reduction of dihydrofolate to tetrahydrofolate

Antibacterial spectrum

Cotrimoxazole has a broader spectrum of antibacterial action than the sulfa drugs alone.

1. effective in treating UTIs and respiratory tract infections, Pneumocystis jirovecii pneumonia(PCP), toxoplasmosis, and *ampicillin*– or *chloramphenicol*–resistant
2. salmonella infections.
3. activity against MRSA and can be particularly useful for community-acquired skin and soft tissue infections
4. the drug of choice for infections caused by susceptible *Nocardia* species and *Stenotrophomonas maltophilia*.


Trimethoprim and *sulfamethoxazole* together (*cotrimoxazole*) show greater inhibition of bacterial growth.
No drug
Trimethoprim alone
Sulfamethoxazole alone
Both drugs
Number of bacteria (arbitrary units)
100
50
0
0
5
10
Hours

Pharmacokinetics

1. *Cotrimoxazole* is generally administered orally.
2. Intravenous administration may be utilized in patients with severe pneumonia caused by PCP.
3. Both agents distribute throughout the body.

Cotrimoxazole readily crosses the blood–brain barrier.

Both parent drugs and their metabolites are excreted in the urine.

Resistance

Resistance to the *trimethoprim–sulfamethoxazole* combination is less frequently encountered than resistance to either of the drugs alone, because it requires that the bacterium have simultaneous resistance to both drugs.

Significant resistance has been documented in a number of clinically relevant organisms, including *E. coli* and *MRSA*.

Adverse effects

Nausea and vomiting are the most common gastrointestinal adverse effects. Glossitis and stomatitis have been observed.

Hyperkalemia may occur, especially with higher doses.

Megaloblastic anemia, leukopenia, and thrombocytopenia may occur and have been fatal.

Hemolytic anemia may occur in patients with G6PD deficiency due to the *sulfamethoxazole* component.

prothrombin times in patients receiving both *sulfamethoxazole* and *warfarin*.

The plasma half-life of *phenytoin* may be increased due to inhibition of its metabolism.

Methotrexate levels may rise due to displacement from albumin-binding sites by *sulfamethoxazole*.

URINARY TRACT ANTISEPTICS/ANTIMICROBIALS

UTIs are prevalent in women of child-bearing age and in the elderly population.

E. coli is the most common pathogen, causing about 80% of uncomplicated upper and lower UTIs.

Staphylococcus saprophyticus is the second most common bacterial pathogen causing UTIs.

In addition to *cotrimoxazole* and the quinolones previously mentioned, UTIs may be treated with any one of a group of agents called urinary tract antiseptics, including *methenamine*, *nitrofurantoin*, and the quinolone *nalidixic acid*.

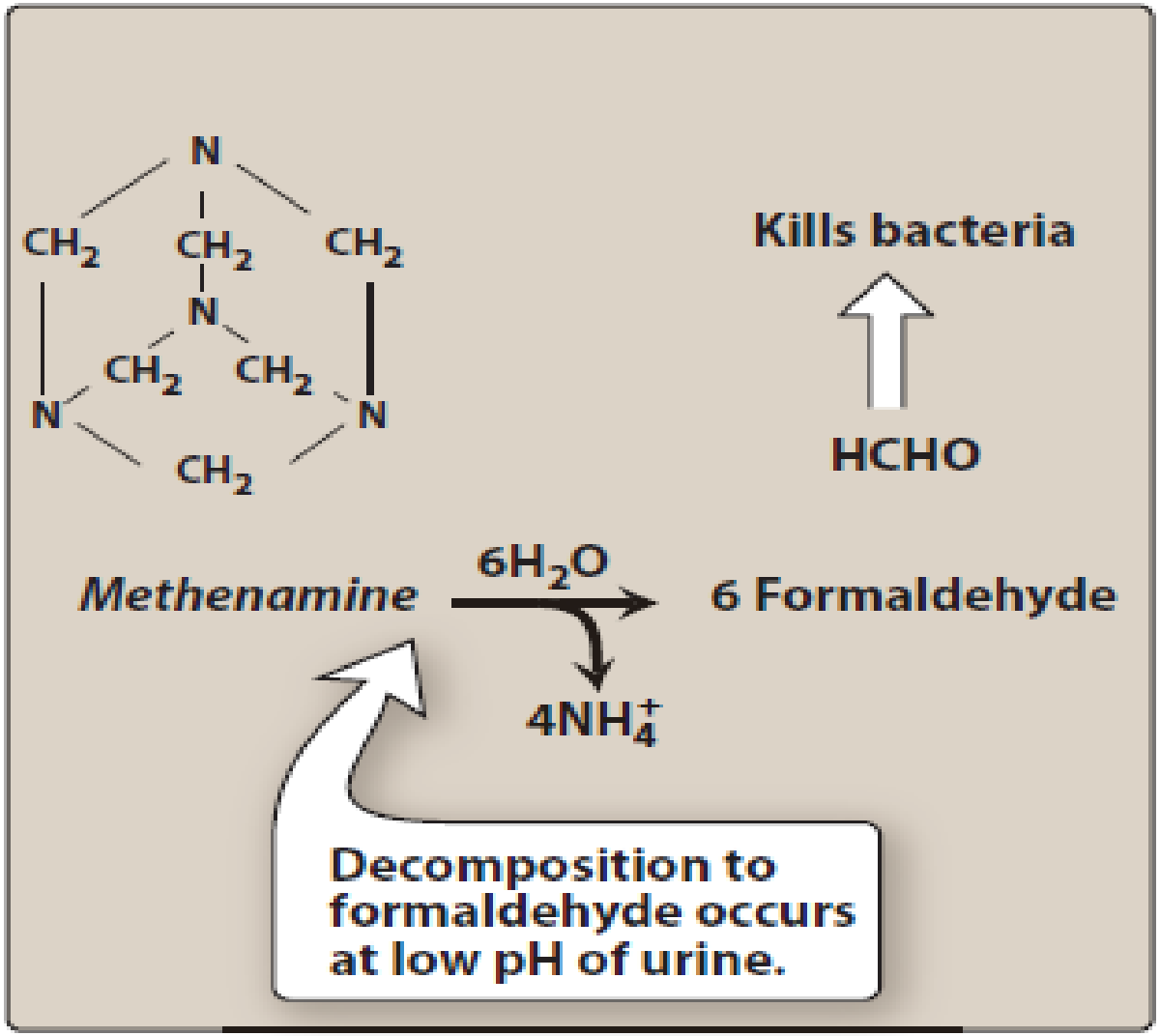
These drugs do not achieve antibacterial levels in the circulation, but because they are concentrated in the urine, microorganisms at that site can be effectively eradicated.

Methenamine

Mechanism of action: *Methenamine* decomposes at an acidic pH of 5.5 or less in the urine, thus producing formaldehyde, which acts locally and is toxic to most bacteria.

Bacteria do not develop resistance to formaldehyde, which is an advantage of this drug.

[Note: *Methenamine* is frequently formulated with a weak acid (for example, mandelic acid or hippuric acid) to keep the urine acidic. The urinary pH should be maintained below 6. Antacids, such as *sodium bicarbonate*, should be avoided


N
CH2
CH2
CH2
N
CH2
CH2
N
N
CH2
Kills bacteria
HCHO
Methenamine
6H2O
6 Formaldehyde
4NH4+
Decomposition to formaldehyde occurs at low pH of urine.

Antibacterial spectrum:

Methenamine is primarily used for chronic suppressive therapy to reduce the frequency of UTIs.

Routine use in patients with chronic urinary catheterization to reduce catheterassociated bacteriuria or catheter-associated UTI is not generally recommended.

Methenamine should not be used to treat upper UTIs (for example, pyelonephritis).

Urea-splitting bacteria that alkalinize the urine, such as Proteus species, are usually resistant to the action of *methenamine*.

Pharmacokinetics:

Methenamine is administered orally.

In addition to formaldehyde, ammonium ions are produced in the bladder.

Because the liver rapidly metabolizes ammonia to form urea, *methenamine* is contraindicated in patients with hepatic insufficiency, as ammonia can accumulate.

Methenamine is distributed throughout the body fluids, but no decomposition of the drug occurs at pH 7.4.

Thus, systemic toxicity does not occur, and the drug is eliminated in the urine.

Adverse effects:

The major side effect of *methenamine* is gastrointestinal distress,

at higher doses, albuminuria, hematuria, and rashes may develop. *Methenamine mandelate* is contraindicated in patients with renal insufficiency, because mandelic acid may precipitate.

[Note: Sulfonamides, such as *cotrimoxazole*, react with formaldehyde and must not be used concomitantly with *methenamine*.

The combination increases the risk of crystalluria and mutual antagonism.]

Nitrofurantoin

Nitrofurantoin sensitive bacteria reduce the drug to a highly active intermediate that inhibits various enzymes and damages bacterial DNA. useful against *E. coli*, but other common urinary tract gram-negative bacteria may be resistant.

Grampositive cocci (*S. saprophyticus*) are typically susceptible.

Hemolytic anemia may occur with *nitrofurantoin* use in patients with G6PD deficiency.

Other adverse effects include gastrointestinal, disturbances, acute pneumonitis, and neurologic problems. Interstitial pulmonary fibrosis has occurred in patients who take *nitrofurantoin* chronically.

The drug should not be used in patients with significant renal impairment or women who are 38 weeks or more pregnant.

Non-steroidal Anti-inflammatory Drugs (NSAIDS)

By
Dr. Samir AL-Shujairy

CONTENTS

- INTRODUCTION
- MECHANISM OF ACTION
- CLASSIFICATION
- THERAPEUTIC USES
- DOSES OF FEW DRUGS
- ADVERSE EFFECTS
- DENTAL CONSIDERATIONS

NSAIDs

- Non-steroidal anti-inflammatory drugs
- Large & chemically diverse group of drugs with the following properties :

- Analgesic
- Anti-inflammatory
- Antipyretic

NSAIDs : Mechanism of Action

- It inhibits cyclooxygenase (COX) enzymes, which is responsible for the formation of prostaglandins that promote pain & inflammation.

NSAIDs : Mechanism of Action

- Analgesic effect : Blocks the undesirable effects of prostaglandin which causes pain.
- Anti-inflammatory effect : Inhibit the leukotriene pathway or the prostaglandin pathway or both.
- Antipyretic effect : Inhibit prostaglandin E2 (dinoprostone) within the area of the brain that controls temperature

CLASSIFICATION

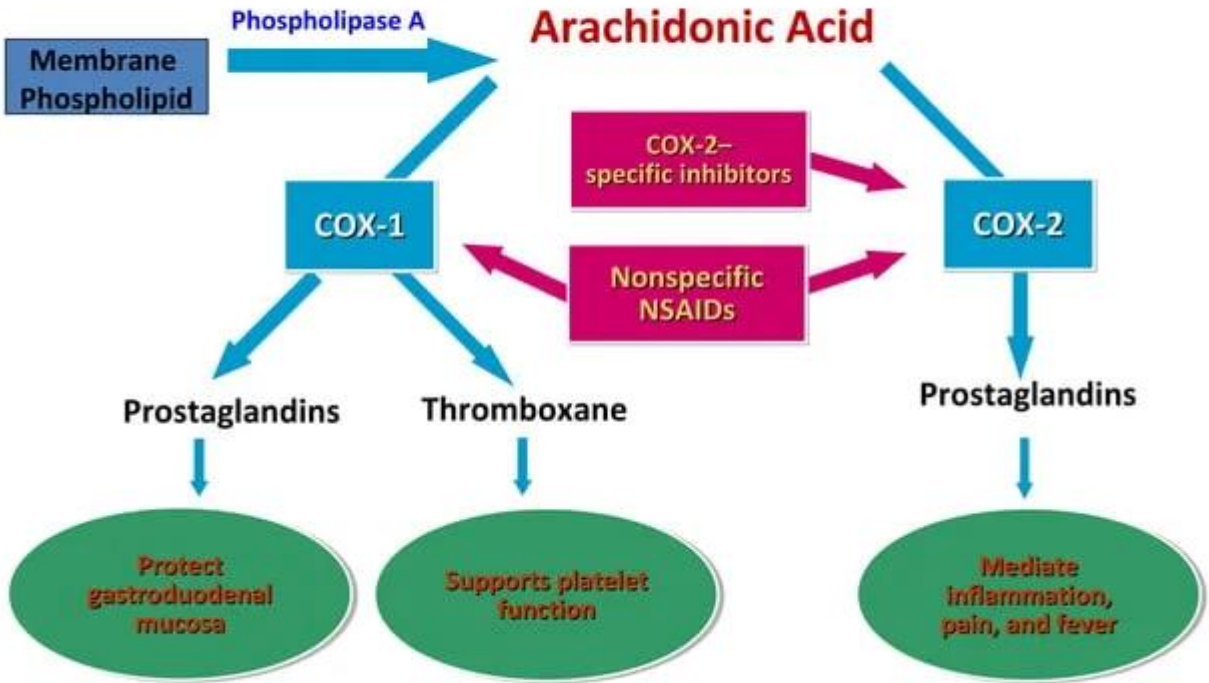
- A. Nonselective COX inhibitors (traditional NSAIDs) :

1. Salicylates : Aspirin
2. Propionic acid derivatives : Ibuprofen, Ketoprofen, Naproxen
3. Anthranilic acid derivative : Mephenamic acid
4. Aryl-acetic acid derivatives : Diclofenac, Aceclofenac
5. Oxicam derivatives : Piroxicam, Tenoxicam
6. Pyrrolo-pyrrole derivative : Ketorolac
7. Indole derivative : Indomethacin
8. Pyrazolone derivatives : Phenylbutazone, Oxyphenbutazone

NSAIDs and Prostaglandins

- All NSAIDs inhibit PG synthesis
- Prostaglandins, prostacyclines (PGI_2) and Tromboxane A_2 (TXA_2) are produced from Arachidonic acid
- The enzyme responsible is **prostaglandin synthase**, also known as **cycloxygenase** or **COX**
- COX in 2 isoforms: constitutive - COX-1 and inducible COX-2
- **COX-1** serves ***house keeping*** functions
- **COX-2** is generated by cytokines and others during inflammation (constitutive in brain and JG cells) – PG synthesis
- Most NSAIDs inhibit COX-1 and COX-2 non-selectively and inhibit PG synthesis
- Aspirin inhibits COX irreversibly – acetylation
- Other NSAIDs are competitive reversible inhibitors

NSAIDs and Prostaglandin



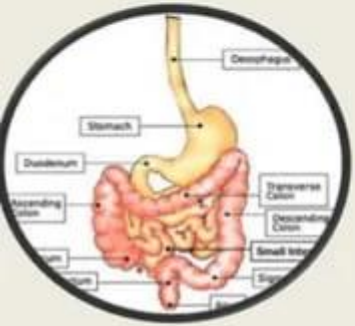
THERAPEUTIC USES

- Relief of mild to moderate pain
- Acute gout
- Various bone, joint & muscle pain
- Osteoarthritis
- Rheumatoid arthritis
- Juvenile rheumatoid arthritis
- Dysmenorrhea

Table 3-13 Selected Non-Steroidal Anti-Inflammatory Drugs for Mild to Moderate Nociceptive Pain[151,152]

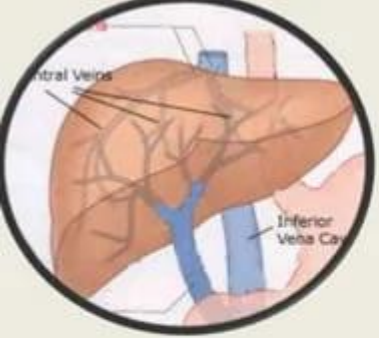
Generic Name	Celecoxib	Diclofenac	Ibuprofen	Naproxen	Naproxen Sodium
Brand name(s)	Celebrex	Voltaren	Motrin, Advil	Naprelan, Naprosyn	Aleve, Anaprox
Prescription status	Rx only	Rx only	Rx and OTC	Rx	Rx and OTC
Usual adult dosages*	200 mg q12h	50mg q12h	200–400 mg q4–6h	250 mg q6–8h or 500 mg q12h	275 mg q6–8h or 550 mg q12h
Maximum recommended daily dose	600 mg first day then 400 mg	200 mg	2400 mg	1250 mg first day, then 1000 mg	1375 mg first day, then 1100 mg
Notes	Less effective than full doses of naproxen or ibuprofen	Do not crush or chew	Available as OTC suspension (100 mg/5 mL)	Available as Rx suspension (125 mg/5 mL)	220 mg dose is available OTC

ADVERSE EFFECTS

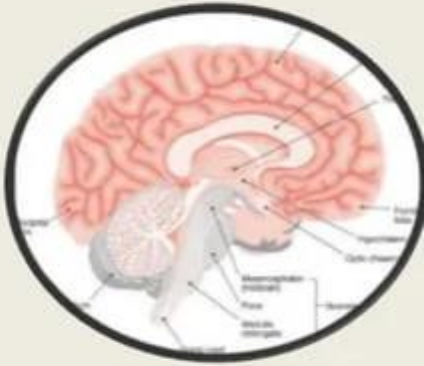


Gastric irritation, erosions, peptic ulceration, gastric bleeding/perforation, esophagitis

NA+ & water retention, chronic renal failure, interstitial nephritis, papillary necrosis (rare)



Raised transaminases, hepatic failure (rare)



Headache, mental confusion, behavioural disturbances, seizure precipitation

Bleeding, thrombocytopenia, hemolytic anemia, agranulocytosis

OTHERS

- Asthma exacerbation
- Nasal polyposis : Soft, painless, noncancerous growths on the lining of nasal passages or sinuses.
- Skin rashes
- Pruritus : Severe itching of the skin
- Angioedema : Rapid swelling of the dermis, subcutaneous tissue, mucosa & submucosal tissues.

DENTAL CONSIDERATIONS

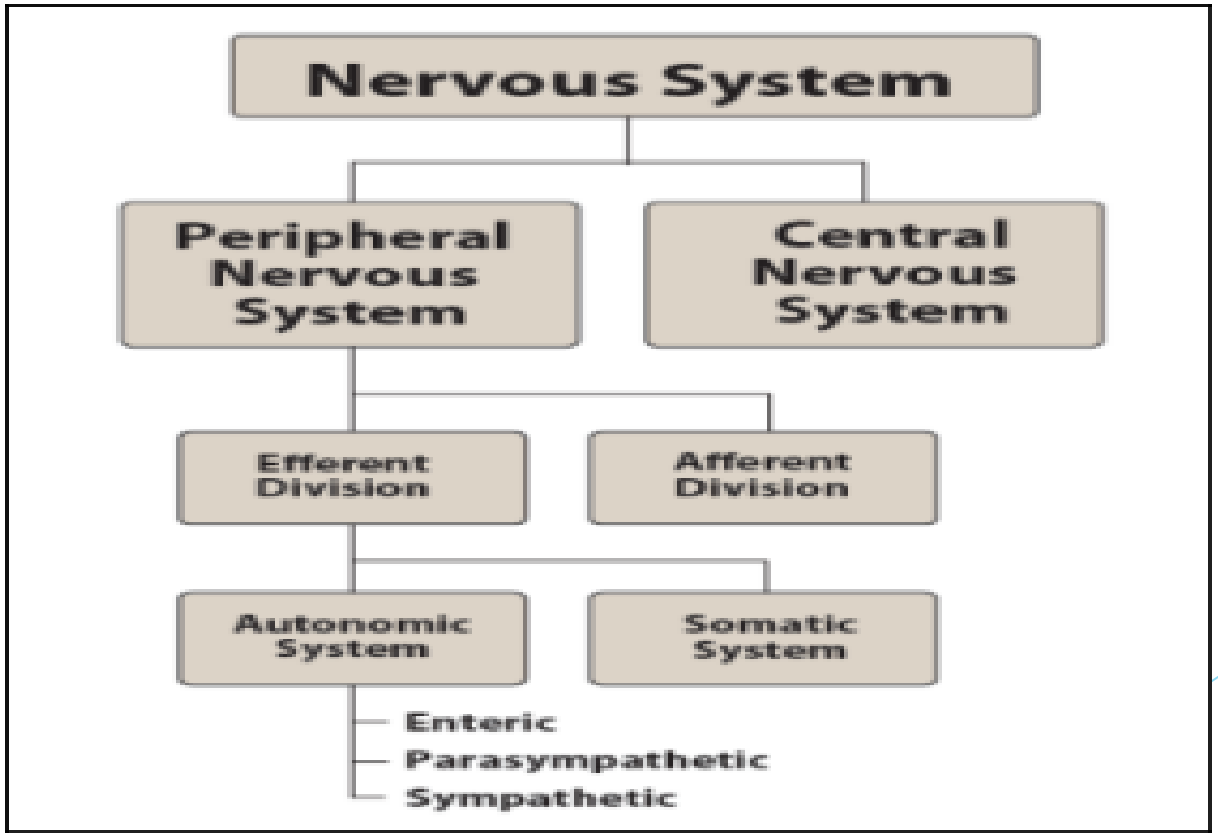
- If patient is allergic to any NSAID, you will have to avoid them.
- Paracetamol is the safest NSAID.
- Ibuprofen is contraindicated in asthma patients as it causes bronchoconstriction.
  - It is not recommended for pregnant or nursing women.
- If the patient is taking aspirin, then no surgery or even simple extraction should be done.
  - As it can lead to profuse bleeding because of its antiplatlet-action. Aspirin should be stopped before 7-10 days of any surgical procedure till 2-3 days after procedure.
  - Young children are highly susceptible to aspirin poisoning (therapeutic overdose).

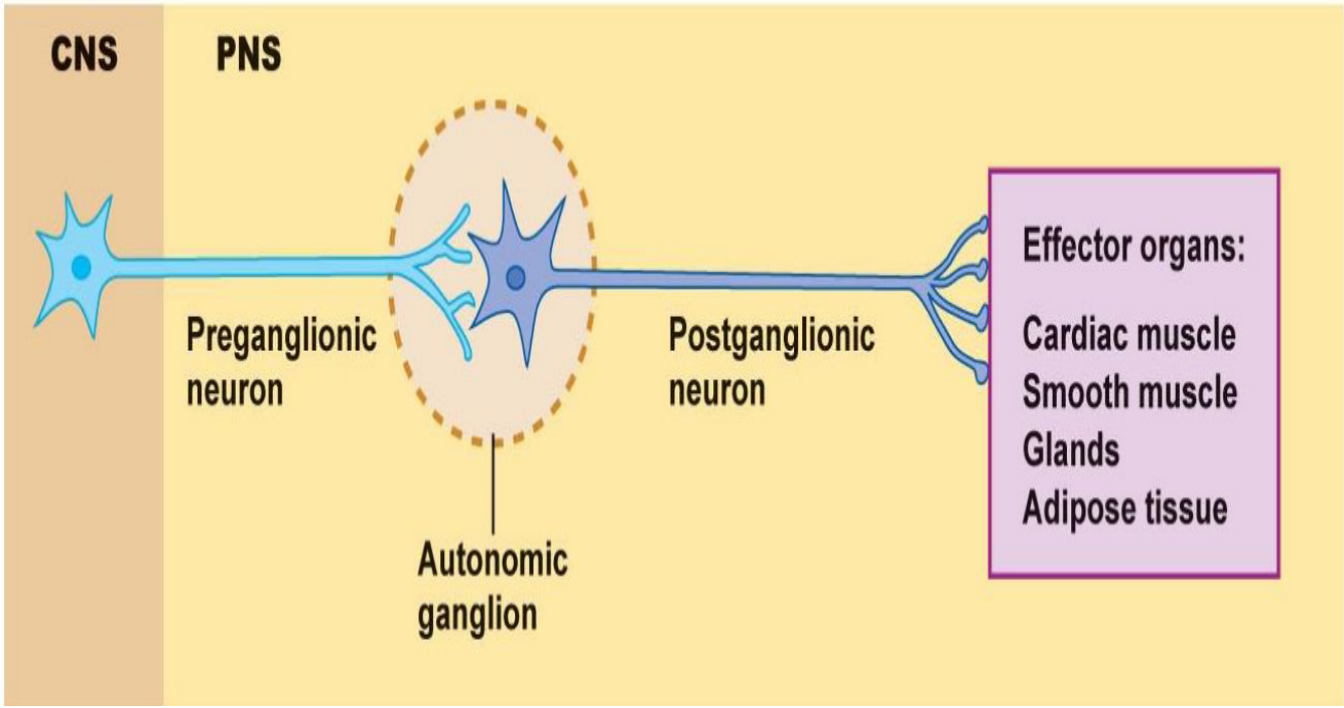
THANK YOU

The Autonomic Nervous System

LEC3

Nervous system (NS) can be defined as the system of cells, tissues and organs that regulates the body's responses to internal and external stimuli



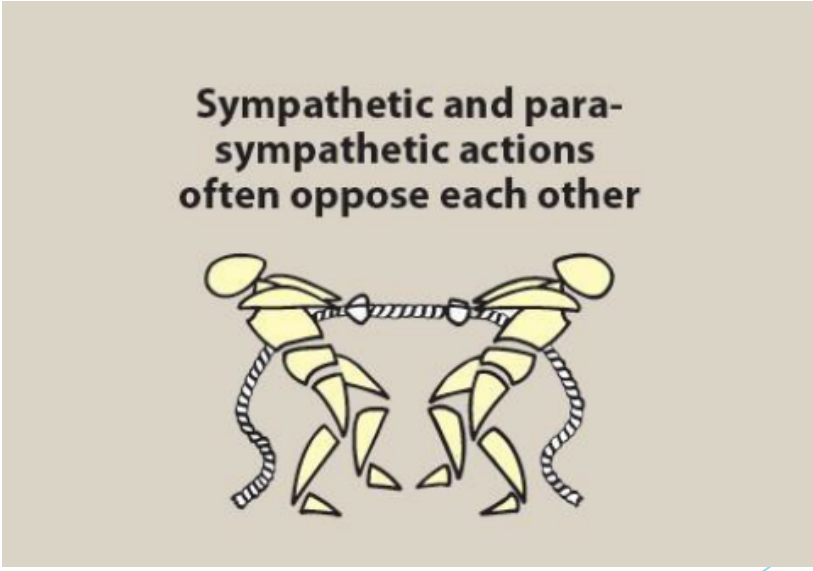

CNS
PNS
Preganglionic neuron
Autonomic ganglion
Postganglionic neuron
Effector organs:
Cardiac muscle
Smooth muscle
Glands
Adipose tissue

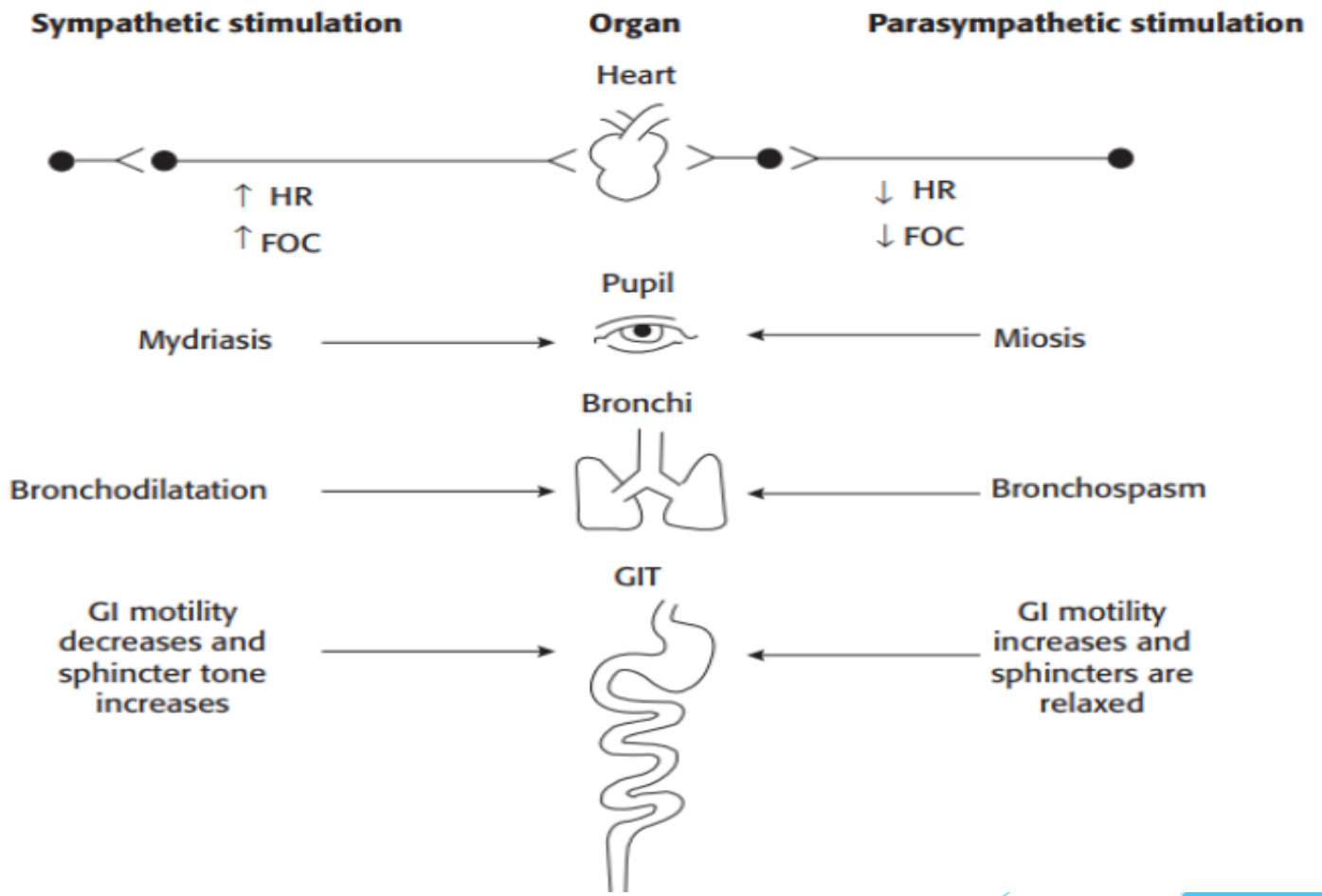
The efferent ANS is divided into:

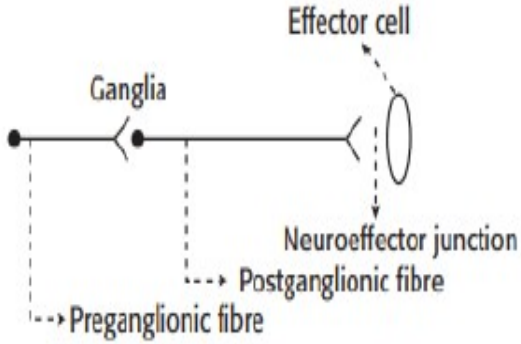
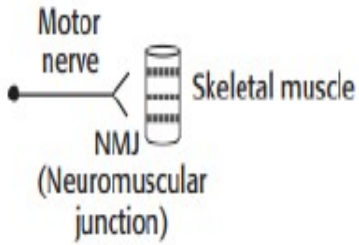
A- Autonomic system:

* the sympathetic and ** the parasympathetic nervous systems as well as *** the enteric nervous system, and

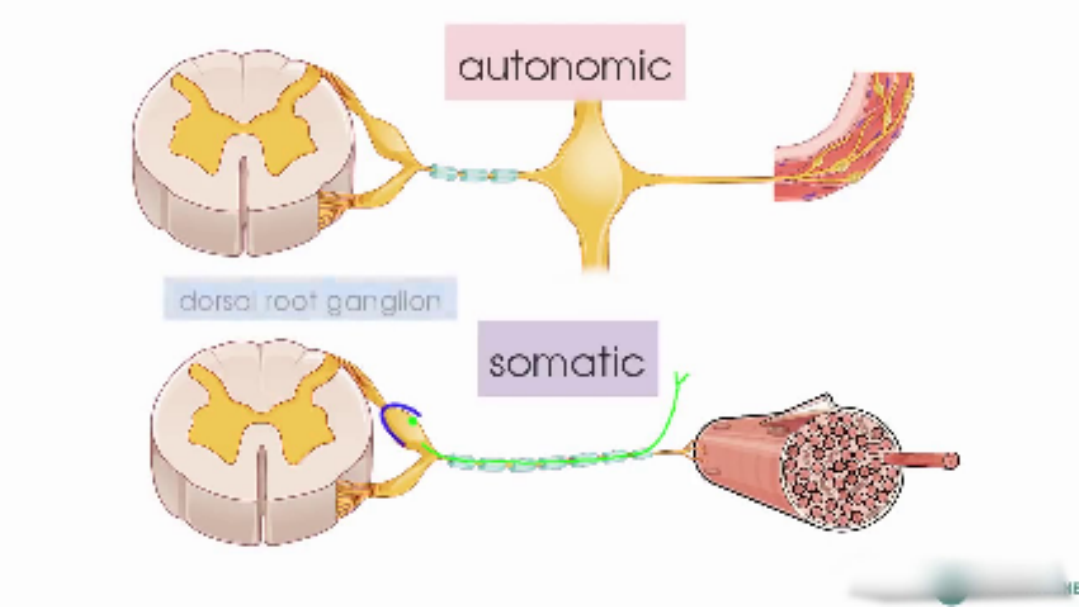
B- Somatic system.




Sympathetic stimulation
Organ
Parasympathetic stimulation
Heart
↑ HR
↑ FOC
↓ HR
↓ FOC
Pupil
Mydriasis
Miosis
Bronchi
Bronchodilatation
Bronchospasm
GIT
GI motility decreases and sphincter tone increases
GI motility increases and sphincters are relaxed

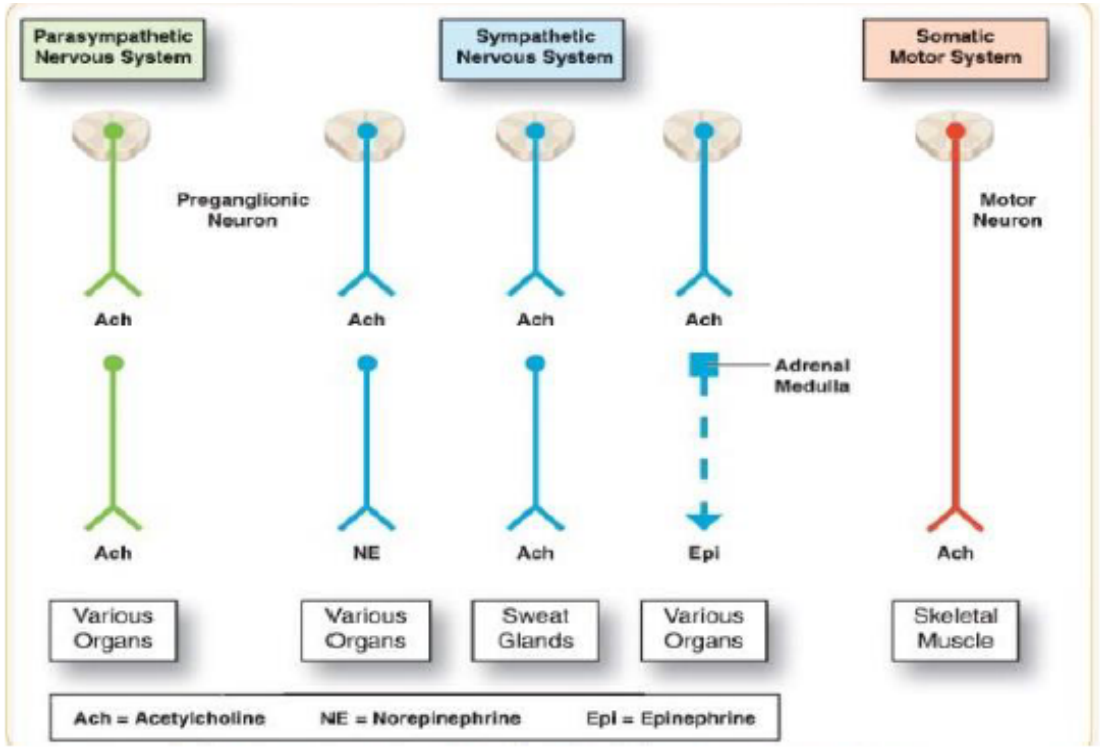
Autonomic Nervous System	Somatic Nervous System
Auto: self; *nomos*: governing; this system is involuntary and maintains homeostasis	Somatic nervous system is under voluntary control
Each autonomic fibre is made up of two neurons arranged in series	Each somatic fibre is made up of single motor neuron, which connects CNS to skeletal muscle
	
It innervates the heart, smooth muscles and exocrine glands	It innervates skeletal muscle
It controls visceral functions such as circulation, digestion, excretion, etc.	It controls skeletal muscle tone

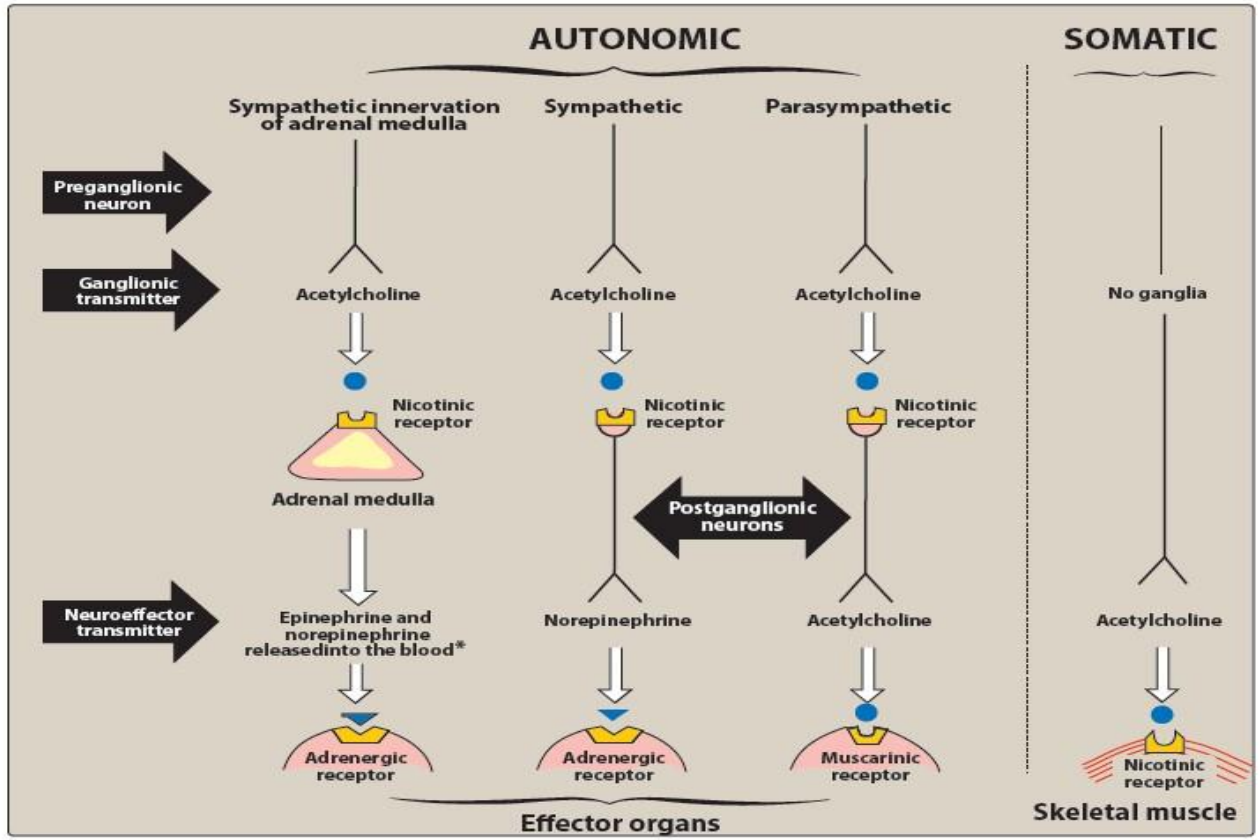
Somatic and autonomic reflex arc:
the autonomic reflex arc that affects the inner organs, and the somatic reflex arc that affects muscles



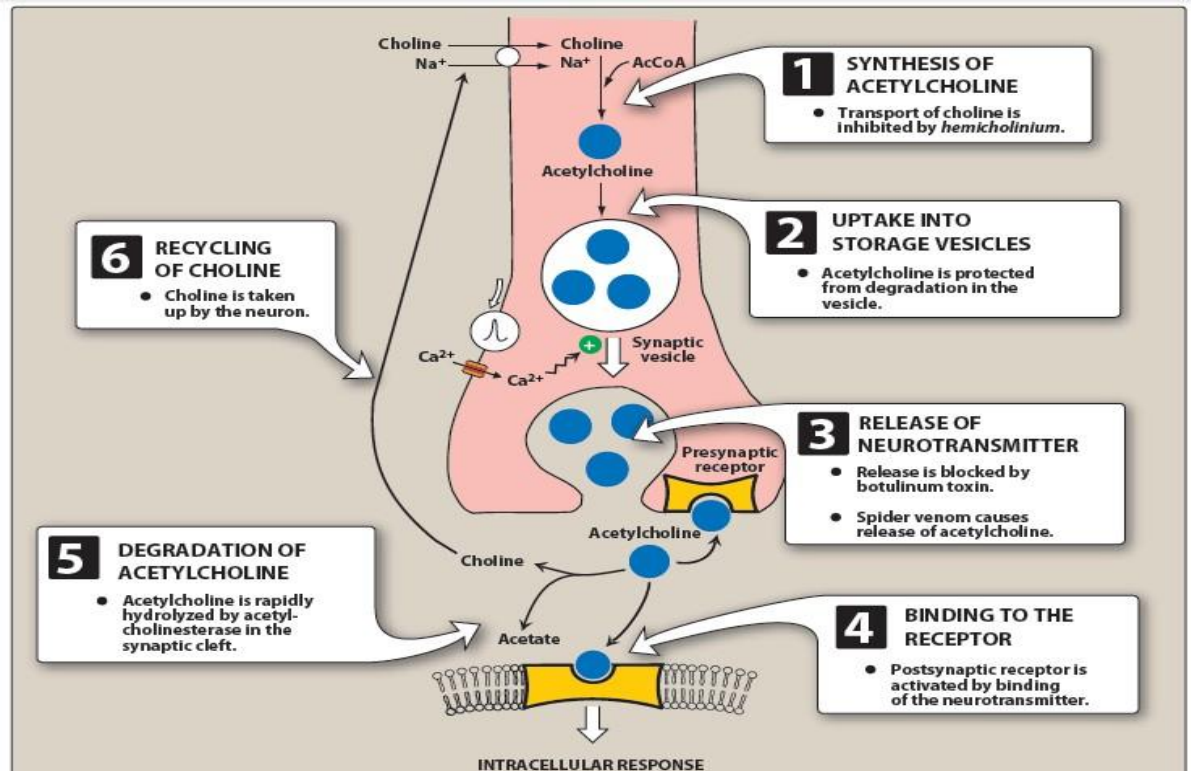
Neurotransmitters

Neurotransmission in the ANS is an example of the more general process of chemical signaling between cells using neurotransmitters. Neurotransmitters are specific chemical signals that are released from nerve terminals to establish the communication between nerve cells, and between nerve cells and effector organs.


Parasympathetic Nervous System
Sympathetic Nervous System
Somatic Motor System
Preganglionic Neuron
Motor Neuron
Ach
Ach
Ach
Ach
Adrenal Medulla
Ach
NE
Ach
Epi
Ach
Various Organs
Various Organs
Sweat Glands
Various Organs
Skeletal Muscle
Ach = Acetylcholine
NE = Norepinephrine
Epi = Epinephrine


AUTONOMIC
SOMATIC
Sympathetic innervation of adrenal medulla
Sympathetic
Parasympathetic
Preganglionic neuron
Ganglionic transmitter
Acetylcholine
Acetylcholine
Acetylcholine
No ganglia
Nicotinic receptor
Nicotinic receptor
Nicotinic receptor
Adrenal medulla
Postganglionic neurons
Neuroeffector transmitter
Epinephrine and norepinephrine releasedinto the blood*
Norepinephrine
Acetylcholine
Acetylcholine
Adrenergic receptor
Adrenergic receptor
Muscarinic receptor
Nicotinic receptor
Effector organs
Skeletal muscle

The Parasympathetic Nervous System: Cholinergic Agonists



CHOLINERGIC RECEPTORS (CHOLINOCEPTORS)

There are two families of cholinoceptors: muscarinic and nicotinic receptors.

CHOLINERGIC RECEPTORS (CHOLINOCEPTORS)

Cholinoceptors can be classified into two types: muscarinic and nicotinic receptors. They are different mainly in their affinities for agents that mimic the action of ACh (cholinomimetic agents).

1- Muscarinic receptors: It is one of the G protein–coupled receptors that have high affinity to bind with muscarine (an alkaloid that is present in certain poisonous mushrooms) and ACh but low affinity to bind with nicotine. Five sub-classes are recognised for this receptor family; however, only M1, M2, and M3 receptors have been functionally characterised.

a- Locations of muscarinic receptors:

b- Muscarinic agonists: *Pilocarpine* is an example of a nonselective muscarinic

b- Muscarinic agonists: *Pilocarpine* is an example of a nonselective muscarinic agonist used in clinical practice to treat xerostomia and glaucoma. Attempts are currently underway to develop muscarinic agonists and antagonists that are directed against specific receptor subtypes. M1 receptor agonists are being investigated for the treatment of Alzheimer's disease.

2- Nicotinic receptors

These receptors, in addition to binding ACh, also recognise nicotine but show only a weak affinity for muscarine. Nicotine at low concentration stimulates the receptor, whereas nicotine at high concentration blocks the receptor. The nicotinic receptor functions as a ligand-gated ion channel.

Location: Nicotinic receptors are located in the CNS, the adrenal medulla, autonomic ganglia, and the neuromuscular junction (NMJ) in skeletal muscles.

Those

LEC 4

1-DIRECT-ACTING CHOLINERGIC AGONISTS

Cholinergic agonists (also known as parasympathomimetics) mimic the

effects of ACh by binding directly to cholinoceptors. These agents may be

broadly classified into **two** groups:

i. **Choline esters**, which include ACh, and synthetic esters of choline,

such as **carbachol** and **bethanechol.**

ii. **Naturally occurring alkaloids**, such as **pilocarpine**.

Acetylcholine:

Acetylcholine is a quaternary ammonium compound that, ACh has both muscarinic and nicotinic activity. Its actions include:

1. Decrease in heart rate and cardiac output
2. Decrease in blood pressure
3. Other actions:

- In the gastrointestinal (GI) tract, acetylcholine increases salivary secretion and stimulates intestinal secretions and motility.
- It also enhances bronchiolar secretions.
- In the genitourinary tract, ACh increases the tone of the detrusor urinae muscle, causing expulsion of urine.
- In the eye, ACh causes miosis (marked constriction of the pupil).cannot penetrate membranes.

Therapeutic uses of direct-acting cholinergic agonists:

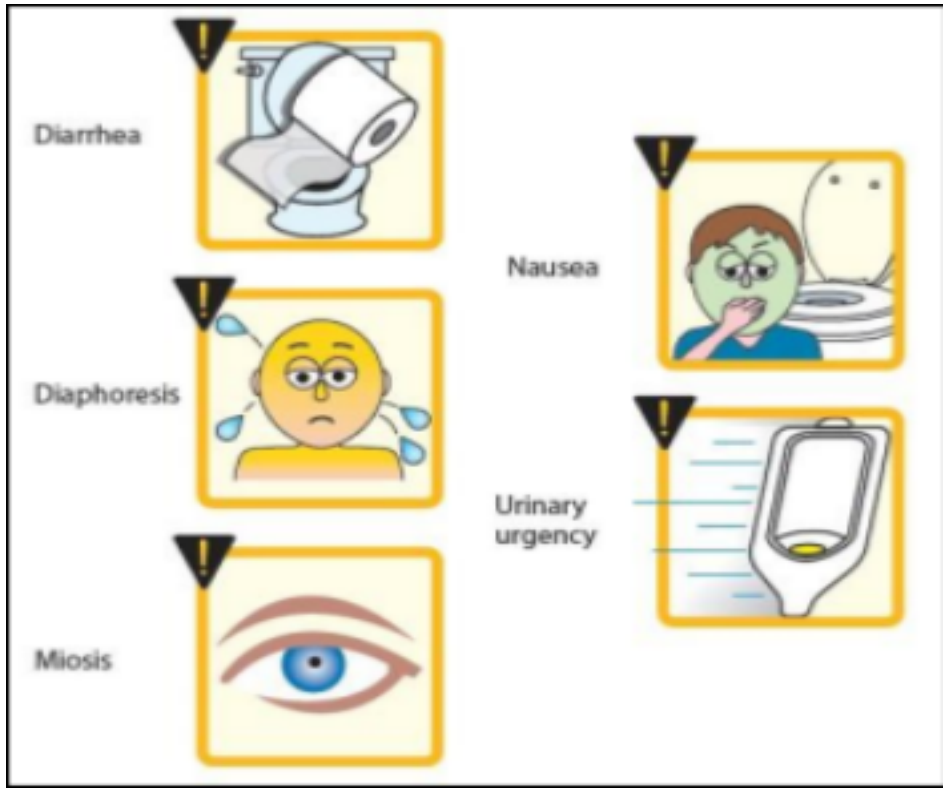
✔ ACh (1% solution) is instilled into the anterior chamber of the eye to produce miosis during ophthalmic surgery.

✔ bethanechol is used to stimulate the atonic bladder, particularly in postpartum or postoperative, nonobstructive urinary retention.

✔ Carbachol eye as a miotic agent to treat glaucoma by causing pupillary contraction and a decrease in intraocular pressure.

✔ Pilocarpine is used to treat glaucoma and is the drug of choice in the emergency lowering of intraocular pressure in glaucoma.

Adverse effects of Ach and other cholinergic agonists:



Adverse effects of Ach and other cholinergic agonists:

causes the effects of generalized cholinergic stimulation.

- Bronchospasm and increase secretions.
- GI: nausea, vomiting, and diarrhea.
- Miosis.
- Urinary urgency.
- Sweating (diaphoresis) and salivation.

- **Pilocarpine can enter the brain (because it's a tertiary amine (unionized)) and cause CNS disturbances. Poisoning with this agent is characterized by exaggeration of various parasympathetic effects.**

To counteract the poisoning effect of the **pilocarpine and Bethanechol, Parenteral atropine,** at doses that can cross the blood–brain barrier, is administered to counteract the toxicity of the cholinergic material.

2-INDIRECT-ACTING CHOLINERGIC AGONISTS (ANTICHOLINESTERASE AGENTS)

A-((REVERSIBLE))

ACh is uaually deactivated by the AChE (Acetylcholine esterase), which is an enzyme that specifically cleaves ACh to **acetate** and **choline.** It can be found at both pre- and postsynaptically in the nerve terminal where it is membrane bound.

Accordingly, inhibition of AchE can **indirectly** provide a cholinergic action by preventing the degradation of **ACh.** This results in an accumulation of **ACh in the synaptic space**. This process can be carried out by using the anticholinesterase agents or cholinesterase inhibitors. These drugs can provoke a response at all **cholinoceptors** in the body, including both muscarinic and nicotinic receptors of the ANS, as well as at the NMJ and in the brain.

Therapeutic uses of acetylcholinesterase inhibitors ((reversible))

***Edrophonium, pyridostigmine, and ambenonium:**

They are used in the diagnosis and management of **myasthenia gravis,** which is an autoimmune disease caused by antibodies to the nicotinic receptor at NMJs.

This causes their degradation, making fewer **receptors** available for interaction with the neurotransmitter.

***Physostigmine**

It increases intestinal and bladder motility, which serve as its therapeutic action in atony of either organ.

used to treat glaucoma, but **pilocarpine** is more effective.

as an **antidote** for drugs with anticholinergic actions (atropine).

***Neostigmine**

used to stimulate the bladder and GI tract.

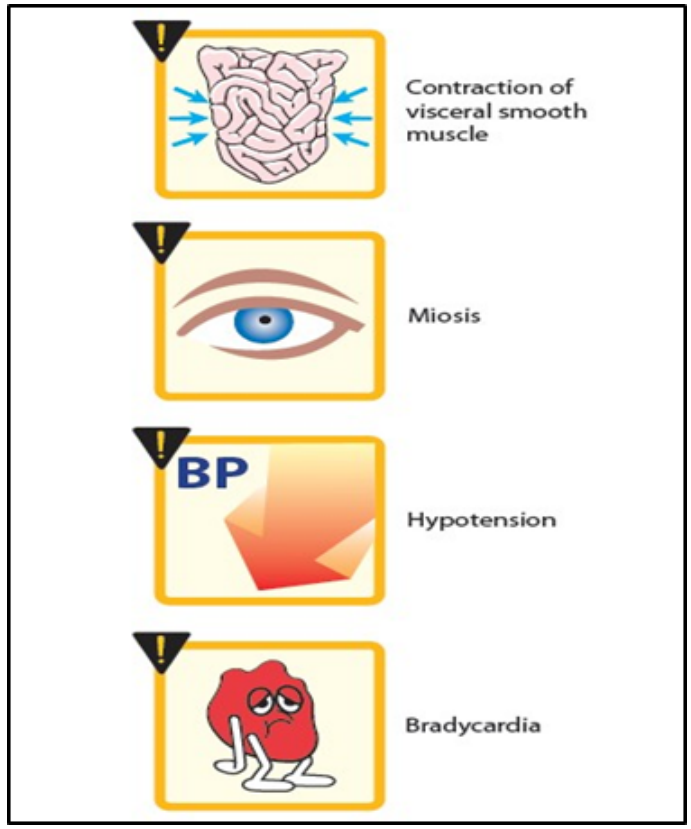
as an antidote for **tubocurarine** and other competitive neuromuscularblocking agents.

also used to treat **myasthenia gravis**.

Tacrine, donepezil, rivastigmine, and galantamine

Patients with **Alzheimer disease** have a deficiency of cholinergic neurons in the CNS. This observation led to the development of anticholinesterases as possible remedies for the loss of cognitive function. **Tacrine** was the **first** to become available, but it has been replaced by others because of its hepatotoxicity. Despite the ability of **donepezil, rivastigmine, and galantamine** to delay the progression of Alzheimer disease, none can stop its progression.

Adverse effects of acetylcholinesterase inhibitors (reversible):



II. INDIRECT-ACTING CHOLINERGIC AGONISTS: ANTICHOLINESTERASES

B- ((IRREVERSIBLE))

A number of synthetic organophosphate compounds have the capacity to bind covalently to AChE. The result is a **long-lasting** increase in ACh at all sites where it is released.

Many of these drugs are extremely toxic and were developed by the military as nerve agents. Related compounds, such ***as parathion***, are used as **insecticides.**

Therapeutic uses:

Echothiophate: An ophthalmic solution of the drug is applied topically to the eye for the chronic treatment of **glaucoma**.

Adverse effects: Actions include generalized cholinergic stimulation, **paralysis** of motor function (causing breathing difficulties), and **convulsions**.

3-Cholinergic Antagonists

Cholinergic antagonist is a general term for agents that bind to cholinoceptors (muscarinic or nicotinic) and prevent the effects of acetylcholine (ACh) and other cholinergic agonists.

ANTIMUSCARINIC AGENTS (ANTAGONISTS)

Atropine It is a **non**selective antagonist of muscarinic receptors.

Effects:

1-CNS: confusion/delirium.

2-Decrease GI motility and acid secretions.

3-Increase heart rate

4-Decrease body secretions like saliva, bronchial secretions, and sweat.

5-Mydriasis.

Therapeutic uses:

1-Atropin :

Poisoning:

a. In organophosphorous poisoning, atropine is the life-saving drug.

b. In some types of mushroom poisoning, atropine is the drug of choice .

c. Atropine is used in curare poisoning with **neostigmine** to counteract the muscarinic effects of neostigmine.

Treatment of **bradycardia**

In ophthalmology to cause **cycloplegia and mydriasis.**

Antimotility agent to treat **diarrhea**.

Side effects: Blurred vision, decrease secretions, hyperthermia,constipation, urinary retention, delirium, and hallucinations.

2-Scopolamine is another antagonists used for **motion sickness**.

3-Ipratropium used as inhaler to decrease bronchoconstriction and bronchial secretions in **COPD** (chronic obstructive pulmonary disease) **and asthma**

Nicotine(Ganglionic blockers):

although nicotine considers as an agonist at nicotinic receptors, but **at higher dose** it blocks the autonomic ganglia

Nicotine is a component of cigarette smoke, is a poison with many undesirable actions.
However, it can be used in a controlled way to help in giving up smoking.
It is found in more than one pharmaceutical dosage forms like sublingual tablets, lozenges and as chewing gum.

NICOTINIC AGONISTS*

Succinylcholine: Binds to Nm receptors, causing their channels to open and the membrane to **depolarize**. It is **not** inactivated by AChE, so prolonged **depolarization** occurs. This leads to paralysis of the muscles. Thus, it is used to induce paralysis for **brief** surgical procedures.

ANTINICOTINIC AGENTS (ANTAGONISTS)*

They are competitive antagonists of Nm receptors. They cause **nondepolarizing** blockage which results in skeletal muscle paralysis. They are used to induce paralysis for surgical procedures.
For example:
Tubocurarine (Curare) is a toxic alkaloid that had been used as a source of arrow poison by South American natives to hunt animals, by providing skeletal muscle relaxation (anesthetic effect).

Drugs that Inhibit Cell Wall Synthesis

Penicillins

Cephalosporins

Vancomycin

- Some antimicrobial drugs selectively interfere with synthesis of the bacterial cell wall

- The cell wall is composed of a **polymer** called **peptidoglycan** that consists of **glycan** units joined to each other by **peptide cross-links**.

- They have **little or no effect on bacteria** that are **not growing and dividing.**

PENICILLINS

Amoxicillin AMOXIL
Ampicillin PRINCIPEN
Dicloxacillin DYNAPEN
Nafcillin
Oxacillin
Penicillin G PFIZERPEN
Penicillin V
Piperacillin
Ticarcillin

CEPHALOSPORINS

Cefaclor CECLOR
Cefadroxil DURACEF
Cefazolin KEFZOL
Cefdinir OMNICEF
Cefepime MAXIPIME
Cefixime SUPRAX
Cefotaxime CLAFORAN
Cefotetan CEFOTAN
Cefoxitin MEFOXIN
Cefprozil CEFZIL
Ceftaroline TEFLARO
Ceftazidime FORTAZ
Ceftibuten CEDAX
Ceftizoxime CEFIZOX
Ceftriaxone ROCEPHIN
Cefuroxime CEFTIN
Cephalexin KEFLEX

CARBAPENEMS

Doripenem DORIBAX
Ertapenem INVANZ
Imipenem/cilastatin PRIMAXIN
Meropenem MERREM

MONOBACTAMS

Aztreonam AZACTAM

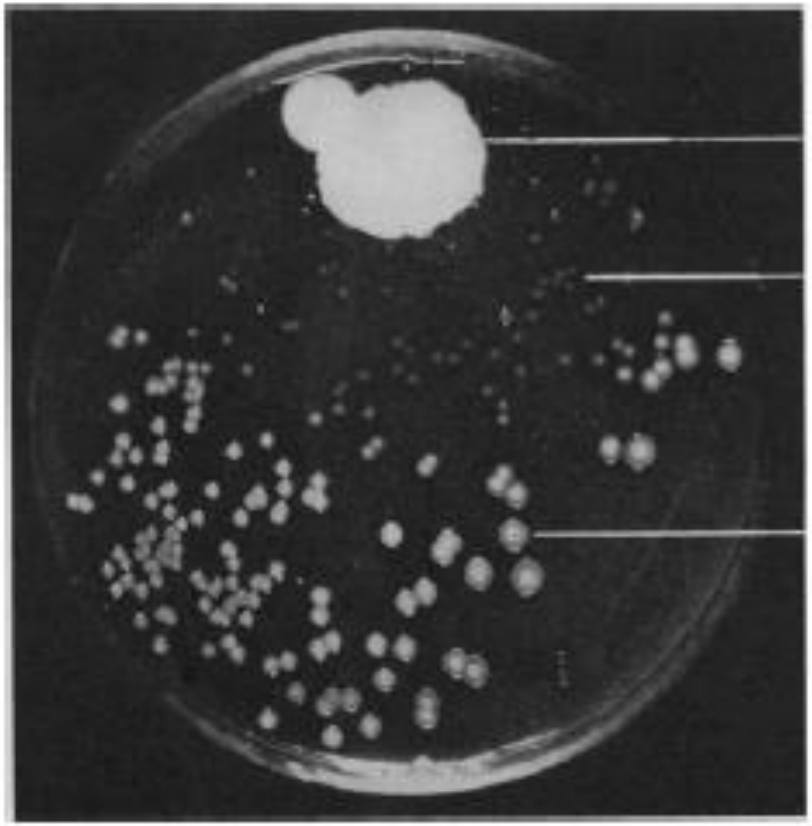
β-LACTAMASE INHIBITOR + ANTIBIOTIC COMBINATIONS

Clavulanic acid + amoxicillin AUGMENTIN
Clavulanic acid + ticarcillin TIMENTIN
Sulbactam + ampicillin UNASYN
Tazobactam + piperacillin ZOSYN

OTHER ANTIBIOTICS

Colistin COLOMYCIN, COLY-MYCIN M
Daptomycin CUBICIN
Fosfomycin MONUROL
Polymyxin B AEROSPORIN
Telavancin VIBATIV
Vancomycin VANCOCIN

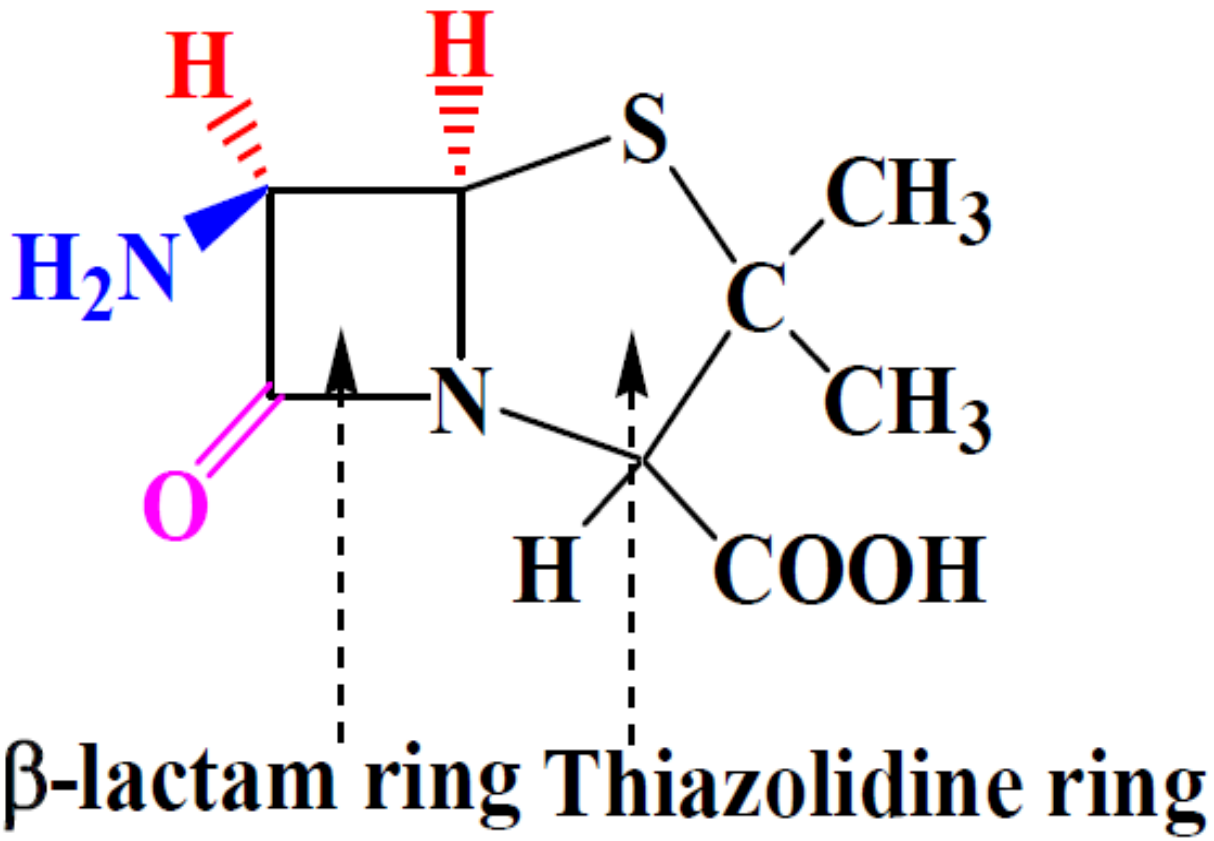
Accidental discovery of penicillin



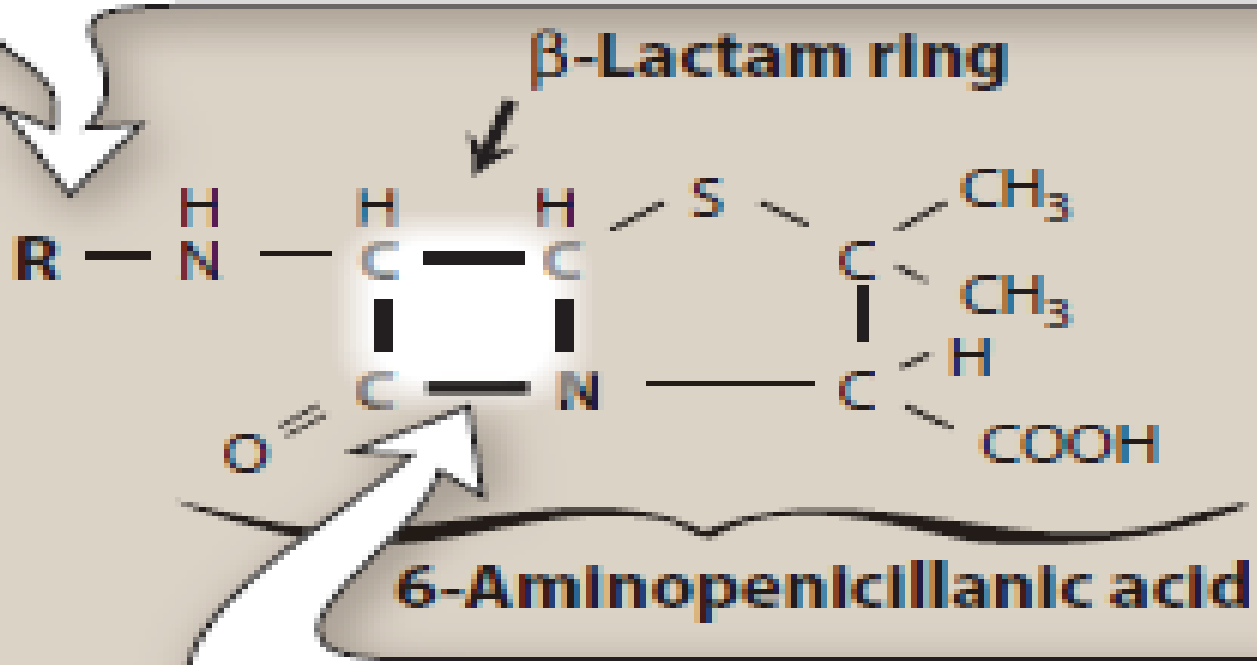
Penicillins

- Penicillin G was the first penicillin in 1942
- Advantages compared to sulfonamides
  - Much greater potency
  - Much less toxicity
  - Effective against organisms that were resistant to sulfonamides
  - Effective in wounds and purulent lesions

6-Aminopenicillanic Acid



Nature of the R group determines the drug's stability to enzymatic or acidic hydrolysis and affects its antibacterial spectrum.



6-Aminopenicillanic acid

Site of hydrolysis by bacterial penicillinase or by acid.

A. Mechanism of action of Penicillins

The penicillins **interfere with the last step of bacterial cell wall synthesis (transpeptidation or cross-linkage)**: resulting in

1. The osmotically less stable membrane.
2. Cell lysis can then occur.
3. osmotic pressure or activation of autolysins. These drugs are

bactericidal and work **in a time-dependent**.

Penicillins are only effective against rapidly growing organisms that synthesize a peptidoglycan cell wall.

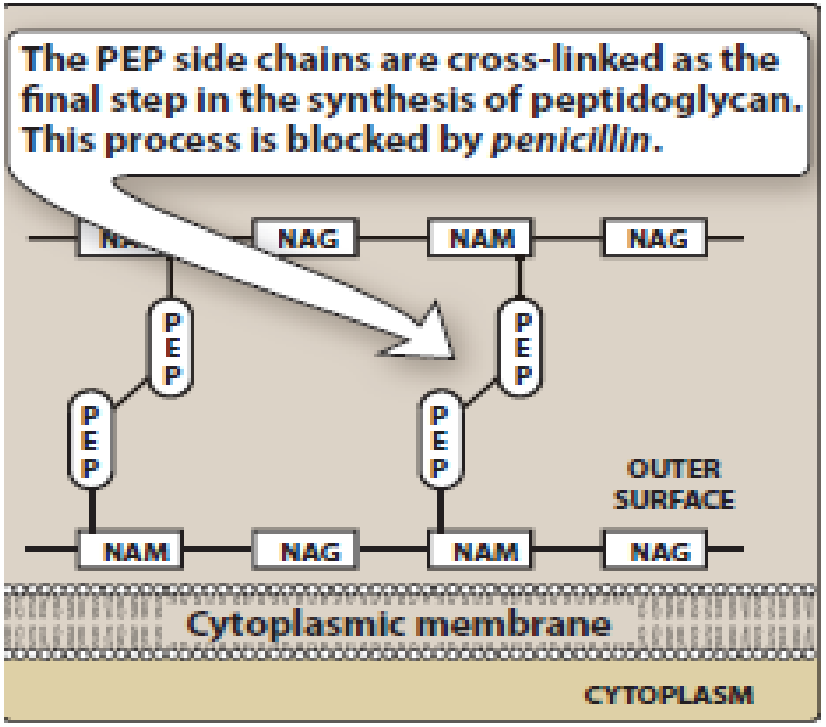
Consequently, they **are inactive** against organisms devoid of this structure, such as **mycobacteria, protozoa, fungi, and viruses.**

1. Penicillin-binding proteins:

1. Penicillin **inactivate** numerous proteins on the bacterial cell membrane.
2. penicillin-binding proteins (PBPs) are bacterial enzymes involved in the synthesis of the cell wall and in the maintenance of the morphologic features of the bacterium.
3. **Antibiotics not only prevent cell wall synthesis but also lead to morphologic changes or lysis of susceptible bacteria.**
4. **Alterations** in some PBPs provide the organism with resistance to the penicillins. [e.g.: *Methicillin* resistant *Staphylococcus aureus* (MRSA)

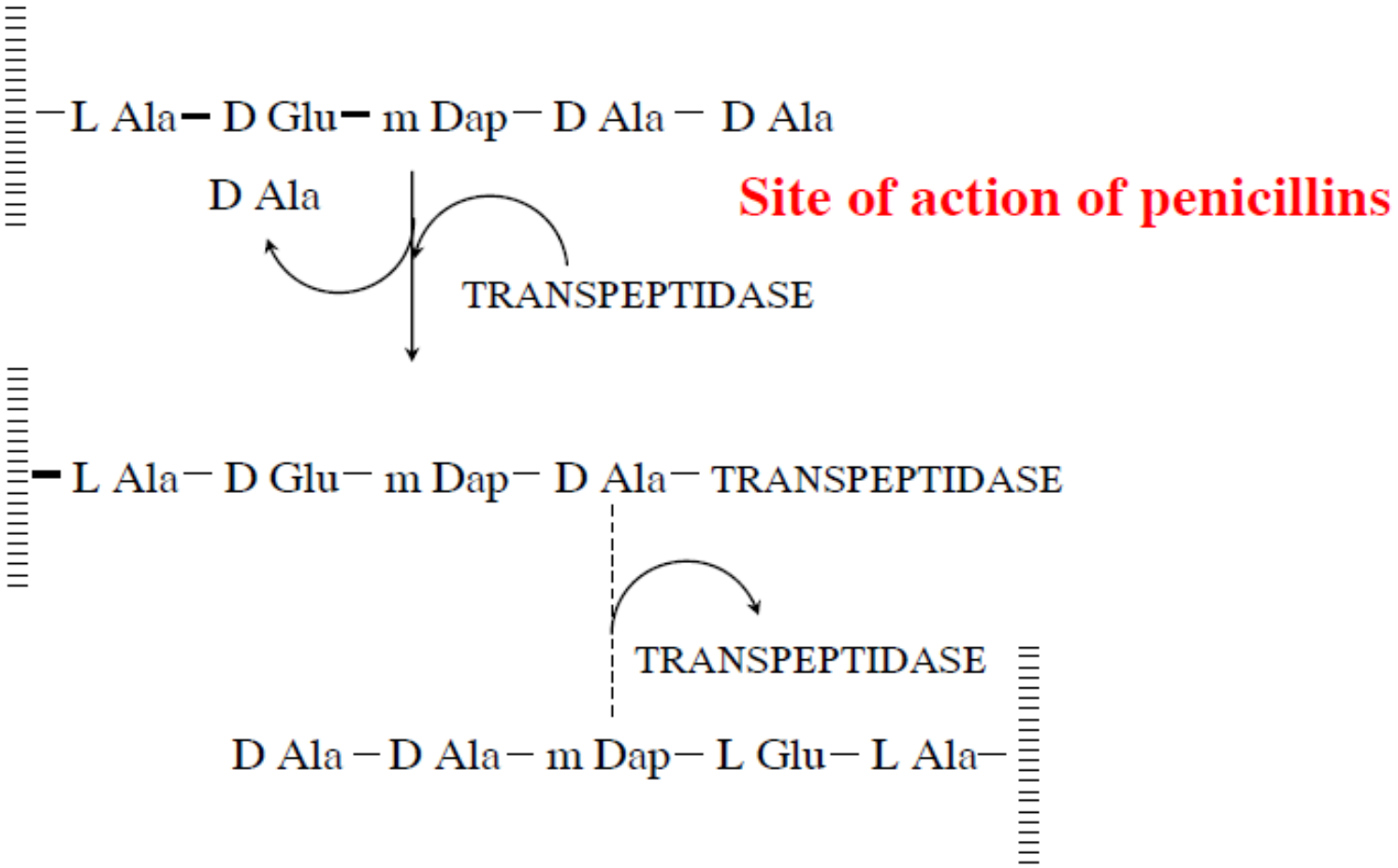
2. Inhibition of transpeptidase:

1. PBPs catalyze formation of the cross-linkages between peptidoglycan chains.
2. **Penicillins inhibit this transpeptidase-catalyzed reaction, thus hindering the formation of cross-links essential for cell wall integrity.**

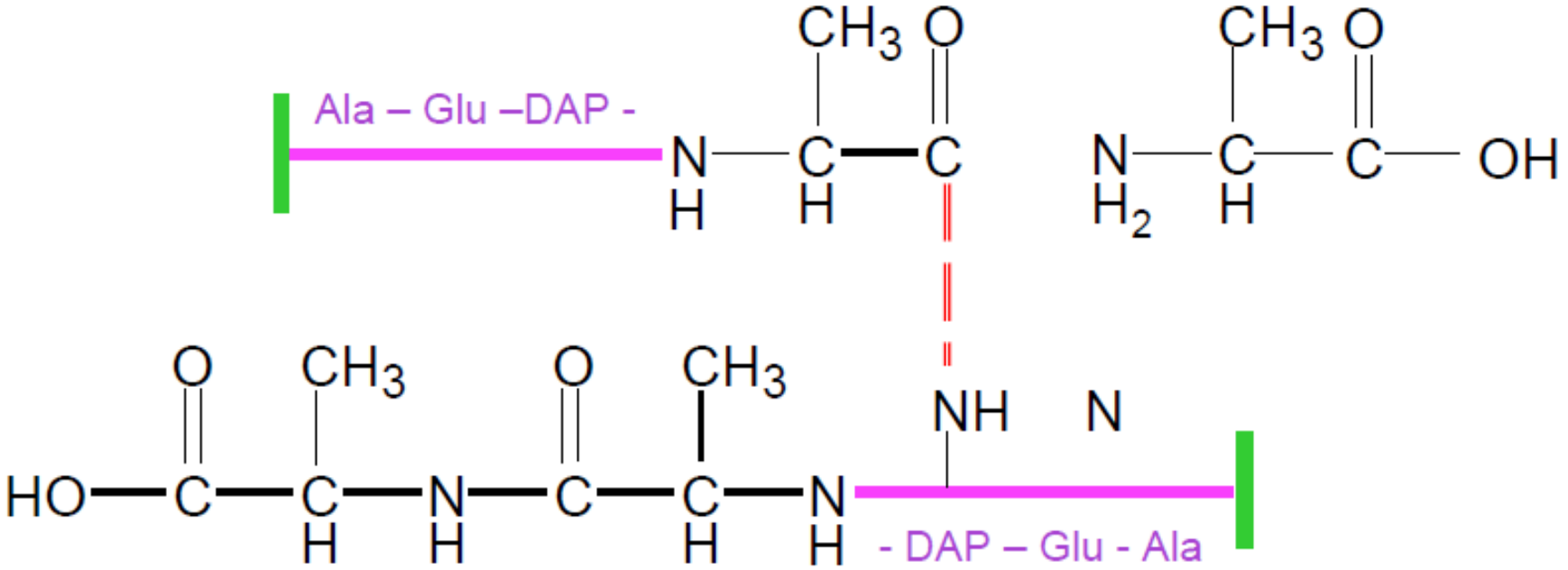


Bacterial cell wall of gram-positive bacteria.
(NAM = *N*-acetylmuramic acid;
NAG = *N*-acetylglucosamine;
PEP = cross-linking peptide.)

Peptidoglycan Cross Linking



Peptidoglycan Cross Linking



glycan (N acetyl glucosamine-N acetyl muramic acid)$_n$ —

free amino group of DAP (m-diaminopimelic acid) — NH_2

cross link —

3. Production of autolysins:

Many bacteria, **gram positive** cocci, produce degradative enzymes (autolysins) that participate in the normal remodeling of the bacterial cell wall.

In the presence of a penicillin, the degradative action of the autolysins proceeds in the absence of cell wall synthesis.

Thus, the antibacterial effect of a penicillin is the result of both inhibition of cell wall synthesis and destruction of the existing cell wall by autolysins.

B. Antibacterial spectrum

1. Natural penicillins:

- **Natural penicillins** (***penicillin G*** and ***penicillin V***) are obtained from fermentations of the fungus ***Penicillium chrysogenum***.
- **Semisynthetic penicillins**, such as ***amoxicillin*** and ***ampicillin***

penicillin remains the drug of choice for the treatment of gas gangrene (***Clostridium perfringens***)

Penicillin V similar spectrum to that of *penicillin G*, but it is not used for treatment of **bacteremia because of its poor oral absorption.**

Penicillin V is more acid stable than ***penicillin G***

2. Antistaphylococcal penicillins:

Methicillin, nafcillin, oxacillin ,and dicloxacillin **are β-lactamase (penicillinase)-resistant penicillins**. Their use is restricted to the treatment of infections caused by penicillinase-producing staphylococci, including ***methicillin*** **sensitive** ***Staphylococcus aureus*** (MSSA).

3. Extended-spectrum penicillins:

- ***Ampicillin* and *amoxicillin*** have an antibacterial spectrum similar to that of *penicillin G* but are more effective against gr -ve bacilli .
- *Ampicillin* (with or without the addition of *gentamicin*) is the drug of choice for the gram-positive bacillus *Listeria monocytogenes* and susceptible enterococcal species.
- These extended-spectrum agents are also **widely used in the treatment of respiratory infections**

- Formulation with a **β-lactamase inhibitor, such as *clavulanic acid* or *sulbactam*, protects *amoxicillin* or *ampicillin*, respectively, from enzymatic hydrolysis** and extends their antimicrobial spectra. For example, **without the β-lactamase inhibitor, MSSA is resistant to *ampicillin* and *amoxicillin*.**

4. Antipseudomonal penicillins:

- ***Piperacillin* and *ticarcillin*** are called **antipseudomonal penicillins** because of their activity against ***Pseudomonas aeruginosa***. These agents are available in **parenteral** formulations only.

- ***Piperacillin*** is the most potent of these antibiotics. **They are effective against many gram-negative bacilli, but not against *Klebsiella* because of its constitutive penicillinase.**

Mechanism of resistance

Microbial resistance to penicillins is caused by four factors:

1- Production of β-lactamases (penicillinases).

2- Lack of penicillin-binding proteins or decreased affinity of penicillin-binding protein for β-lactam antibiotic receptors or impermeability of cell envelope.

3- Failure of activation of autolytic enzymes in the cell wall (tolerance).

4- Cell wall-deficient (L) forms or mycoplasmas, which do not synthesize peptidoglycans.

1. β-Lactamase activity:

This family of enzymes hydrolyzes the cyclic amide bond of the β-lactam ring, which results in loss of bactericidal activity. They are the major cause of resistance to the penicillins and are an increasing problem.

produced by the bacterial chromosome or, more commonly, are acquired by the transfer of plasmids. Some of the β-lactam antibiotics are poor substrates for β-lactamases and resist hydrolysis, thus retaining their activity against β-lactamase–producing organisms. [Note: Certain organisms may have chromosome-associated β-lactamases that are inducible by β-lactam antibiotics (for example, second and third generation cephalosporins).] **Gram-positive organisms secrete β-lactamases extracellularly, whereas gram-negative bacteria inactivate β-lactam drugs in the periplasmic space**

2. Decreased permeability to the drug:

Decreased penetration of the antibiotic through the outer cell membrane of the bacteria prevents the drug from reaching the target PBPs. The presence of an efflux pump can also reduce the amount of intracellular drug (for example, *Klebsiella pneumoniae*).

3. Altered PBPs:

Modified PBPs have a lower affinity for β-lactam antibiotics, requiring clinically unattainable concentrations of the drug to effect inhibition of bacterial growth.

D. Pharmacokinetics

1. Administration:

a. Routes of administration:

b. Depot forms: *Procaine penicillin G* and *benzathine penicillin G* are administered IM and serve as depot forms. They are slowly absorbed into the circulation and persist at low levels over a long time period.

2. Absorption:

3. Distribution: The β-lactam antibiotics **distribute** well throughout the body.

- All the penicillins cross the placental barrier, but none to have teratogenic effects.
- However, **penetration** into bone or cerebrospinal fluid (CSF) is **insufficient** for therapy unless **these sites are inflamed**, Inflamed meninges are more permeable to the penicillins, resulting in an increased ratio of the drug in the CSF compared to the serum.
- Penicillin levels in the prostate are insufficient to be effective against infections.

4. Metabolism:

5. Excretion: The primary route of excretion is through (**tubular**) **secretory system** of the kidney as well as by **glomerular filtration**. Patients with **impaired renal** function must have dosage regimens adjusted.

Nafcillin **and** ***oxacillin*** are exceptions to the rule. They are primarily metabolized in the liver and do not require dose adjustment for renal insufficiency.

Probenecid inhibits the secretion of penicillins by competing for active tubular secretion by the organic acid transporter and, thus, can increase blood levels.

The penicillins are also excreted in breast milk.

E. Adverse reactions

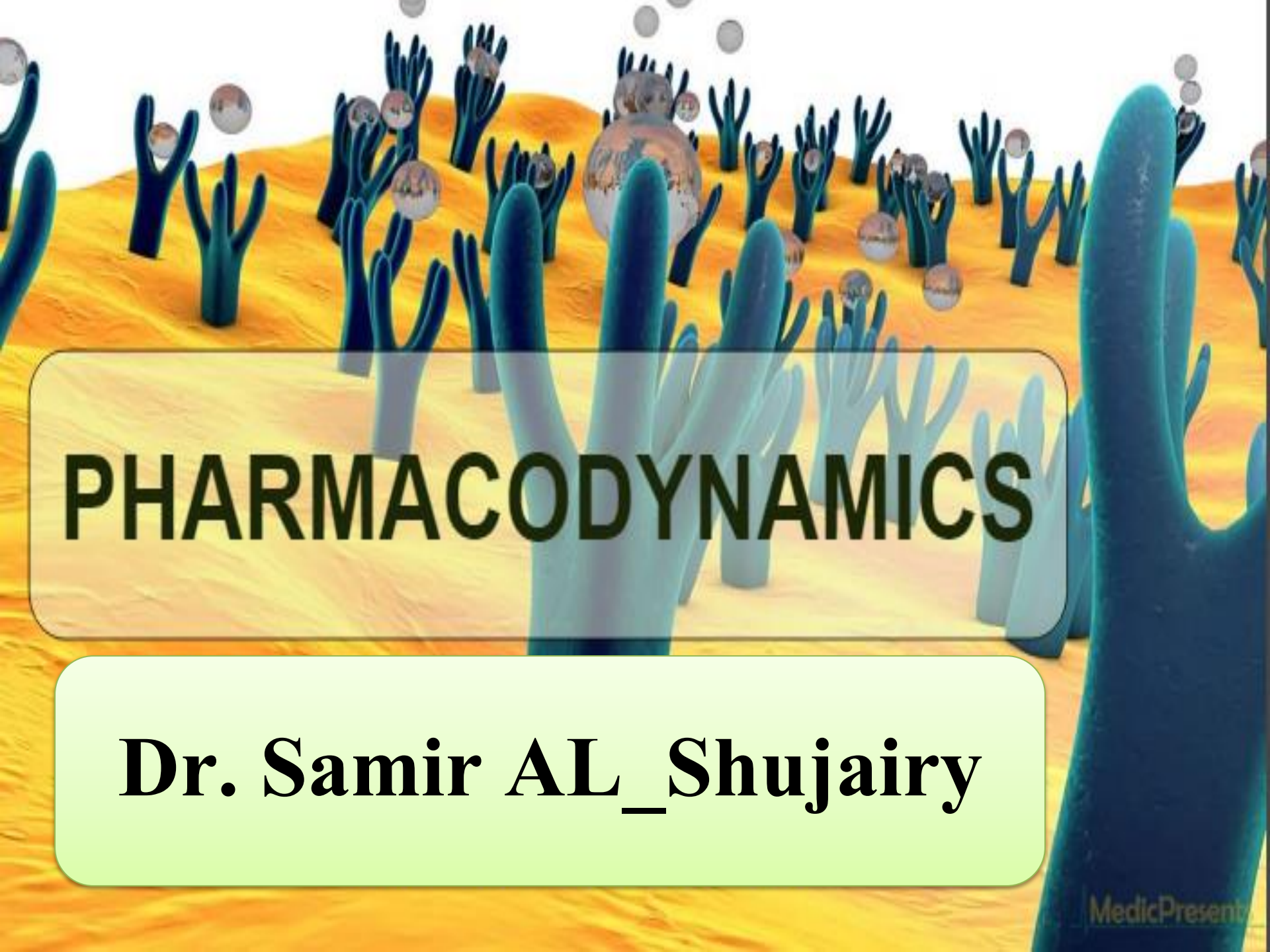
1. **Hypersensitivity:** Approximately 5% of patients have some kind of reaction, ranging from rashes to angioedema (marked swelling of the lips, tongue) and anaphylaxis.

2. Diarrhea: Diarrhea is a common problem that is caused by a disruption of the normal balance of intestinal microorganisms.

3. Nephritis: Penicillins, particularly *methicillin*, have the potential to cause acute interstitial nephritis. [*Methicillin* is therefore no longer used clinically.]

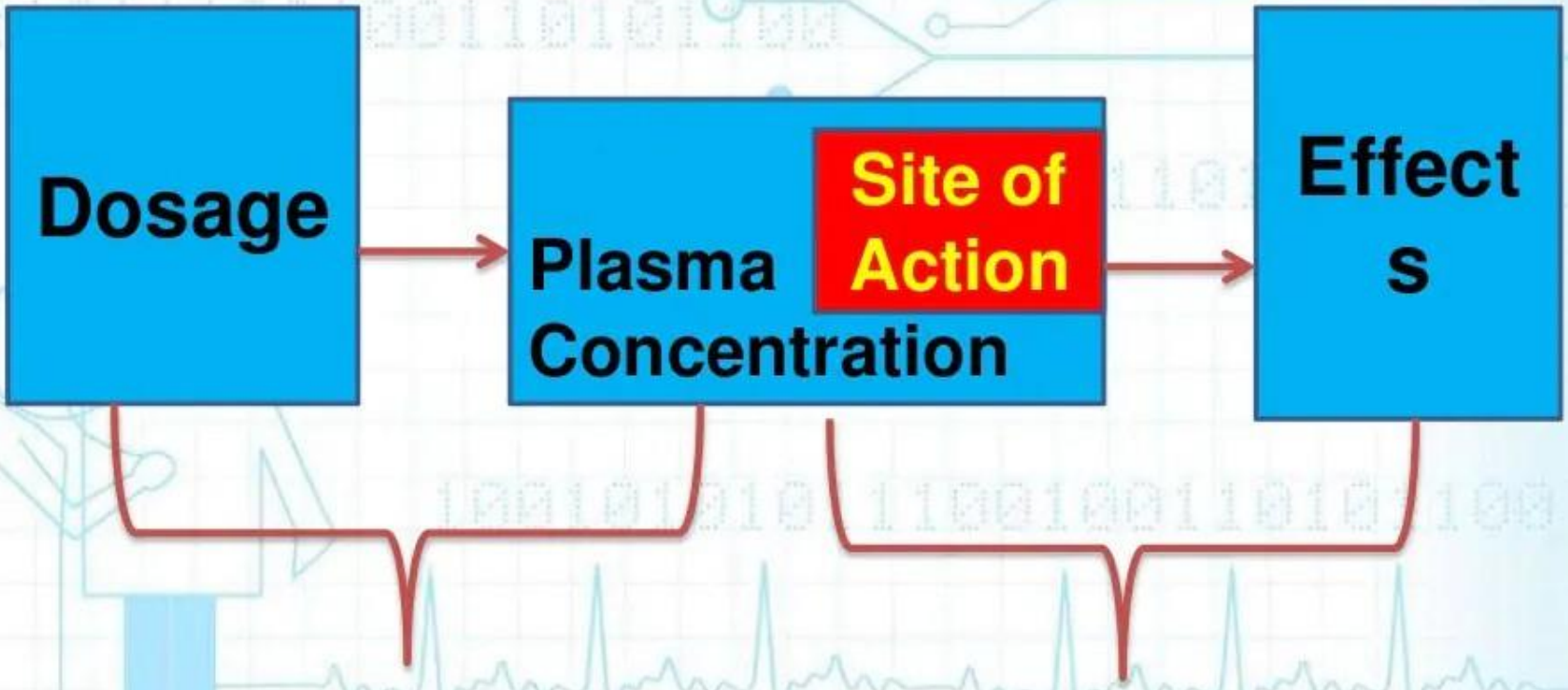
4. Neurotoxicity: The penicillins are irritating to neuronal tissue, and they can provoke seizures if injected intrathecally or if very high blood levels are reached. Epileptic patients are particularly at risk due to the ability of penicillins to cause GABAergic inhibition.

5. Hematologic toxicities: Decreased coagulation may be observed with high doses **of *piperacillin*, *ticarcillin*, and *nafcillin***. Cytopenias have been associated with therapy of greater than 2 weeks, and therefore, blood counts should be monitored weekly for such patients.


PHARMACODYNAMICS
Dr. Samir AL_Shujairy
MedicPresent

PHARMACODYNAMICS

What the drug does to the body?



Pharmacokinetics

Pharmacodynamics

Pharmacodynamics : What the drug does to the body

It deals with

- **Mechanism of action**
- **Pharmacological effects**
- **Adverse drug reaction**
- **Drug receptor interactions**
- **Combined drug action**

Types of Drugs Actions

- **Stimulation**: Adrenaline stimulates heart
- **Depression**: Quinidine depress heart, barbiturates depress CNS.
- **Irritation**: methyl Salicylate
- **Replacement**: insulin in DM.
- **Chemotherapy**: It is either by bactericidal or cytotoxic action.

  Antibiotics and anticancer drugs
- **Modification of immune status**: Vaccines and Glucocorticoids.

PHARMACODYNAMICS

- Site and Mechanism of Drug Actions:

The site of drug action means where a drug acts. It is divided into two areas:

- ✓ **Locally**
- ✓ **Systemically**

✓**Locally:** Drug which act only at the site of administration. Eg. Ointments, local anaesthetics.

✓**Systemically:** The drug will be absorbed into the blood and act systemically. Once in the circulation drugs may act by binding to different sites by different mechanisms. Most drugs produce their effects by binding to specific target proteins like

PHARMACODYNAMICS

- Mechanism of Drug Actions: The fundamental mechanism behind how the drug acts are as follows:
  - Non receptor mediated
  - Receptor mediated

Non receptor mediated actions

1. Physical action: The action could result from its physical properties like Mass of drug - Ispaghula husk, Adsorptive property - char coal.

PHARMACODYNAMICS

- Mechanism of Drug Actions:

Non receptor mediated actions

2. Chemical action: Drugs may act by their chemical properties like acidity/alkalinity, chelating etc. Eg. Antacids neutralise gastric HCl.

3. Through enzymes: Drugs may act by **Inhibition** of various enzymes, thus altering the enzyme mediated reactions. Membrane pumps like ATP, H+ may be inhibited by drugs. Eg. Aspirin inhibits Cyclooxygenase.Some drugs act also by **Stimulation** which occurs commonly with endogenous substances like hormones. Eg. Adrenaline stimulates adenylyl cyclase.

PHARMACODYNAMICS

- Mechanism of Drug Actions:

Non receptor mediated actions

4. Altering the metabolic processes: Drugs like antimicrobials alter the metabolic pathways in the microorganisms resulting in the destruction of microorganisms. Eg. Sulfonamides – interfere with bacterial folic acid synthesis.
5. Through ion channels: Interfere with the movement of ions across specific channels. Eg. Calcium Channel blockers.

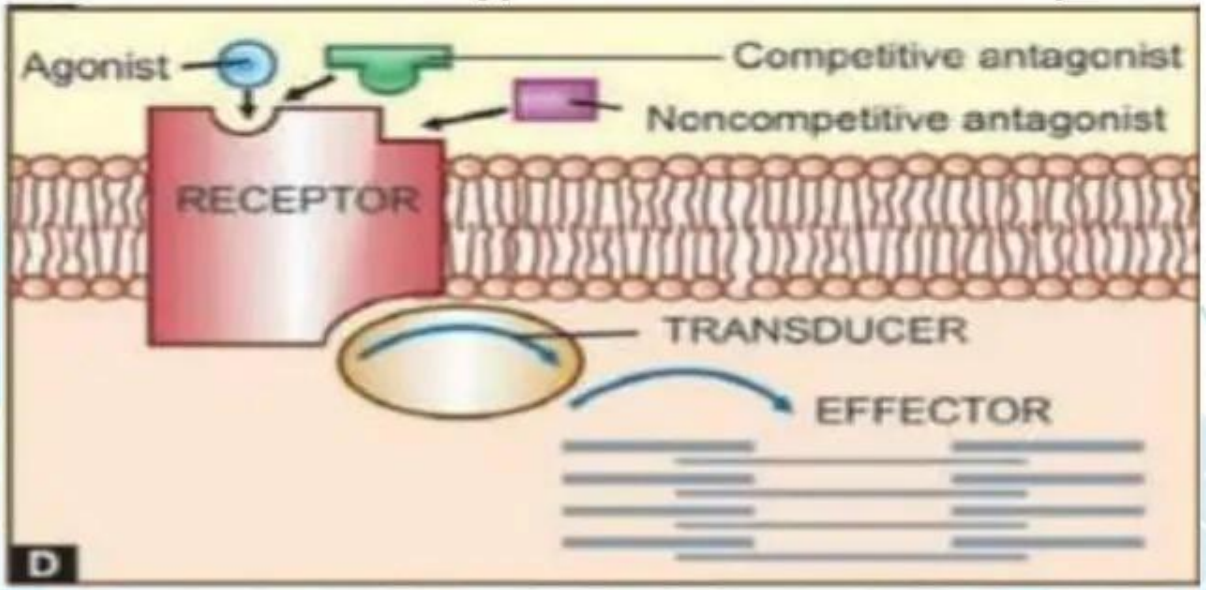
PHARMACODYNAMICS

- Mechanism of Drug Actions:

Receptor mediated actions

What is a receptor ?

Macromolecule or binding site located on the surface or inside the effectors cell that serves to recognise the signal molecule/drug and initiate response to it. Itself has



RECEPTOR TYPES

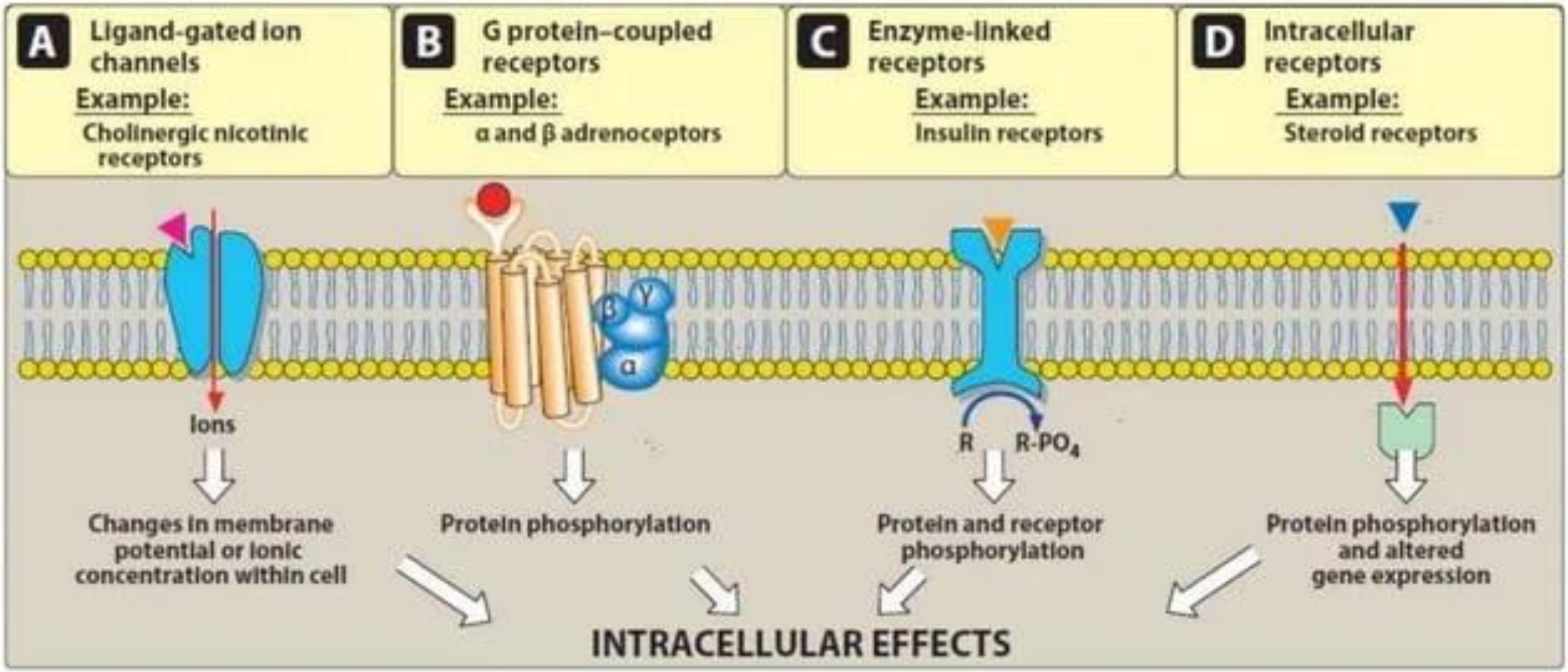


Figure 2.2

Transmembrane signaling mechanisms. **A.** Ligand binds to the extracellular domain of a ligand-gated channel. **B.** Ligand binds to a domain of a transmembrane receptor, which is coupled to a G protein. **C.** Ligand binds to the extracellular domain of a receptor that activates a kinase enzyme. **D.** Lipid-soluble ligand diffuses across the membrane to interact with its intracellular receptor. R = inactive protein.

PHARMACODYNAMICS

- Mechanism of Drug Actions:

Receptor mediated actions

Different terminologies Used to Describe drug-receptor interaction:

- Affinity: Ability of the drug to bind the receptor
- Intrinsic activity: Ability of the drug to elicit a response after binding to a receptor
- Agonist: An agent which activates the receptor to produce an effect similar to that of physiological signal molecule

Has affinity + IA. Eg. Adrenaline on beta receptors

PHARMACODYNAMICS

- Mechanism of Drug Actions:

Receptor mediated actions

Different terminologies Used to Describe drug-receptor interaction:

- Antagonist: Agent which prevents the action of an agonist on a receptor and subsequent response. Does not have any effect of its own

  Affinity + No I.A. Eg. Propranolol on ß receptor

- Partial agonist: Binds to receptor but sub maximal response Eg: Nalorphine

Affinity + sub maximal I.A.

PHARMACODYNAMICS

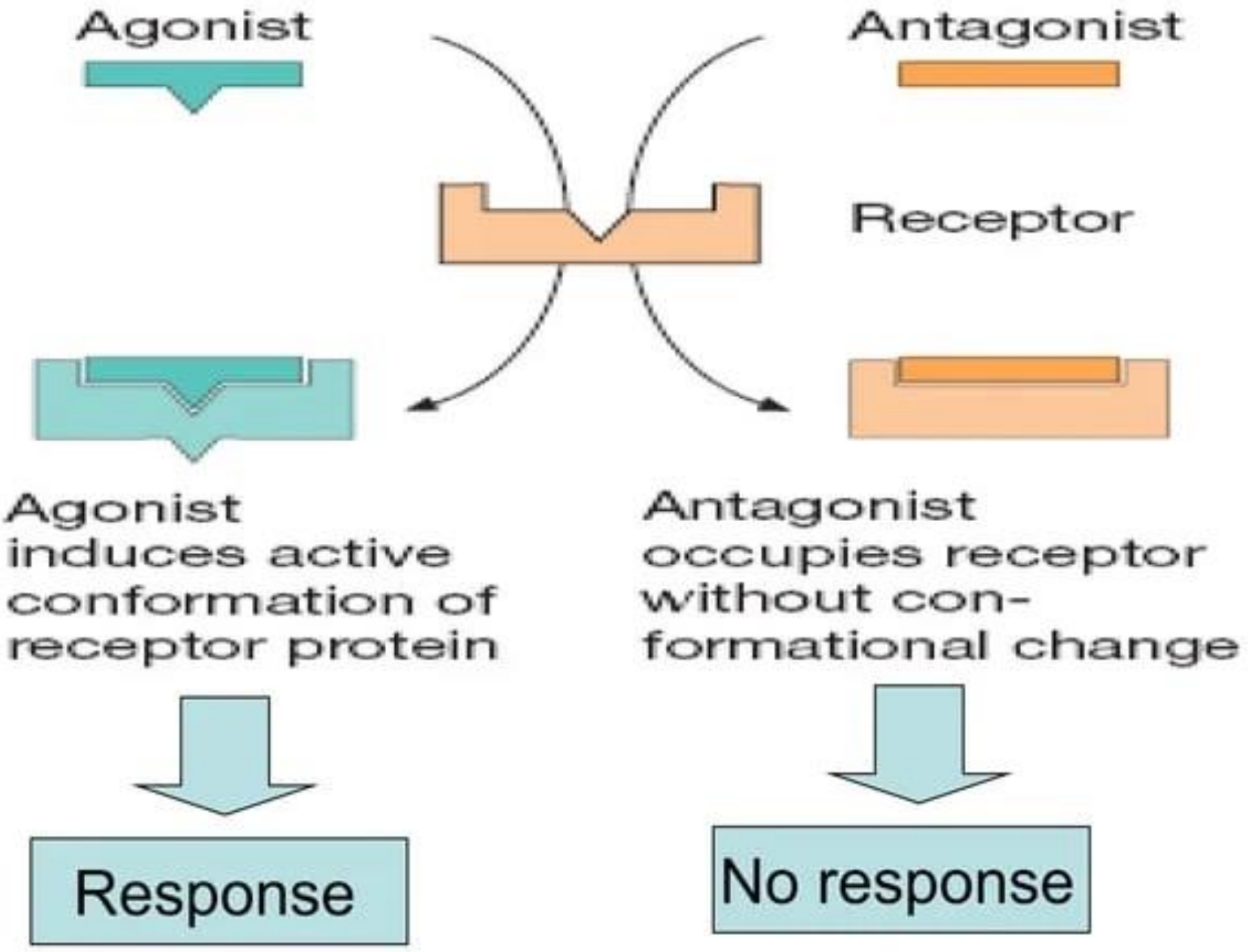
- Mechanism of Drug Actions:

Receptor mediated actions

Different terminologies Used to Describe drug-receptor interaction:

- Inverse agonist: An agent which activates a receptor to produce an effect in the opposite direction to that of the agonist. Eg. ß - Carbolines

Affinity+ I.A with negative sign


Agonist
Antagonist
Receptor
Agonist induces active conformation of receptor protein
Antagonist occupies receptor without con-formational change
Response
No response

Efficacy Vs. Potency

- **Efficacy** is the response that can be produced by a drug.
- **Potency** is the amount of drug required to produce an effect.

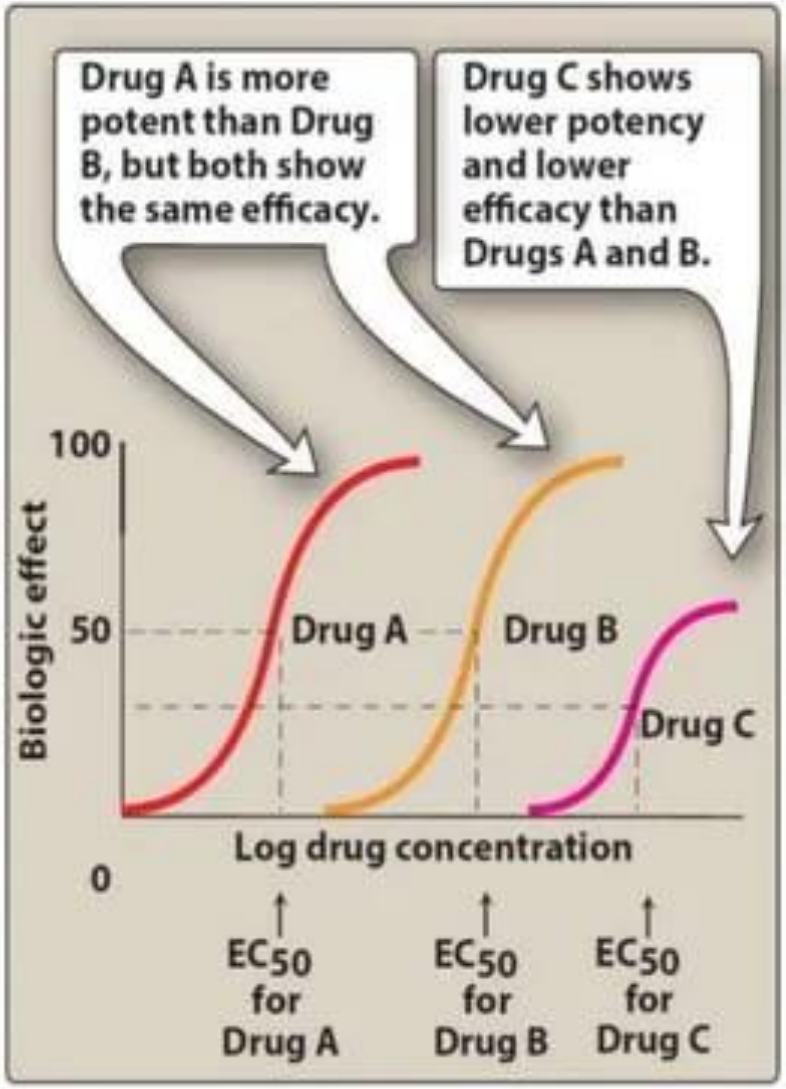


Figure 2.8

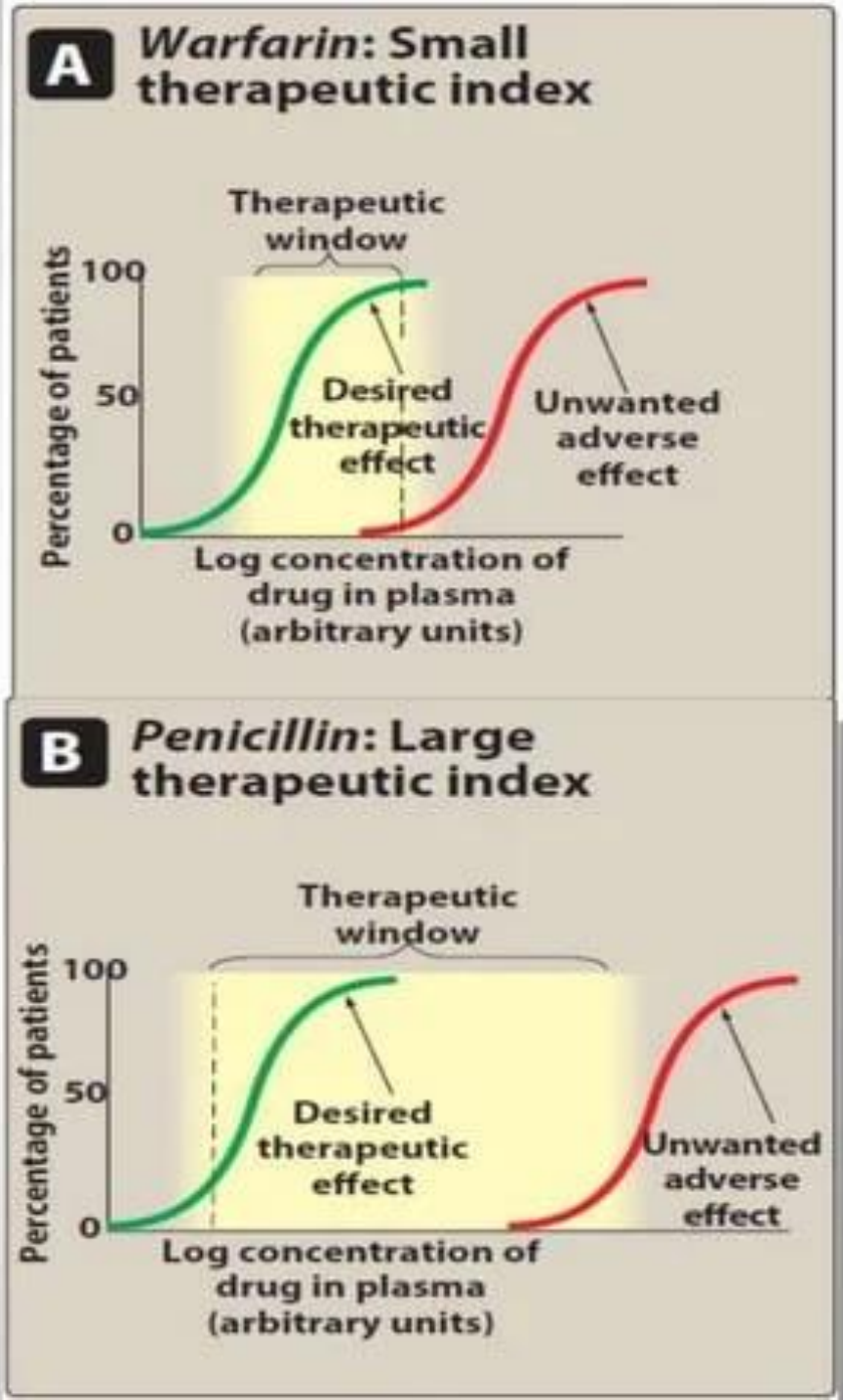
Typical dose–response curve for drugs showing differences in potency and efficacy. EC_{50} = drug dose that shows 50% of maximal response.

Therapeutic Index

$$TI = LD_{50} / ED_{50}$$

LD_{50} (Lethal Dose): It is the dose of a drug that is lethal for 50% of the population.

ED_{50} (Effective Dose): It is the dose of the drug that produces desired effect in 50% of the population.



PHARMACODYNAMICS

- Combined drug action

When two or more drugs are given simultaneously or in quick succession, they may be indifferent or exhibit synergism or antagonism.

The drug interaction is the alteration in the duration or the magnitude of the pharmacological effects of one drug by another drug. This response can be greater or lesser than the sum of their individual effects.

PHARMACODYNAMICS

- Combined drug action

The sites of drug interaction may be:

- ✓ In vitro – This take place in the syringe before administration. Eg. Penicillin & Gentamycin should never be mixed.
- ✓ In vivo – This occurs within the body after administration.

The drug - drug interaction may be

- ➢ Synergism
- ➢ Additive
- ➢ Supraadditive (Potentiation)
- ➢ Antagonism

PHARMACODYNAMICS

- Combined drug action

➢ Synergism: Syn – together
Ergon – work

- They may act in same direction
- One may be inactive, but enhances others action

➢ Additive: Effect of combination is equal to the individual effect of components

Effect of drugs A+B = Effect of drug A + Effect of drug B

Eg. Aspirin + Paracetamol – analgesic/ antipyertic
Nitric oxide + Halothane – General anaesthetic

PHARMACODYNAMICS

- Combined drug action

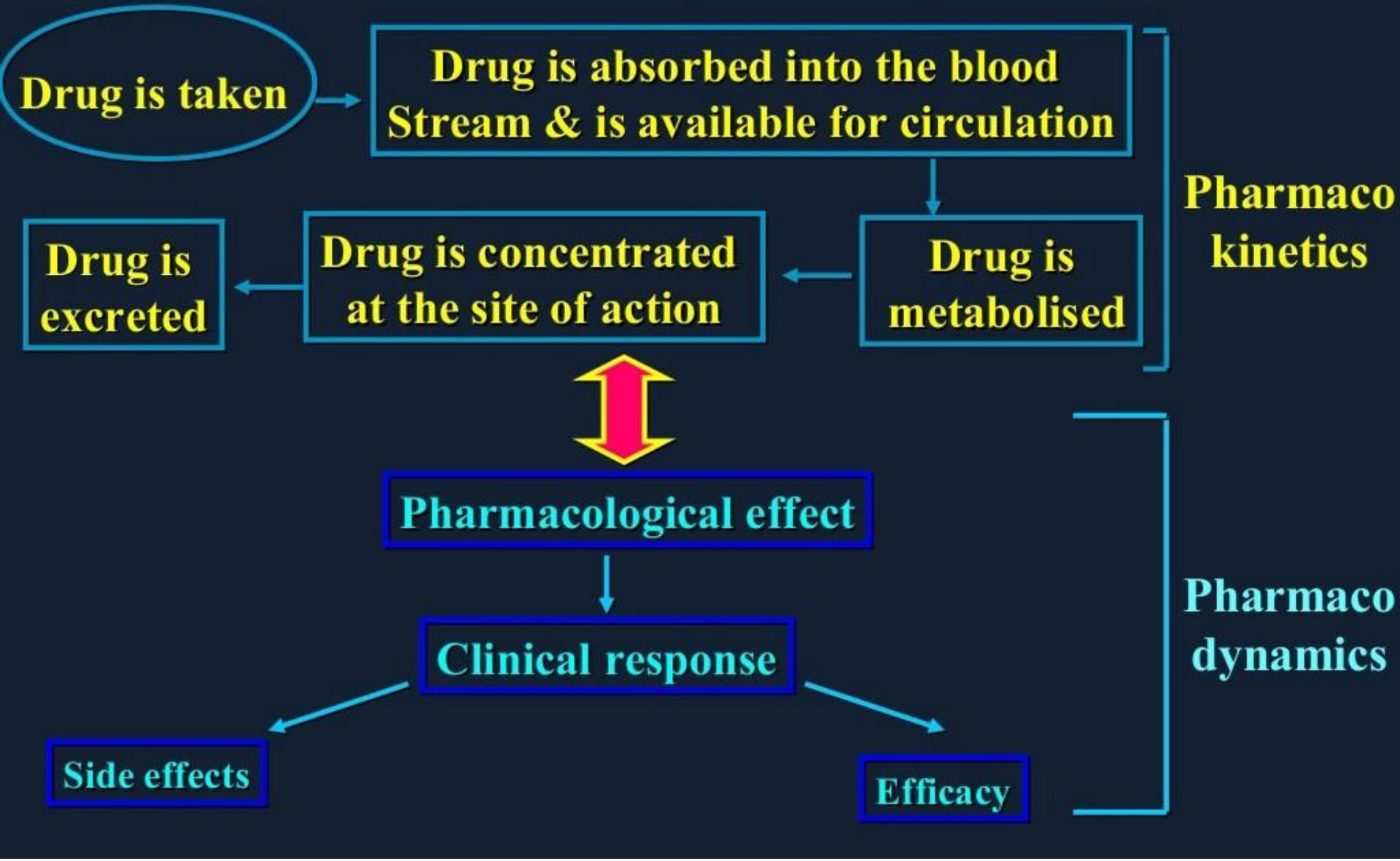
➢ Supraadditive (Potentiation): Effect of combination is greater than the individual effects of components

Effect of drug A+B > Effect of drug A + effect of drug B

Eg. Levodopa + Carbidopa – Inhibition of peripheral metabolism

➢ Antagonism: One drug decreases or inhibits the action of other.

The Relationship between Pharmacokinetic and Pharmacodynamic processes



PHARMACODYNAMICS

- Adverse drug reaction

All drugs can produce unwanted effects.

Definition:

- Any response to a drug that is noxious and unintended and that occurs at doses used in man for prophylaxis, diagnosis/therapy.

PHARMACODYNAMICS

- Adverse drug reaction

Grading of ADR

- Based on Severity

Minor – Moderate – Severe – Lethal

- Based on area affected

Local Vs Systemic

- Based on reversibility

Reversible Vs Irreversible

Basics of Drug Action

- ***Desired action*** – the expected response of a medication

- ***Side effects*** –known and frequently experienced, expected reaction to drug.

- ***Adverse reaction*** –unexpected, unpredictable reactions that are not related too usual effects of a normal dose of the drug.

PHARMACODYNAMICS

- Adverse drug reaction

- **Spectrum of Adverse Drug Reactions:**
  - **Side effects**
  - **Toxic effects**
  - **Intolerance**
  - **Iatrogenic Diseases**
  - **Drug dependence**
  - **Teratogenicity**
  - **Carcinogenicity and Mutagenicity**
  - **Others**

PHARMACODYNAMICS

- Adverse drug reaction

- **Spectrum of Adverse Drug Reactions:**
  - **Intolerance:** Characteristic toxic effects of a drug in an individual at therapeutic doses. It could be in the form of
    - **Idiosyncrasy:** Inherent qualitative abnormal reaction to a drug, usually due to genetic abnormality. Eg. aspirin causing an attack of asthma.
    - **Allergic reaction:** An abnormal reaction of the immune system to a medication. Also called hypersensitivity. Eg. Antibiotics --

PHARMACODYNAMICS

- Adverse drug reaction

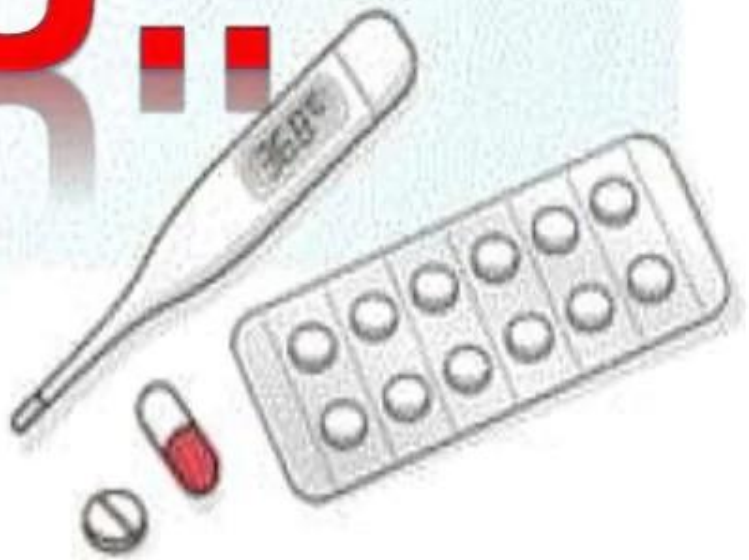
- **Spectrum of Adverse Drug Reactions:**
  - **Teratogenicity:** The capacity of a drug to cause fetal abnormalities when administered to the pregnant mother. Ex. Warfarin Retarded growth, Phenytoin Cleft palate/Cleft lip.
  - **Carcinogenicity and Mutagenicity:** Refers to the capacity of a drug to cause genetic defects (mutagenicity) To cause cancer (carcinogenicity).
  - **Others:** It include photosensitivity, photo toxicity, photo allergic reactions, hepatotoxicity etc.

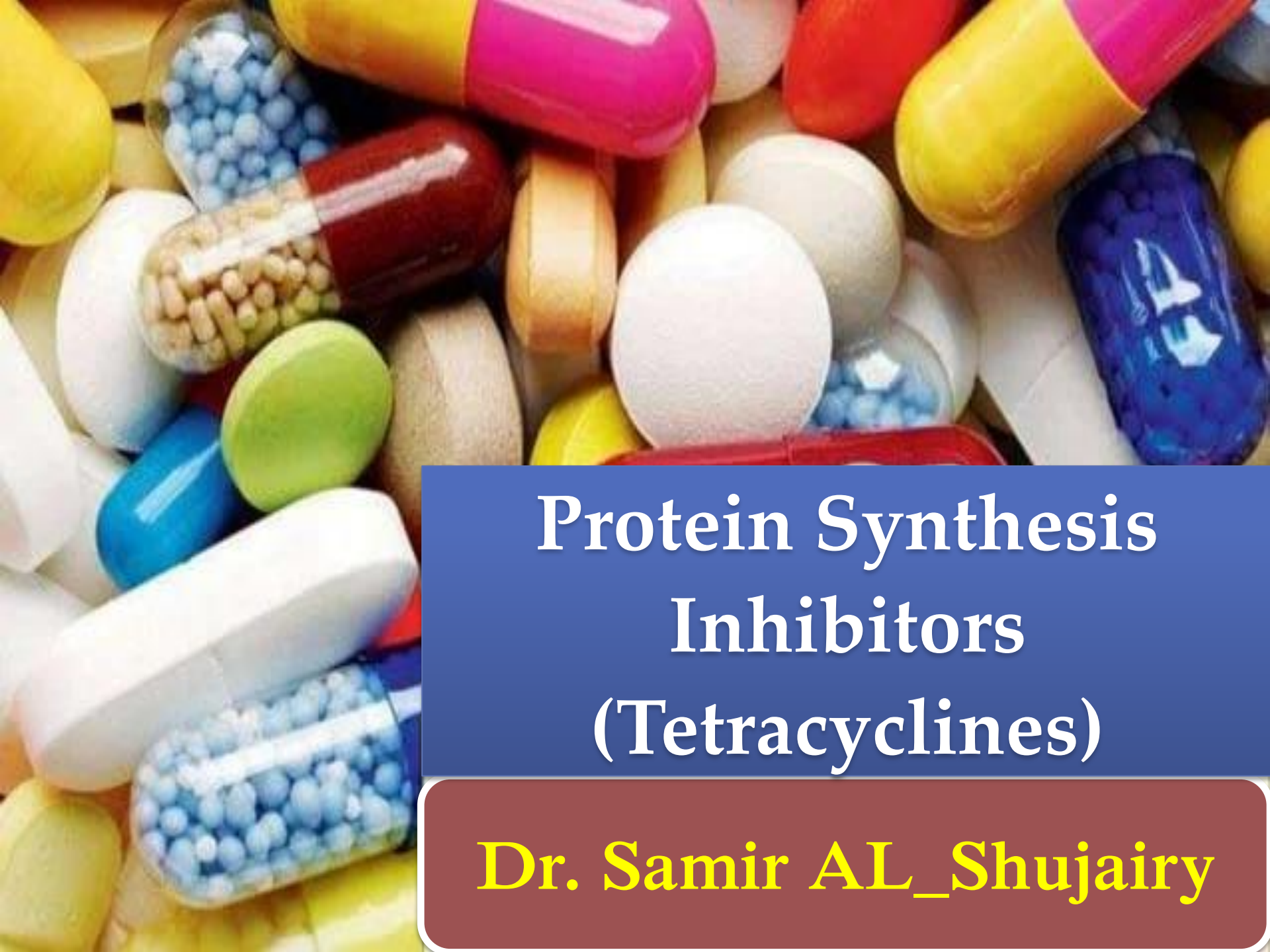
PHARMACODYNAMICS

Factors Affecting Drug Actions:-

- Age:
- Body weight:
- Sex: hormonal effect and smaller body size may influence women.
- Species and race:
- Diet and environment:
- Route of administration:
- Genetic factors:
- Dose:
- Disease:
- Psychological factors:
- Presence of other drugs:

THANK U..





Protein Synthesis Inhibitors (Tetracyclines)

Dr. Samir AL_Shujairy

Antimicrobial effects by targeting bacterial ribosomes and inhibiting bacterial protein synthesis.

Bacterial ribosomes differ structurally from mammalian cytoplasmic ribosomes and are composed of 30S and 50S subunits (mammalian ribosomes have 40S and 60S subunits).

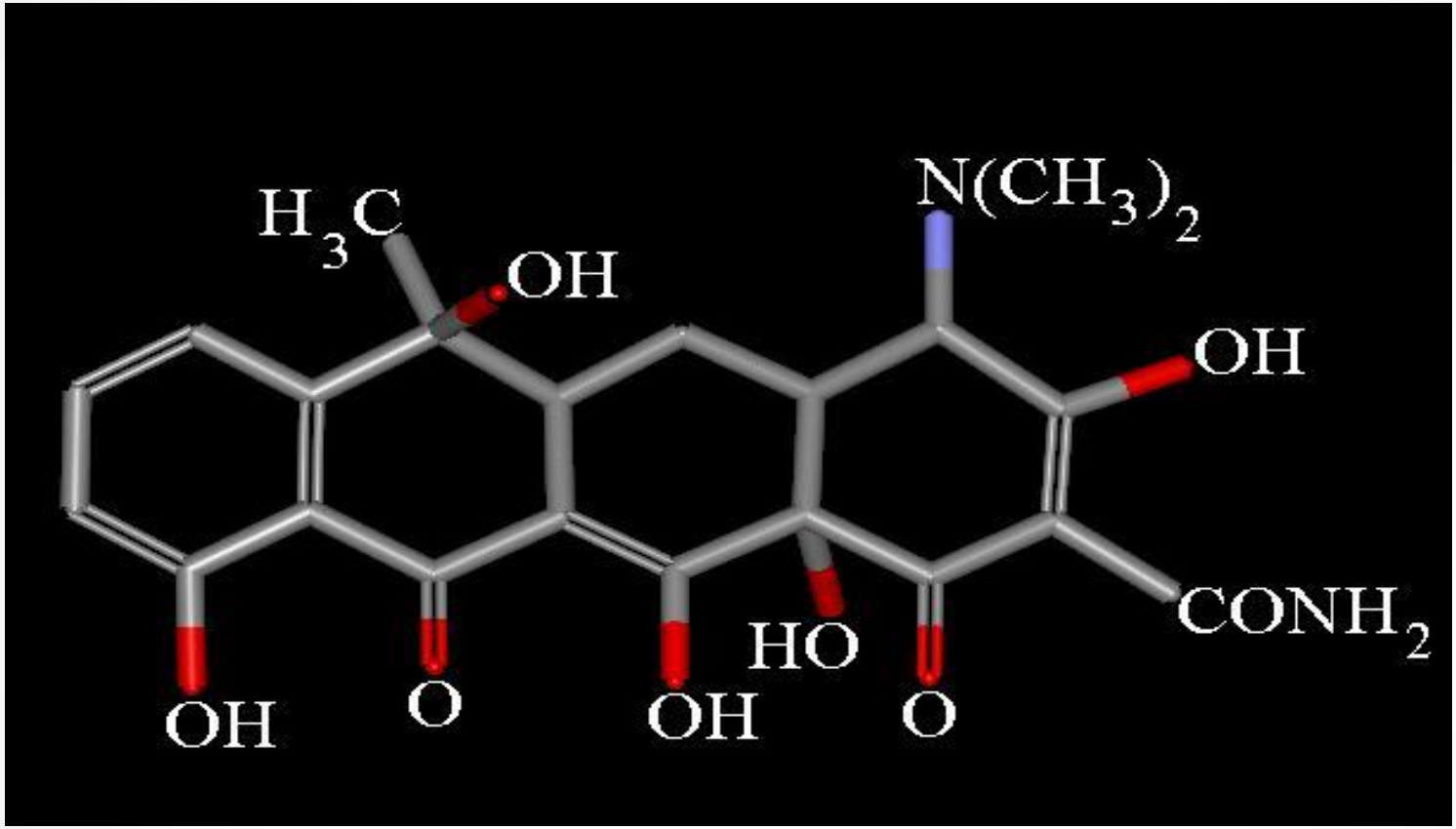
selectivity for bacterial ribosomes minimizes potential adverse consequences.

high concentrations of drugs such as *chloramphenicol* or the **tetracyclines** may cause toxic effects as a result of interaction with mitochondrial mammalian ribosomes, since the structure of mitochondrial ribosomes more closely resembles bacterial ribosomes.

TETRACYCLINES

Tetracyclines consist of four benzene **rings with a system of conjugated double bonds.**

Substitutions on these rings alter the individual pharmacokinetics and spectrum of antimicrobial activity.


H3C
OH
N(CH3)2
OH
CONH2
HO
OH
O
OH
O

Mechanism of action

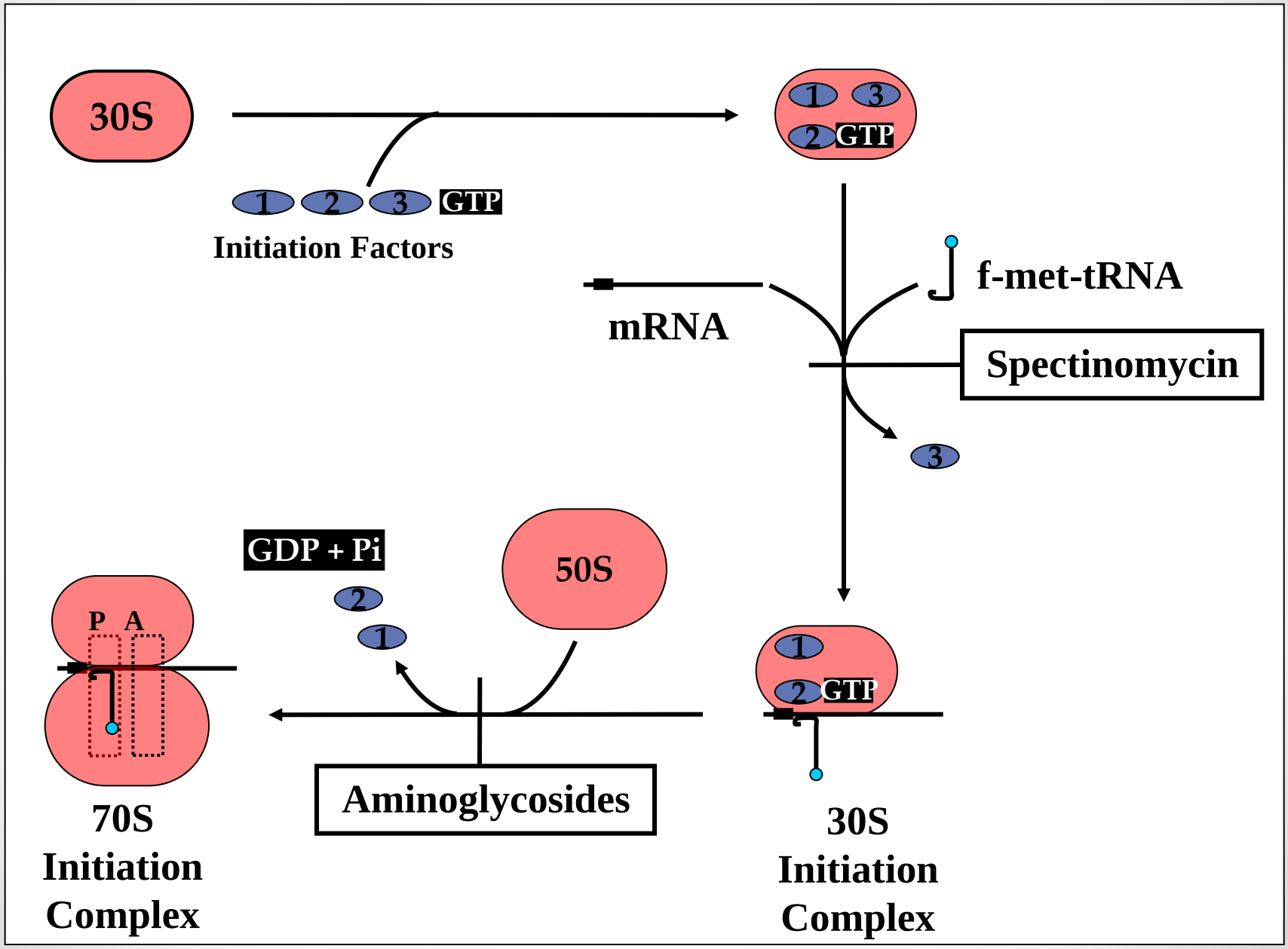
Tetracyclines enter susceptible organisme by passive diffusion and also by an energy-dependent transport protein mechanism unique to the bacterial inner cytoplasmic membrane.

Tetracyclines concentrate intracellularly in susceptible organisms.

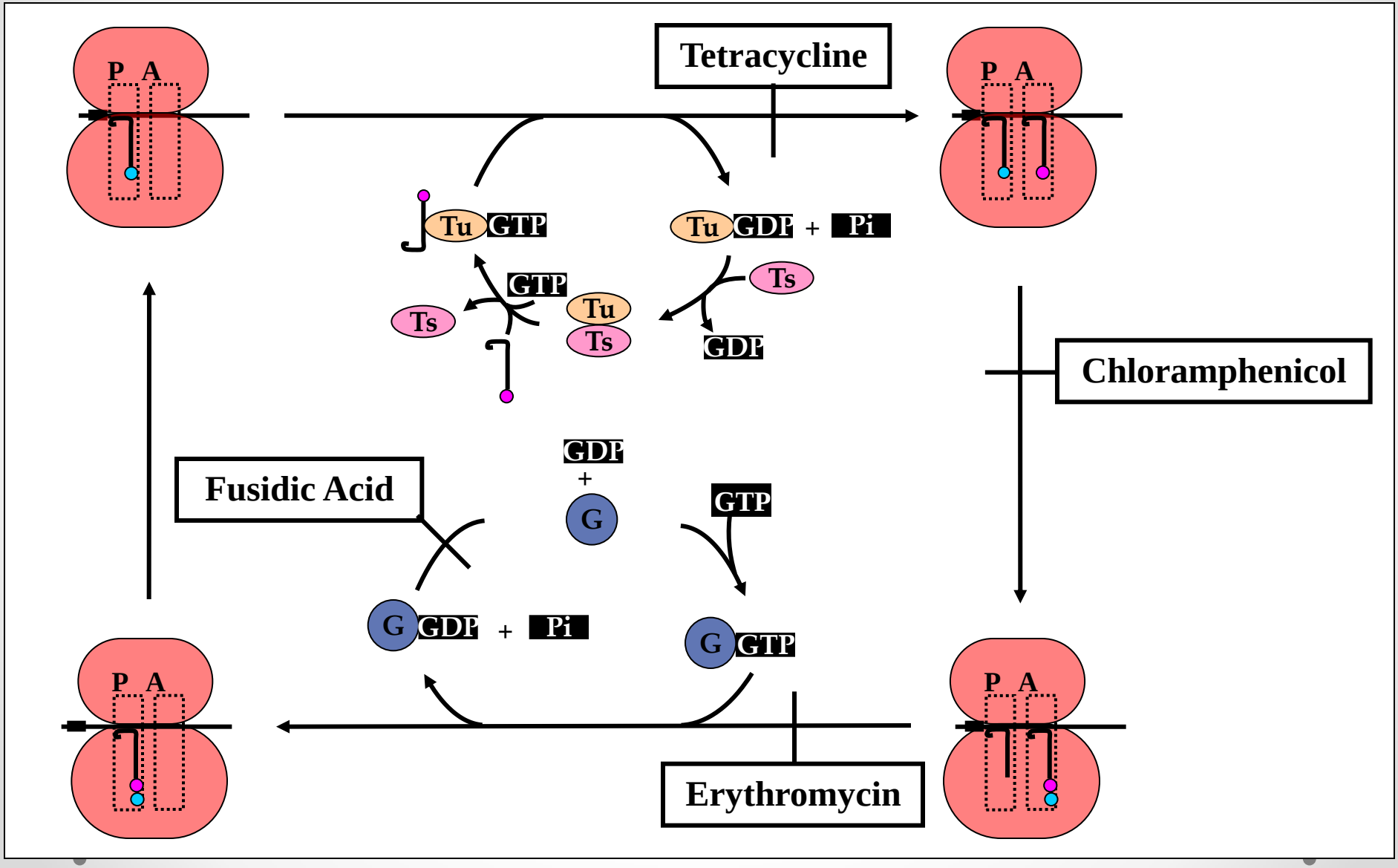
The drugs bind reversibly to the 30S subunit of the bacterial ribosome.

This action prevents binding of tRNA to the mRNA–ribosome complex, thereby inhibiting bacterial protein synthesis

Review of Initiation of Protein Synthesis



Review of Elongation of Protein Synthesis



Antibacterial spectrum

tetracyclines are bacteriostatic antibiotics effective against a wide variety of organisms, including gram-positive and gram-negative bacteria, protozoa, spirochetes, mycobacteria, and atypical species

They are commonly used in the treatment of acne and Chlamydia infections (*doxycycline*).

- *Mycoplasma pneumoniae*
- *Chlamydia trachomatis*
- *Borrelia recurrentis.*
- *Yersinia pestis*
- *Vibrio cholerae*
- *Campylabacter fetus*
- *Brucella specie*
- *Streptococcus pneumoniee .*
- *Neisserie gonorrhoeae*

Pharmacokinetics

1. Tetracyclines are adequately absorbed after oral ingestion.

1. Administration with dairy products or other substances that contain divalent and trivalent cations (for example, magnesium and aluminum antacids or iron supplements) decreases absorption, particularly for *tetracycline*.

2. *Doxycycline* and *minocycline* are available as oral and intravenous (IV) preparations.

Distribution:

1. **tetracyclines concentrate well in the bile, liver, kidney, gingival fluid, and skin. bind to tissues undergoing calcification (teeth and bones).**
2. **Only *minocycline* and *doxycycline* achieve therapeutic levels in the cerebrospinal fluid (CSF).**
3. ***Minocycline* achieves high levels in saliva and tears.**
4. **All tetracyclines cross the placental barrier and concentrate in fetal bones and dentition.**

Elimination:

1. *Tetracycline* and *doxycycline* are not hepatically metabolized.
2. *Tetracycline* is primarily eliminated unchanged in the Urine.
3. *minocycline* hepatic metabolism and is eliminated to a lesser extent via the kidney.
4. In renally compromised patients, *doxycycline* is preferred, as it is primarily eliminated via the bile into the feces

Resistance

1. **efflux pump** that expels drug out of the cell, thus preventing intracellular accumulation.
2. **enzymatic inactivation** of the drug and production of bacterial proteins that prevent tetracyclines from binding to the ribosome.

Adverse effects

- Gastrointestinal upsets
- Super infection
- Discoloration and deformity in growing teeth and bones (contraindicated in pregnancy and in children < 12 years)
- Renal impairment (should be also avoided in renal disease)
- Phototoxicity
- Hepatotoxicity

GLYCYLCYCLINES

Tigecycline **, a derivative of** ***minocycline*****, is the first available member of the glycylcycline antimicrobial class. It is indicated for the treatment of complicated skin and soft tissue infections, as well as complicated intra-abdominal infections.**

Mechanism of action

Tigecycline **exhibits bacteriostatic action by reversibly binding to the 30S ribosomal subunit and inhibiting protein synthesis.**

Antibacterial spectrum

Tigecycline **: broad-spectrum activity that includes** ***methicillin*** **resistant staphylococci (MRSA), multidrug-resistant streptococci, vancomycin-resistant enterococci (VRE), extended-spectrum β-lactamase–producing gram-negative bacteria, Acinetobacter baumannii, and many anaerobic organisms.**

However, ***tigecycline*** **is not active against Morganella, Proteus, Providencia, or Pseudomonas species.**

Resistance

Tigecycline was developed to overcome the recent emergence of tetracycline class–resistant organisms that utilize efflux pumps and ribosomal protection to confer resistance. However, resistance is seen and is primarily attributed to overexpression of efflux pumps

Pharmacokinetics

1. **IV infusion, *tigecycline* exhibits a large volume of distribution.**
2. **penetrates tissues well but has low plasma concentrations.**

Consequently, *tigecycline* is a poor option for bloodstream infections.

The primary route of elimination is biliary/fecal. No dosage adjustments are necessary for patients with renal impairment. However, a dose reduction is recommended in severe hepatic dysfunction.

Autonomic Nervous System

- 1- Central nervous system
- Brain
- Spinal cord

- 2-Peripheral nervous system:
- a-Afferent division
- b-Efferent division:
- 1-Somatic system
- 2-Autonomic system:
- a-Sympathetic NS
- b-Parasympathetic NS
- C-Enteric NS

- **A) Functions of the sympathetic nervous system**
- 1. Increasing heart rate and contractility, and thus, increasing blood pressure.
- 2. Constriction of the blood vessels of skin, mucous membranes, and splanchnic area, and dilation of skeletal muscles vessels.
- 3. Dilation of the pupil (mydriasis).
- 4. Bronchodilation.
- 5. Inhibit salivation.
- 6. Decrease GI motility.
- 7. Inhibit bladder contraction.
- 8. Stimulate glucose production and release

- **Functions of the parasympathetic nervous system**
- 1- Pupil contraction (miosis).
- 2- Bronchoconstriction.
- 3- Stimulation tears and saliva secretion.
- 4- Decreasing heart rate and contractility.
- 5- Increasing the muscle motility and tone of the gastrointestinal system.

C) **Functions of the enteric nervous system (ENS)**

The enteric nervous system is a collection of neurons in the gastrointestinal tract that constitutes the “brain of the gut” and can function independently of the central nervous system. This system controls the motility, exocrine and endocrine secretions, and microcirculation of the gastrointestinal tract.

- **Functions of the somatic nervous system**
- The somatic system is the part of the peripheral nervous system that is responsible for carrying motor and sensory information both to and from the central nervous system *without the mediation of ganglia*. This system is made up of nerves that connect to the skin, sensory organs, and all skeletal muscles. The system is responsible for nearly all voluntary muscle movements as well as for processing sensory information that arrives via external stimuli including hearing, touch, and sight.

- **Neurotransmitters**

Neurotransmitters are specific chemical signals that are released from nerve terminals to establish the communication between nerve cells, and between nerve cells and effector organs. In spite of recognizing more than 50 signals molecules (neurotransmitters) in the nervous system, just norepinephrine (and the closely related epinephrine), acetylcholine, dopamine, serotonin, histamine, glutamate, and γ-aminobutyric acid are the most commonly involved neurotransmitters in the actions of therapeutically useful drugs. Each type of neurotransmitters can bind with a specific receptor in order to give the biological desirable response.

The autonomic nerve fibers can be classified to cholinergic and adrenergic neurons based on the type of the released neurotransmitters whether they are acetylcholine or epinephrine and norepinephrine. Acetylcholine mediates the transmission of nerve impulses across autonomic ganglia in both the sympathetic and parasympathetic nervous systems. Transmission from the autonomic postganglionic nerves to the effector organs in the parasympathetic system, and a few sympathetic system organs also involve the release of acetylcholine .In the somatic nervous system, transmission at the neuromuscular junction (the junction of nerve fibers and voluntary muscles) is also cholinergic.

- In the sympathetic system, norepinephrine mediates the transmission of nerve impulses from autonomic postganglionic nerves to effector organs except few sympathetic fibers, such as those involved in sweating, are cholinergic.

- **Cholinergic agonists**

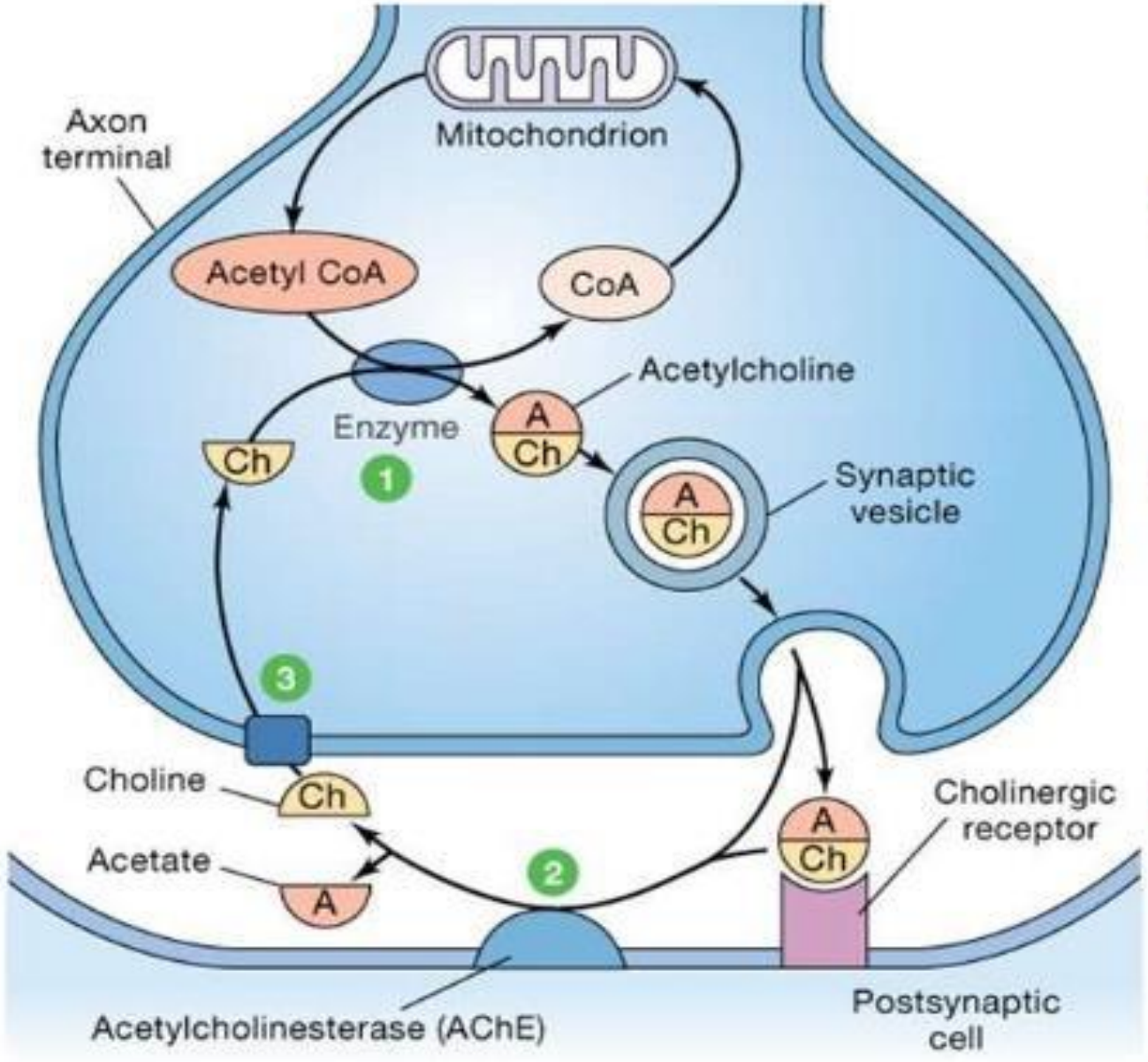
- The cholinergic drugs act on receptors that are activated by acetylcholine (ACh). These receptors include nicotinic and muscarinic receptors and can be mainly recognized in sympathetic and parasympathetic nervous system and somatic nervous system as well
- The two classes of receptor for Ach are defined on the basis of their preferential activation by the alkaloids nicotine and muscarine.

Neurotransmission at cholinergic neurons :Neurotransmission in cholinergic neurons

involves six sequential steps:

- **1.Synthesis of acetylcholine:** Choline is transported from the extracellular fluid into the cytoplasm of the cholinergic neuron by an energy-dependent carrier system. Choline acetyltransferase catalyzes the reaction of choline with acetyl coenzyme A (CoA) to form ACh (an ester) in the cytosol.
- **2.Storage of acetylcholine in vesicles:** ACh is packaged and stored into presynaptic vesicles.
- **3.Release of acetylcholine:** When an action potential propagated at a nerve ending, voltage-sensitive calcium channels on the presynaptic membrane open, causing an increase in the concentration of intracellular calcium. Elevated calcium levels promote the fusion of synaptic vesicles with the cell membrane and the release of their contents into the synaptic space.

- **4.Binding to the receptor:** ACh released from the synaptic vesicles diffuses across the synaptic space and binds its receptors. The postsynaptic cholinergic receptors on the surface of the effector organs are divided into two classes: muscarinic and nicotinic. Binding to a receptor leads to a biologic response within the cell, such as the initiation of a nerve impulse in a postganglionic fiber or activation of specific enzymes in effector cells.
- **5. Degradation of acetylcholine:** The signal at the postjunctional effector site is rapidly terminated, because AChE (acetylcholine esterase) cleaves ACh to choline and acetate in the synaptic cleft.
- **6. Recycling of choline:** Choline may be recaptured by a sodium-coupled uptake system that transports the molecule back into the neuron. There, it is acetylated into ACh that is stored until released by a subsequent action potential.



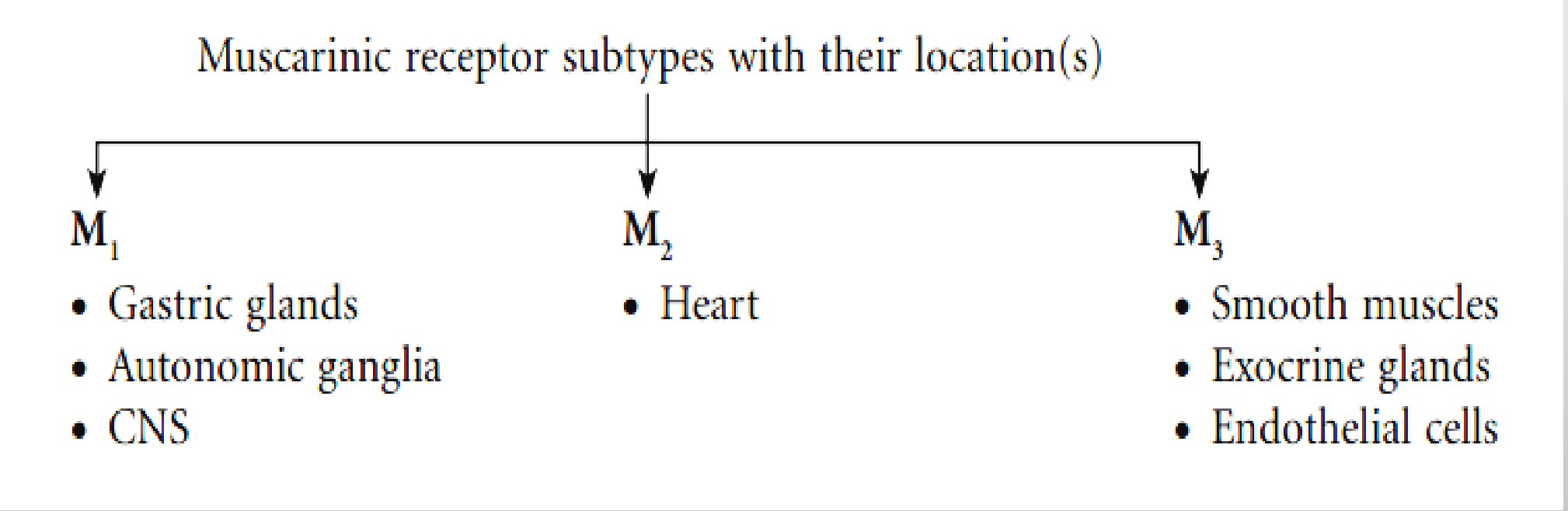
1. **Acetylcholine** (ACh) is made from choline and acetyl CoA.

2. In the synaptic cleft ACh is rapidly broken down by the enzyme **acetylcholinesterase.**

3. Choline is transported back into the axon terminal and is used to make more ACh.

- **Cholinergic receptors (cholinoceptors)**
- Cholinoceptors can be classified into two types: muscarinic and nicotinic receptors. They are different mainly in their affinities for agents that mimic the action of ACh (cholinomimetic agents).
- **1- Muscarinic receptors:** It is one of the G protein–coupled receptors that have high affinity to bind with muscarine (an alkaloid that is present in certain poisonous mushrooms) and ACh but low affinity to bind with nicotine. Five sub-classes are recognised for this receptor family; however, only M1, M2, and M3 receptors have been functionally characterized.

a- Locations of muscarinic receptors



- **b- Muscarinic agonists:** *Pilocarpine* is an example of a nonselective muscarinic agonist used in clinical practice to treat xerostomia and glaucoma. Attempts are currently underway to develop muscarinic agonists and antagonists that are directed against specific receptor subtypes. M1 receptor agonists are being investigated for the treatment of Alzheimer’s disease.

- **2- Nicotinic receptors**
- These receptors, in addition to binding ACh, also recognize nicotine but show only a weak affinity for muscarine. Nicotine at low concentration stimulates the receptor, whereas nicotine at high concentration blocks the receptor. The nicotinic receptor functions as a ligand-gated ion channel.
- **Location**: Nicotinic receptors are located in the CNS, the adrenal medulla, autonomic ganglia, and the neuromuscular junction (NMJ) in skeletal muscles.

Below is a table summarizing the function of each cholinergic receptor

Receptor Type(s)	Functional Response
M_1 and M_3	Promotes glandular secretion and smooth muscle contraction
M_2	Depressant effect on heart
N_N	Depolarization
N_M	Skeletal muscle contraction

- **Direct-acting cholinergic agonists**

- **Definition**: Materials that mimic the effects of ACh by binding directly to cholinoceptors (muscarinic or nicotinic).
- **Types**:
- 1) endogenous choline esters, which include ACh and synthetic esters of choline, such as *carbachol* and *bethanechol*.
- 2) Naturally occurring alkaloids, such as *nicotine* and *pilocarpine*. The main advantage of this group of drugs that have a longer duration of action than ACh.
- The more therapeutically useful drugs (*pilocarpine* and *bethanechol*) preferentially bind to muscarinic receptors and are sometimes referred to as muscarinic agents. As a group, the direct-acting agonists demonstrate little specificity in their actions, which limits their clinical usefulness.

- **Acetylcholine**
- Acetylcholine is a quaternary ammonium compound; hence it cannot penetrate membranes. In spite of considering the ACh as a neurotransmitter of parasympathetic and somatic nerves as well as autonomic ganglia, it lacks therapeutic importance because of its pluralism of actions and its rapid inactivation by the cholinesterases. ACh has both muscarinic and nicotinic activity. Its actions include the following:
- **1- Decrease in heart rate and cardiac output:**, if injected intravenously, ACh produces a brief decrease in cardiac rate (negative chronotropy) and stroke volume as a result of a reduction in the rate of firing at the sinoatrial (SA) node.
- **2- Decrease in blood pressure:** As a result of ACh injection, vasodilation and lowering of blood pressure can be observed. This is due to an indirect mechanism of action because the ACh activates M3 receptors that found on endothelial cells lining the smooth muscles of blood vessels. This leads to produce a nitric oxide that act as a vasodilator from arginine.

- **3- Other actions**
- ACh administration can stimulate:
- a- Salivary secretion stimulates intestinal secretions and motility.
- b- Bronchiolar secretions.
- c- Urination.
- Moreover, ACh causes miosis (marked constriction of the pupil). Accordingly, ACh (1% solution) is instilled into the anterior chamber of the eye to produce miosis during ophthalmic surgery.

- **Therapeutic uses of direct-acting cholinergic agonists:**
- ✓ bethanechol is used to stimulate the atonic bladder, particularly in postpartum or postoperative, non obstructive urinary retention.
- ✓ Carbachol eye as a miotic agent to treat glaucoma by causing pupillary contraction and a decrease in intraocular pressure.
- ✓ Pilocarpine is used to treat glaucoma and is the drug of choice in the emergency lowering of intraocular pressure in glaucoma. It is also beneficial in promoting salivation in patients with xerostomia (dry mouth) resulting from irradiation therapy of the head and neck cancer.

- **Adverse effects of Ach and other cholinergic agonists**: causes the effects of generalized cholinergic stimulation.
- Bronchospasm and increase secretions.
- GI: nausea, vomiting, and diarrhea.
- Miosis.
- Urinary urgency.
- Sweating (diaphoresis) and salivation.

- **Indirect-acting cholinergic agonists (anticholinesterase agents (reversible))**
- ACh is uaually deactivated by the AChE (Acetylcholine esterase), which is an enzyme that specifically cleaves ACh to acetate and choline. It can be found at both pre- and post synaptically in the nerve terminal where it is membrane bound. Accordingly, inhibition of AchE can indirectly provide a cholinergic action by preventing the degradation of ACh. This results in an accumulation of ACh in the synaptic space. This process can be carried out by using the anticholinesterase agents or cholinesterase inhibitors. These drugs can provoke a response at all cholinoceptors in the body, including both muscarinic and nicotinic receptors of the ANS, as well as at the NMJ and in the brain.

- **Therapeutic uses of acetylcholinesterase inhibitors (reversible)**
- **Edrophonium, pyridostigmine, and ambenonium:** They are used in the diagnosis and management of myasthenia gravis, which is an autoimmune disease caused by antibodies to the nicotinic receptor at NMJs. This causes their degradation, making fewer receptors available for interaction with the neurotransmitter.

- **Physostigmine**
- ▪ It increases intestinal and bladder motility, which serve as its therapeutic action in a tony of either organ.
- ▪ used to treat glaucoma, but *pilocarpine* is more effective.
- ▪ as an antidote for drugs with anticholinergic actions.

- **Neostigmine**
- • used to stimulate the bladder and GI tract.
- • also used to treat myasthenia gravis.

- **Tacrine, donepezil, rivastigmine, and galantamine**
- Patients with Alzheimer disease have a deficiency of cholinergic neurons in the CNS. This observation led to the development of anticholinesterases as possible remedies for the loss of cognitive function. *Tacrine* was the first to become available, but it has been replaced by others because of its hepatotoxicity. Despite the ability of *donepezil*, *rivastigmine*, and *galantamine* to delay the progression of Alzheimer disease, none can stop its progression.

- **Adverse effects of acetylcholinesterase inhibitors (reversible):**
- ▪ Adverse effects include those of generalized cholinergic stimulation, such as salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm.
- ▪ Inhibition of AChE at the skeletal NMJ causes the accumulation of ACh and, ultimately, results in paralysis of skeletal muscle.
- ▪ *Physostigmine* can enter and stimulate the cholinergic sites in the CNS. The effects on the CNS may lead to convulsions when high doses are used. Bradycardia and a fall in cardiac output may also occur

- **Indirect-acting cholinergic agonists (anticholinestrase agents (irreversible))**
- A number of synthetic organophosphate compounds have the capacity to bind covalently to AChE. The result is a long-lasting increase in ACh at all sites where it is released. Many of these drugs are extremely toxic and were developed by the military as nerve agents. Related compounds, such as *parathion* and *malathion*, are used as insecticides

- **Cholinergic Antagonists**
- Cholinergic antagonist is a general term for agents that bind to cholinoceptors (muscarinic or nicotinic) and prevent the effects of acetylcholine (ACh) and other cholinergic agonists.
- There are three types of cholinergic antagonist drugs, which are:
- 1- Antimuscarinic agents (anticholinergic drugs) block muscarinic receptors, causing inhibition of muscarinic functions. Because they do not block nicotinic receptors, the anticholinergic drugs (more precisely, antimuscarinic drugs) have little or no action at skeletal neuromuscular junctions (NMJs).
- 2- Ganglionic blockers (specifically act on the nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia)
- 3- The neuromuscular-blocking agents (mostly nicotinic antagonists), which block cholinergic transmission between motor nerve endings and the nicotinic receptors on the skeletal muscle

- **1- Atropine** (antimuscarinic agents): It is an alkaloid with a high affinity for muscarinic receptors. It binds competitively and prevents ACh from binding to those sites. Atropine acts both centrally and peripherally. Its general actions last about 4 hours, except when placed topically in the eye, where the action may last for days. Neuro effector organs have varying sensitivity to atropine.
- **Effects:**
- • CNS: confusion, delirium.
- • Decrease GI motility and acid secretions without interfering with hydrochloric secretion.

- **Increase heart rate at high doses, i.e. higher than (0.5 mg). At low doses slight decrease in heart rate:** At low doses, the predominant effect is a slight decrease in heart rate. This effect results from blockade of the M1 receptors on the inhibitory prejunctional (or presynaptic) neurons, thus permitting increased ACh release. Higher doses of atropine cause a progressive increase in heart rate by blocking the M2 receptors on the sinoatrial node
- • Decrease body secretions like saliva (xerostomia), bronchial secretions, and sweat (elevate body temperature).
- • Mydriasis (cycloplegic to permits the measurement of refractive errors without interference by the accommodative capacity of the eye).

- **Therapeutic uses:**
- ▪ As mydriatic and cycloplegic: Atropine is used topically for producing mydriasis and cycloplegia. The action of atropine lasts 7–10 days.
- ▪ As preanaesthetic medication: Atropine is used prior to the administration of general anaesthetics: To prevent vagal bradycardia during anaesthesia. To prevent laryngospasm by decreasing respiratory secretions. Antisecretory agent to block the secretions in the upper and lower respiratory tracts before surgery.
- ▪ Anticholinergics are useful as antispasmodics in dysmenorrhea, intestinal and renal colic.
- ▪ Poisoning: a- In organophosphorous poisoning, atropine is the life-saving drug. b- In some types of mushroom poisoning, atropine is the drug of choice . c- Atropine is used in rare poisoning with neostigmine to counteract the muscarinic effects of neostigmine.
- ▪ As vagolytic: Atropine is used to treat sinus bradycardia and partial heart block due to increased vagal activity.

- **Side effects:** Blurred vision, decrease secretions, hyperthermia, constipation, urinary retention, delirium, and hallucinations.
- ✓ ***Scopolamine*** is another antagonist used for motion sickness.
- ✓ ***Ipratropium*** used as inhaler to decrease bronchoconstriction and bronchial secretions in COPD (chronic obstructive pulmonary disease) and asthma

- **2- Nicotine (**Ganglionic blockers)**:** although nicotine considers as an agonist at nicotinic receptors, but at higher dose it blocks the autonomic ganglia .
- Nicotine is a component of cigarette smoke, is a poison with many undesirable actions. However, it can be used in a controlled way to help in giving up smoking. It is found in more than one pharmaceutical dosage forms like sublingual tablets, lozenges and as chewing gum. Its action can be summarized in these points: Increasing the blood pressure and cardiac rate and at higher doses, the blood pressure falls because of ganglionic blockade, and activity in both the GI tract and bladder musculature ceases.

- **3- The neuromuscular-blocking agents:** These drugs block cholinergic transmission between motor nerve endings and the nicotinic receptors on the skeletal muscle. They possess some chemical similarities to ACh, and they act either as antagonists (non depolarizing type) or as agonists (depolarizing type) at the receptors on the endplate of the NMJ. Neuromuscular blockers are clinically useful during surgery to facilitate tracheal intubation and provide complete muscle relaxation at lower anesthetic doses, allowing for more rapid recovery from anesthesia and reducing postoperative respiratory depression.

- **1- Non depolarizing (competitive) blockers: At low doses:** Non depolarizing agents competitively block ACh at the nicotinic receptors. That is, they compete with ACh at the receptor without stimulating it. Thus, these drugs prevent depolarization of the muscle cell membrane and inhibit muscular contraction. On the other hand, **on high doses**, these drugs can lead to complete blockade and the muscle does not respond to direct electrical stimulation. All neuromuscular-blocking agents are injected intravenously or occasionally intramuscularly since they are not effective orally. In general, these agents are safe with minimal side effects; however, they can rarely cause bronchospasm.

- ***2-*** **Depolarizing agents:** Depolarizing blocking agents work by depolarizing the plasma membrane of the muscle fiber, similar to the action of ACh. However, these agents are more resistant to degradation by acetylcholinesterase (AChE) and can thus more persistently depolarize the muscle fibers. *Succinylcholine* is the only depolarizing muscle relaxant in use today. *Succinylcholine* attaches to the nicotinic receptor and acts like ACh to depolarize the junction. This leads to a transient twitching of the muscle. Continued binding of the depolarizing agent renders the receptor incapable of transmitting further impulses leading to flaccid paralysis. Therapeutically, *succinylcholine (which is administered IV)* is useful when rapid endotracheal intubation is required during the induction of anesthesia. The main side effects of this drug are the hyperthermia, apnea and hyperkalemia.