Pharmacokinetic 2
Pharmacodynamics 2

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Drug Metabolism

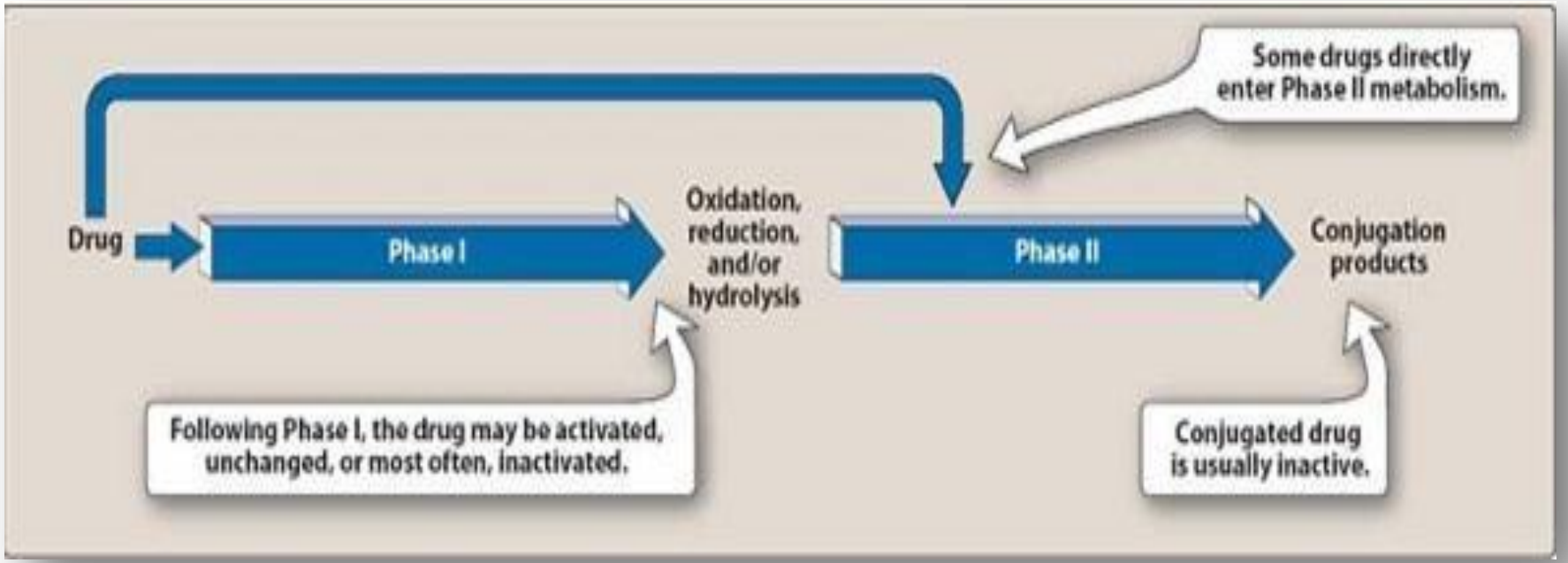
The process of metabolism transforms lipophilic drugs into more polar readily excretable products; the liver is the major site for drug metabolism in addition of the kidney and the intestines (Some agents are initially administered as inactive compounds (pro-drugs) and must be metabolized to their active forms)

Reactions of drug metabolism

The kidney cannot efficiently eliminate lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal tubules. Therefore, lipid soluble agents must first be metabolized in the liver using two general sets of reactions, called Phase I and Phase II

1. Phase I: Phase I reactions function to convert lipophilic molecules into more polar molecules by introducing or unmasking a polar functional group,

a. Phase I reactions utilizing the P450 system: The Phase I reactions most frequently involved in drug metabolism are catalyzed by the cytochrome P450 system (also called microsomal mixed function oxidase)



P450 system (microsomal mixed function oxidase): is composed of many families of heme-containing isozymes that are located in most cells but are primarily found in the liver and GI tract, six isozymes are responsible for the vast majority of P450-catalyzed reactions: CYP3A4, CYP2D6, CYP2C9/10, CYP2C19, CYP2E1, and CYP1A2

P450 system (microsomal mixed function oxidase) Inducers:

as phenobarbital, rifampin's, and carbamazepine, are capable of increasing the synthesis of one or more CYP isozymes, increased biotransformation of drugs and can lead to significant decreases in plasma concentrations of drugs metabolized by these CYP isozymes For example, rifampin, an ant tuberculosis drug , significantly decreases the plasma concentrations of protease inhibitors

Consequences of increased drug metabolism include:

1) Decreased plasma drug concentrations,
2) decreased drug activity if metabolite is inactive,
3) increased drug activity if metabolite is active,
4) Decreased therapeutic drug effect.

P450 system (microsomal mixed function oxidase) Inhibitors:

Inhibition of CYP isozyme activity is an important source of drug interactions that leads to serious adverse events such as ketoconazole and omeprazole inhibit one or more of the CYP-dependent biotransformation pathways of warfarin, plasma concentrations of warfarin increase, which leads to greater inhibition of coagulation and risk of hemorrhage and other serious bleeding reactions

More important CYP inhibitors are erythromycin, ketoconazole, and ritonavir
Cimetidine blocks the metabolism of theophylline, clozapine, and warfarin
Grapefruit juice inhibits CYP3A4 and, thus, drugs such as amlodipine, clarithromycin, and Indinavir

2.Phase II: If the metabolite from Phase I metabolism is sufficiently polar, many Phase I metabolites are too lipophilic to be retained in the kidney tubules

A subsequent conjugation reaction with an endogenous substrate, such as glucuronic acid, sulfuric acid, acetic acid, or an amino acid, results in polar, usually more water-soluble

• Reversal of order of the phases: Not all drugs undergo Phase I and II reactions in that order. For example, isoniazid is first acetylated (a Phase II reaction) and then hydrolyzed to isonicotinic acid (a Phase I reaction).

Drug Elimination:

Removal of a drug from the body occurs via a number of routes, the most important being through the kidney into the urine.

Plasma clearance: is expressed as the volume of plasma from which all drug appears to be removed in a given time.

Clearance = renal blood flow * extraction ratio

Extraction ratio: This ratio is the decline of drug concentration in the plasma from the arterial to the venous side of the kidney

The elimination of a drug usually follows first-order kinetics, and the concentration of drug in plasma drops exponentially with time. This can be used to determine the half-life, ,½ of the drug t1/2 = 0.693/Ke where Ke = elimination rate

Elimination rate: amount of drugs that loss per unite time

Drug half-life: it's the time that drug required it to reach of its half con in the circulation.

Clinical situations resulting in changes in drug half-life

A. First-Order Elimination

- The rate of elimination is proportional to the concentration (ie, the higher the concentration, the greater the amount of drug eliminated per unit time).
- Drugs with first-order elimination have a characteristic half-life of elimination that is constant regardless of the amount of drug in the body

B. Zero-Order Elimination

The rate of elimination is constant regardless of concentration

This occurs with drugs that saturate their elimination mechanisms

This is typical of ethanol and of phenytoin and aspirin at high therapeutic or toxic concentrations.

When a patient has an abnormality that alters the half-life of a drug, adjustment in dosage is required. It is important to be able to predict in which patients a drug is likely to have a change in half-life.

The half-life of a drug is increased by

1) Diminished renal plasma flow or hepatic blood flow for example, in cardiogenic shock, heart failure, or hemorrhage;

2) Decreased extraction ratio for example, as seen in renal disease

3) Decreased metabolism for example, when another drug inhibits its biotransformation or in hepatic insufficiency, as with cirrhosis.

Half-life of a drug may decrease by

1) Increased hepatic blood flow,

2) Decreased protein binding,

3) Increased metabolism.

Kinetics of IV infusion :

(iv infusion is continuous while iv injection either single or repeated doses):

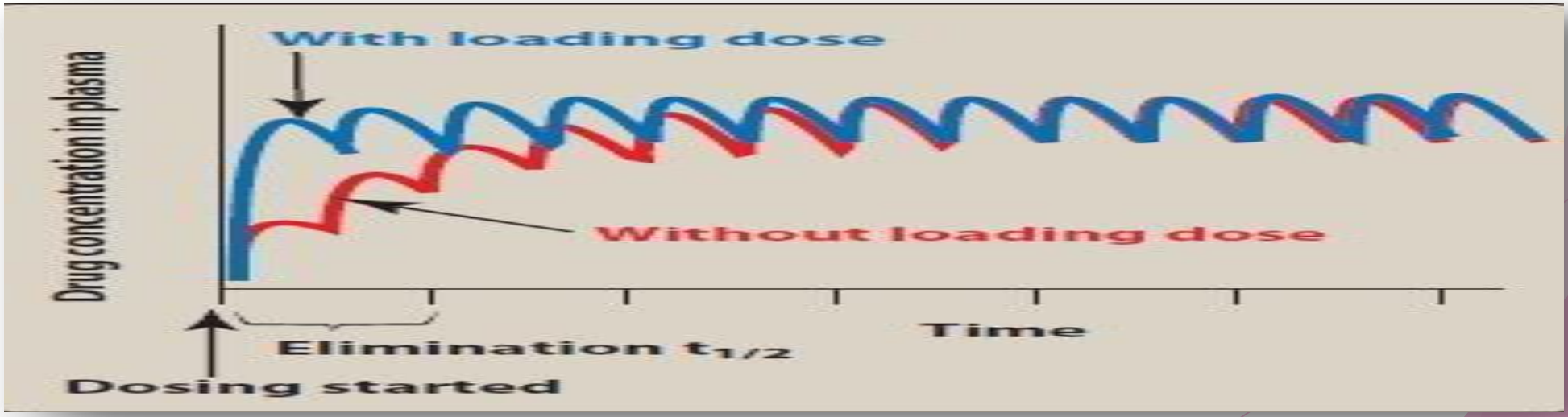
With continuous IV infusion, the rate of drug entry into the body is constant. In the majority of cases, the elimination of a drug is first order; that is, a constant fraction of the agent is cleared per unit of time. Therefore, the rate of drug exit from the body increases proportionately as the plasma concentration increases, and at every point in time, it is proportional to the plasma concentration of the drug.

Steady-state drug levels in blood:

Following the initiation of an IV infusion, the plasma concentration of drug rises until the rate of drug eliminated from the body precisely balances the input rate. Thus, a steady-state is achieved in which the plasma concentration of drug remains constant , A steady state plasma concentration of a drug occurs when the rate of drug elimination is equal to the rate of administration.

Rate of drug decline when the infusion is stopped: When the infusion is stopped, the plasma concentration of a drug declines (washes out) to zero with the same time course observed in approaching the steady state.

Loading dose: A delay in achieving the desired plasma levels of drug may be clinically unacceptable. Therefore, a loading dose of drug can be injected as a single dose to achieve the desired plasma level rapidly, followed by an infusion to maintain the steady state (maintenance dose).



Pharmacodynamics: Are the action of the drugs on the body, and the influence of drug concentration on the magnitude of the response

Receptors: it's a specialized target macromolecules present either on cell surface or within the cell , Drugs exert either beneficial or harmful effect by interaction with the receptor (drug – receptor complex) initiate alteration in biochemical or molecular activity by signal transduction in the cell

Signal transduction: drug consider as (signal) while receptors consider as (signal detector), receptor recognized the bounded agonist cause a series of reaction that ultimately produce specific intracellular response.

Agonist: its naturally occurring small molecules, bound to the site on receptor and activate its.

Second messenger: it's a part of a cascade of events that translate agonist binding into cellular response.

Drug-receptor complex:

Each cell contains different types of receptors, which recognized deferent type of agonist ligand producing a unique response, As example heart cells (cardiocyte) contain adrenergic receptor β1 cell recognized epinephrine and norepinephrine, and contains muscarinic receptor M2 that recognized acetylcholine, each receptor control vital function of the heart, The magnitude of drug response depends on the number of drug – receptor complex (which follow a concept of enzyme – substrate or Ab-Ag complex), Receptors usually named according to its binding ligand (as histamine receptor), Note: all drugs need receptors to exert its effect but there is some of exception as antacid drugs that (neutralized gastric acid).

All drugs exert their effects by interacting with a receptor.

Chemistry of Receptors and Ligands:

- Interaction of receptors with ligands involves the formation of chemical bonds, most commonly electrostatic and hydrogen bonds, as well as weak interactions involving vander Waals forces. (this bonds determined the affinity of drugs to the receptors)

- The successful binding of a drug requires an exact fit of the ligand atoms with the complementary receptor atoms.

- The metaphor of the "lock and key" is a useful concept for understanding the interaction of receptors with their ligands. The precise fit required of the ligand echoes the characteristics of the "key," whereas the opening of the "lock" reflects the activation of the receptor.

- Induced-fit model has largely replaced the lock-and-key concept,

In the presence of a ligand, the receptor undergoes a conformational change to bind the ligand. The change in conformation of the receptor caused by binding of the agonist activates the receptor, which leads to the pharmacologic effect. This model suggests that the receptor is flexible, not rigid as implied by the lock-and-key model.

Major Receptor Families

Generally receptor is a biological molecules that bind to agonist and produce a measurable response, these receptors either enzyme, nucleic acid or structural protein which is the richest source for receptor structure. Its transport extracellular signal to intracellular response.

Four types of receptors are found:

1) ligand-gated ion channels, (hydrophilic ligands):

- The extracellular portion of the receptor contains a specific portion for ligand binding that regulate the shape of pore which allow to ions to transport a cross the membranes
- This channels or pores open for few milliseconds
- This types of receptors mediate (neurotransmitters , cardiac and skeletal muscles)
- As example of this type of receptors (cholinergic nicotinic receptor) where activate it cause influx of Na and out flux of K causing generation of action potential in neurons and skeletal muscle contraction
- Another example (GABA) receptors, where activate it cause influx of CL leading to hyperpolarization of neurons.
- As example of drugs that targeting this types of receptor, local anesthesia (lidocaine) which prevent neuron Na influx causing minimize in neural conducted.

2) G protein–coupled receptors, (hydrophilic ligands):

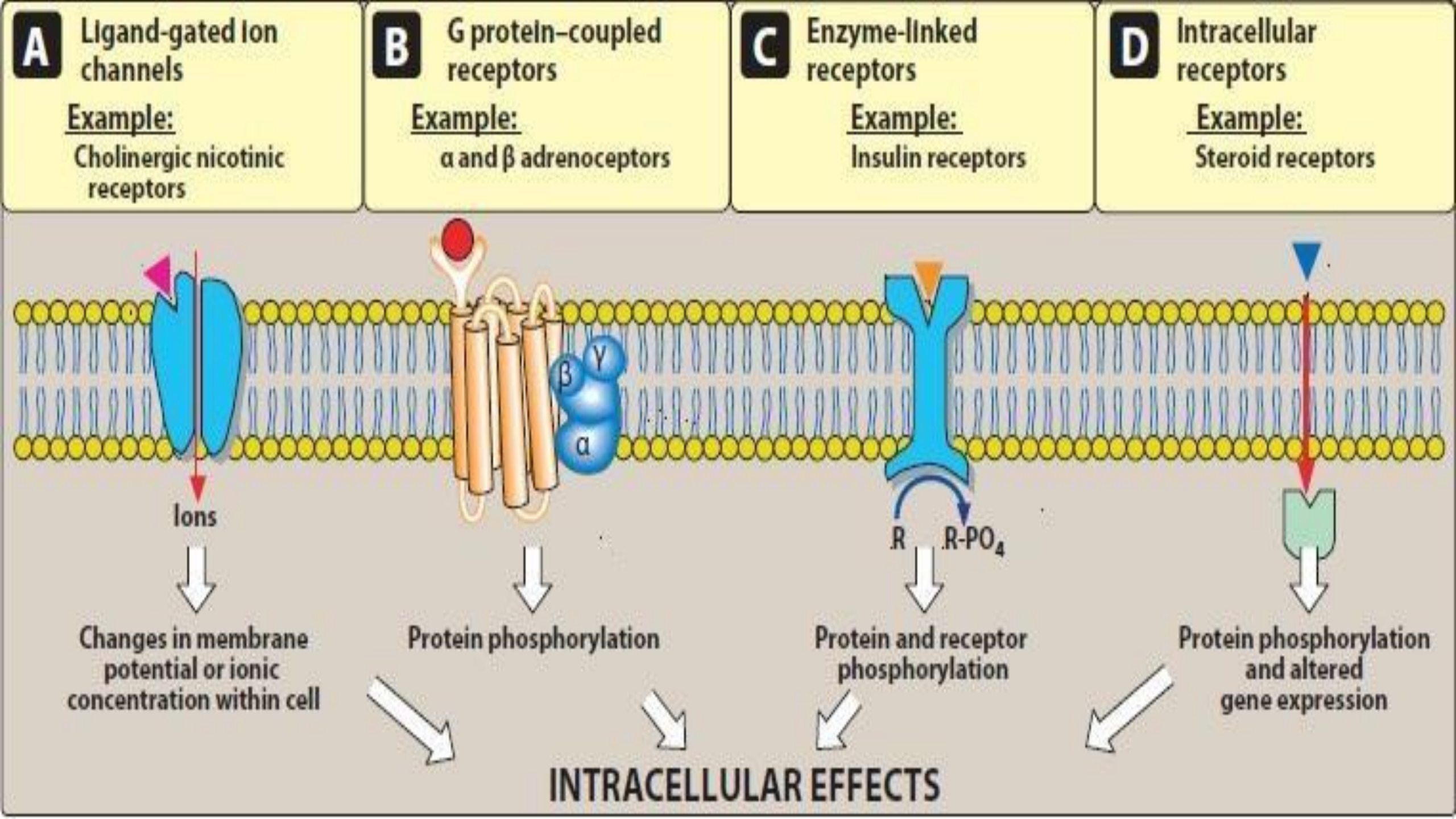
- These receptors are comprised of a single peptide that has seven membrane-spanning regions, and these receptors are linked to a G protein (having three subunits, an α subunit that binds guanosine triphosphate (GTP) and a βγ subunit) Binding of ligand to the extracellular region of the receptor activates the G protein so that GTP replaces guanosine diphosphate (GDP) on the α subunit, Stimulation of these receptors results in responses that last several seconds to minutes.
- Second messengers: These are essential in conducting and amplifying signals coming from G protein–coupled receptors. A common pathway turned on by G proteins , the activation of adenylyl cyclase by α-GTP subunits which results in the production of cyclic adenosine monophosphate (cAMP)—a second messenger that regulates protein phosphorylation. G proteins also activate phospholipase C, which is responsible for the generation of two other second messengers, namely inositol trisphosphate and diacylglycerol.

3) enzyme-linked receptors, (hydrophilic ligands):

- Extracellular portion consist from two dimer or multi-subunit , when binding with ligand causing activation of intracellular enzyme .
- Binding of ligand to the receptor causing activation to the tyrosin kinase in β subunit of the receptor , causing autophosphorylation to tyrosin residue
- Then subsequently phosphorylate other intracellular receptor like (insulin receptor substrate tyrosin) phosphorylated
- Then activation of other tyrosin kinase and phosphatase enzymes to produce a desirable biological effect.
- As example of this type of receptors (epidermal growth factor, platelet-derived growth factor, insulin receptors).
- Duration last from minutes to hours.

4) Intracellular receptors (hydrophobic Ligands):

- Because of these receptors are entirely occur intracellular, the ligand must be lipophilic and can penetrate the cell membrane intracellularly.
- The primary target is ligand receptor complex, which work as transcription factor in cell nucleus.
- Binding of ligand to the receptors cause dissociation of the receptor suppressor binding protein
- The activated ligand–receptor complex then translocates to the nucleus, where it often dimerizes before binding to transcription factors that regulate gene expression. The activation or inactivation of these factors causes the transcription of DNA into RNA and translation of RNA into an array of proteins
- The time course of activation and response of these receptors is on the order of hours to days.
- For example, (steroid hormones) targeting cells via intracellular receptors. Other targets of intracellular ligands are structural proteins, enzymes, RNA, and ribosomes. For example, tubulin is the target of antineoplastic agents such as paclitaxel, the enzyme dihydrofolate reductase is the target of antimicrobials such as trimethoprim.


A
Ligand-gated Ion channels
Example:
Cholinergic nicotinic receptors
B
G protein–coupled receptors
Example:
α and β adrenoceptors
C
Enzyme-linked receptors
Example:
Insulin receptors
D
Intracellular receptors
Example:
Steroid receptors
β
γ
α
Ions
R
R-PO4
Changes in membrane potential or ionic concentration within cell
Protein phosphorylation
Protein and receptor phosphorylation
Protein phosphorylation and altered gene expression
INTRACELLULAR EFFECTS

Desensitization and down-regulation of receptors

- Continuous administration of agonist leads to changes in the responsiveness of the receptor, to prevent potential damage to the cell (for example, high concentrations of calcium, initiating cell death),
- Two mechanism occurs to protect the cells from further damage including

1- Desensitization (tachyphylaxis) : the cells became unresponsiveness to the action of agonist

2- Downregulation: where the cells are internalized and sequestered within the cell, unavailable for further agonist interaction. But the cells may be restoring its activity after a fints of time as (ion channels receptor), or may be further processed and degraded, decreasing the total number of receptors available. (Some receptor became up regulated by the action antagonist causing increase in the number of receptors leading to increase in the sensitivity of agonist and decrease in the response to antagonist).

Dose response relationship:

- The action of Agonist drug mimic the action of endogenous ligand as (isoproterenol action resemble to the action of norepinephrine on β1 receptor on heart.
- The magnitude of drug action depends on drug concentration and drug pharmacological profile (absorption, distribution, metabolism and excretion).

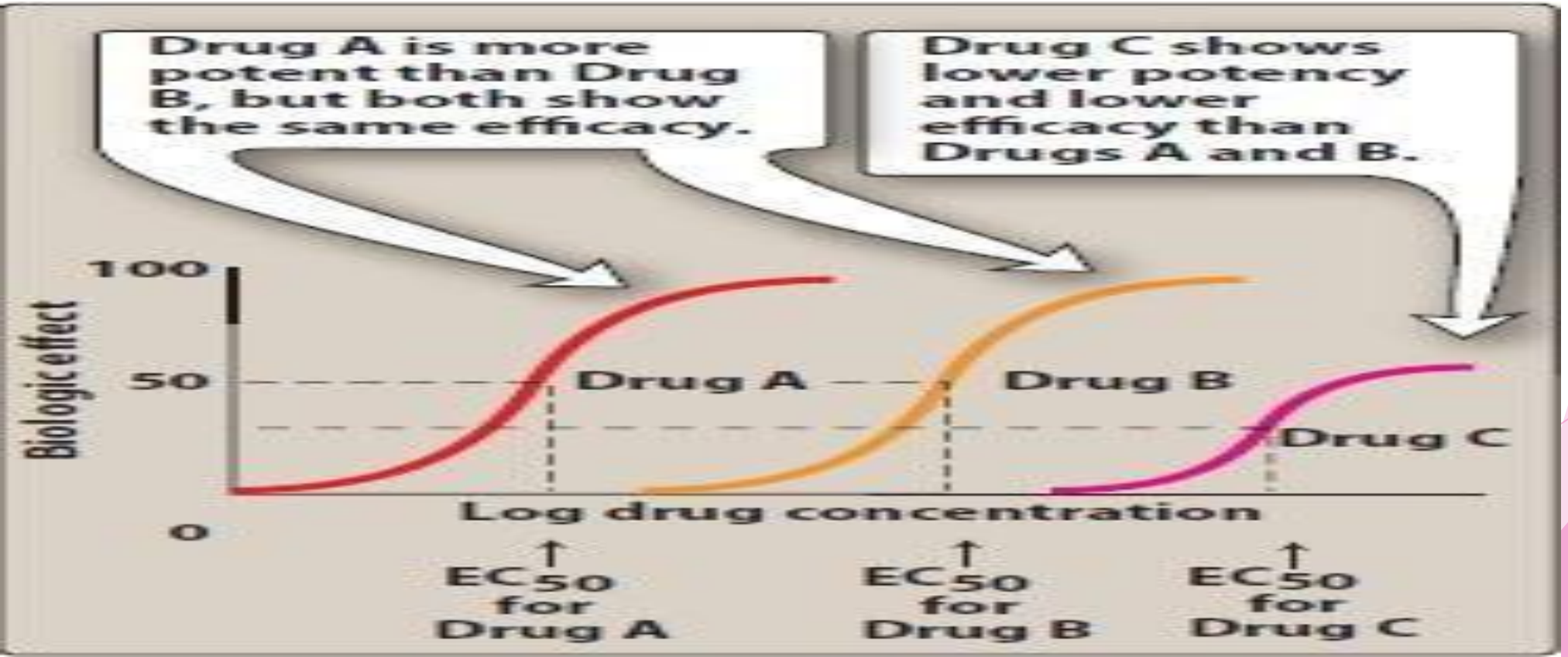
Graded dose – response relationship:

- As the concentration of a drug increases its pharmacologic effect also gradually increases until all the receptors are occupied (the maximum effect).
- Two important properties of drugs, potency and efficacy, can be determined by graded dose–response curves.

1. Potency:

- Measure the amount of drug to produce the response of a give magnitude.
- can be calculated by determined the EC50 (concentration of the drug that produce 50% of a maximal response)

As example (candesartan dose 4-32mg) more potent and have a lower EC50 value than (irbesartan 75-300 mg).



2. Efficacy:

- Is the magnitude of response a drug cause when interact with the receptor.
- Its depend on the number of drug-receptor complex and intrinsic drug activity (ability of drug to activate the receptors and produce a response).
- Full bound of drug with receptor , produce E-max agonist , while antagonist have a E-zero
- Its more useful clinically than potency

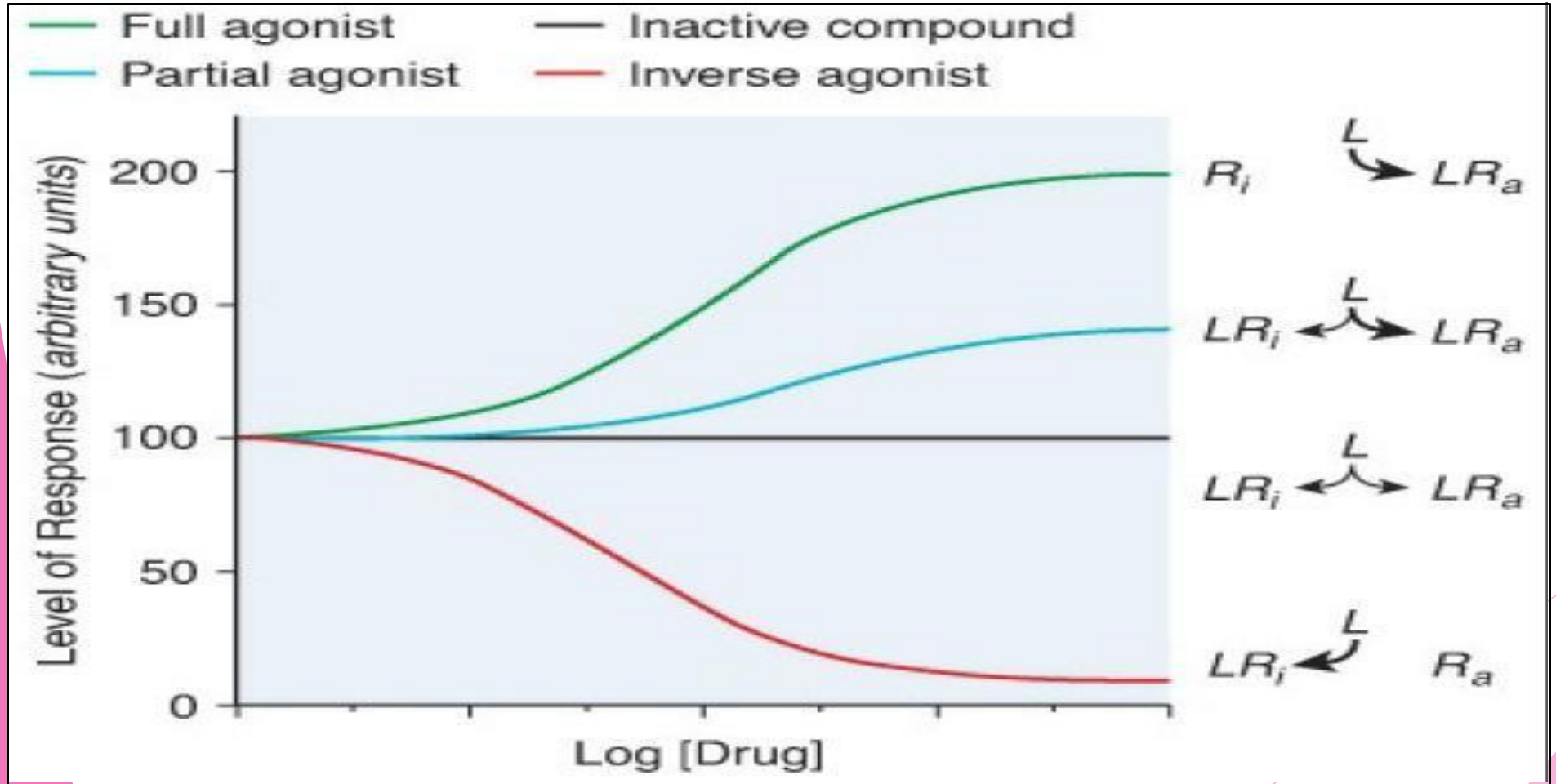
Intrinsic activity:

- Drugs bind to receptor produce a biological response by depending on drug concentration and fraction of occupied receptors
- The intrinsic activity of a drug determines its ability to fully or partially activate the receptors. Drugs may be categorized according to their intrinsic activity and resulting **Emax** values.

1- **Full agonists:** a ligand that produce a biological response as same as the effect of endogenous ligand binding, all full agonist must have the same Emax , as example (Phenylephrine) it's an α- adrenergic agonist , causing vasoconstriction and elevation in blood pressure.

2- **Partial agonists:** partial agonist agents have intrinsic activity greater than zero but less than one , its cannot produce same full agonist Emax, it may have less or more affinity than full agonist, when two agents given together (full and partial agonist) given at the same time , Emax decrease until to reach to partial agonist Emax .as aripiprazole (antipsychotic) which have a partial agonist on dopamine receptor to minimized of extra pyramidal side effect.

Antagonists: it's kind of agents that bind to a receptor with high affinity but possess zero intrinsic activity, has no effect in the absence of an agonist but can decrease the effect of an agonist when present, antagonism done by either by blocking the drug's ability to bind to the receptor or by blocking its ability to activate the receptor.

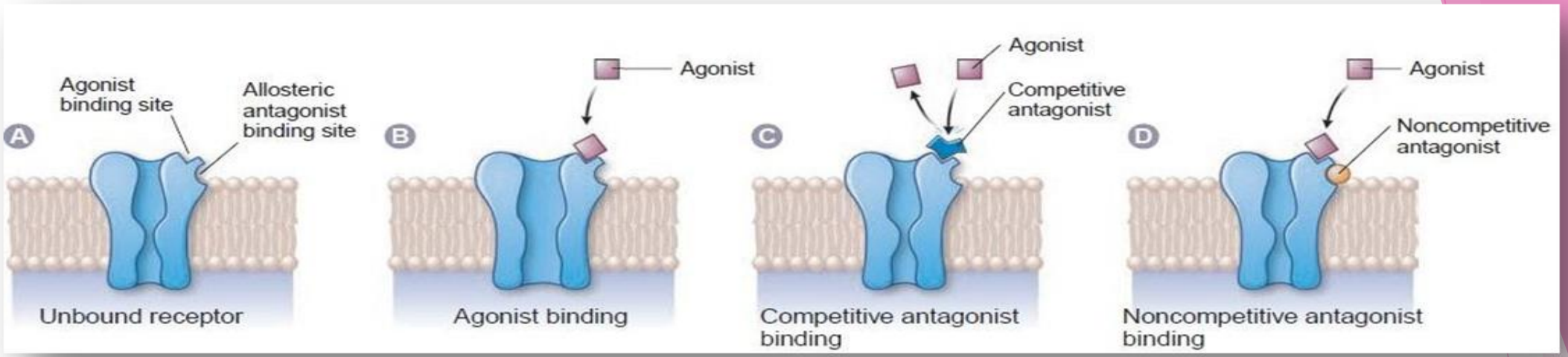


Five types of antagonism were founded:

a) Competitive antagonists: If both the antagonist and the agonist bind to the same site on the receptor in a reversible manner , its prevents an agonist from binding to its receptor and maintains the receptor in its inactive state, For example, the antihypertensive drug terazosin competes with the endogenous ligand norepinephrine at α1adrenoceptors, thus decreasing vascular smooth muscle tone and reducing blood pressure.

b) Irreversible antagonists: bind covalently to the active site of the receptor, thereby reducing the number of receptors available to the agonist, protamine ionically binds to heparin, rendering it inactive and antagonizing heparin's anticoagulant effect.

c) Allosteric antagonists: this kind of antagonists the drugs binds to a site ("allosteric site") other than the agonist–binding site and prevents the receptor from being activated by the agonist , An example of an allosteric agonist is picrotoxin, which binds to the inside of the GABA–controlled chloride channel. When picrotoxin is bound inside the channel, no chloride can pass through the channel, even when the receptor is fully activated by GABA.



d) Functional antagonism: "physiologic antagonism." An antagonist may act at a completely Separate receptor, initiating effects that are functionally opposite those of the agonist, As example the functional antagonism of epinephrine to histamine induced bronchoconstriction. Histamine binds to H1 histamine receptors on bronchial smooth muscle, causing bronchoconstriction of the bronchial tree. Epinephrine is an agonist at β2-adrenoceptors on bronchial smooth muscle, which causes the muscles to relax.

e) Chemical antagonism: there is no clearly receptor founded, it's a chemical reaction between the chemical ligands and chemical nature receptor, as example antacid drugs.

Therapeutic index:

Is the ratio of the dose that produces toxicity in half the population (TD50) to the dose that produces a clinically desired or effective response (ED50) in half the population.

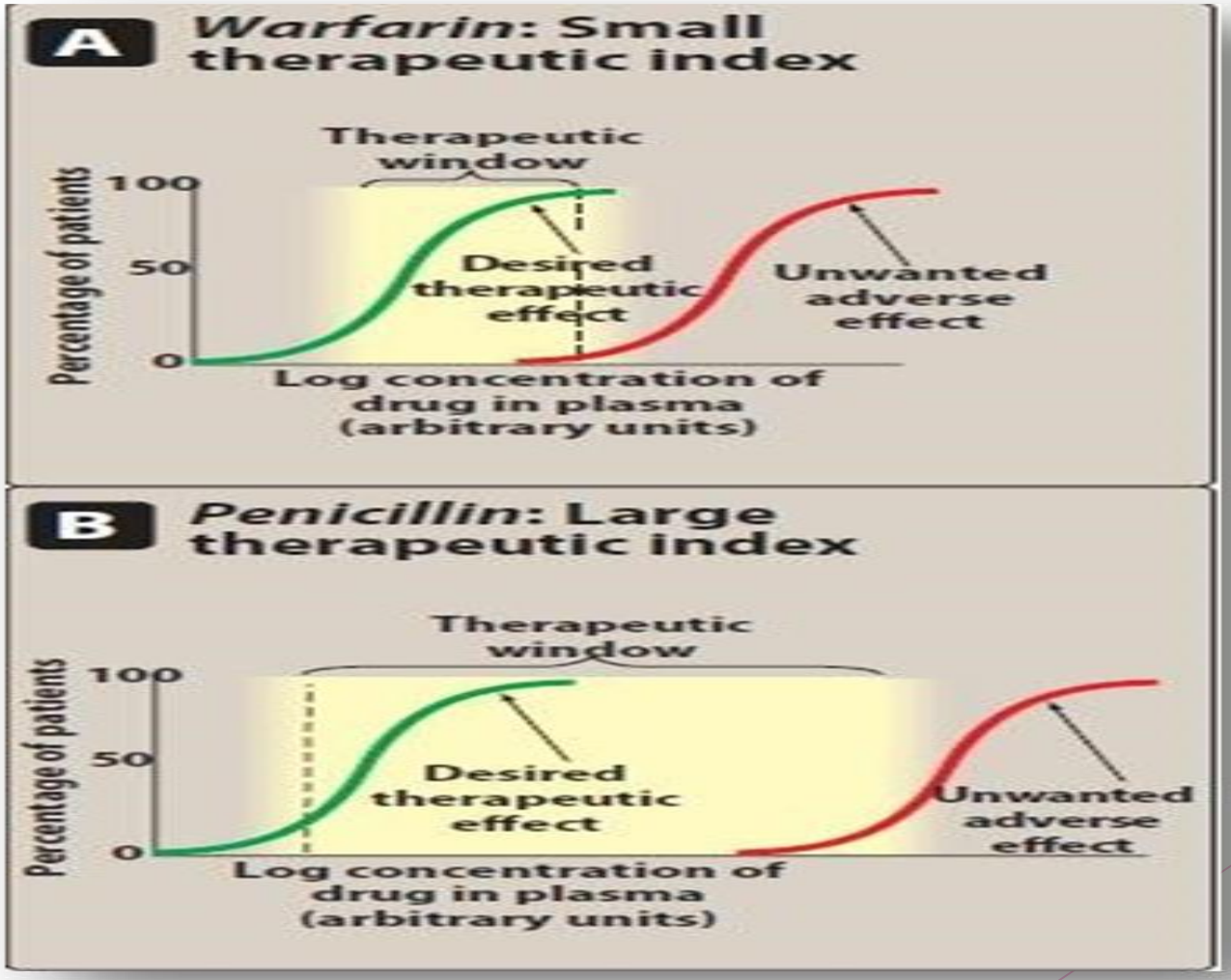
TI = TD50 / ED 50

TI is a measure of a drug's safety, because a larger value indicates a wide margin between doses that are effective and doses that are toxic.

Clinical usefulness of the therapeutic index:

• Drugs with low therapeutic indices are routinely used to treat serious diseases. In these cases, the risk of experiencing side effects is not as great as the risk of leaving the disease untreated. Warfarin (example of a drug with a small therapeutic index): As the dose of warfarin is increased, a greater fraction of the patients respond (for this drug, the desired response is a two- to threefold increase in the international normalized ratio [INR]) until, eventually, all patients respond, at higher doses of warfarin, anticoagulation resulting in hemorrhage. Agents with a low TI (that is, drugs for which dose is critically important) are those drugs for which bioavailability critically alters the therapeutic effects.

Penicillin (example of a drug with a large therapeutic index): it is safe and common to give doses in excess of that which is minimally required to achieve a desired response without the risk of adverse side effects. In this case, bioavailability does not critically alter the therapeutic or clinical effects.

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THE AUTONOMIC NERVOUS SYSTEM 3

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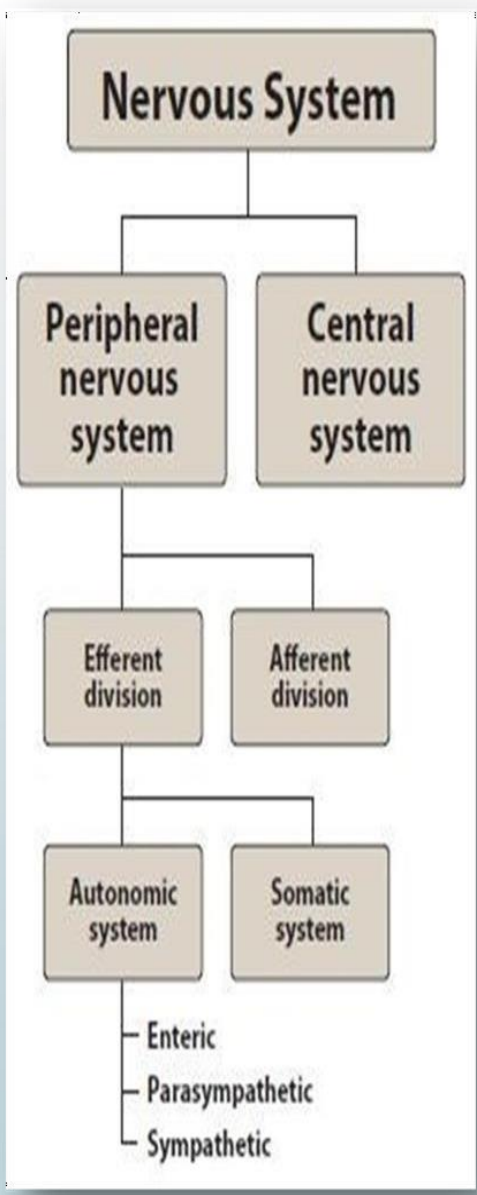
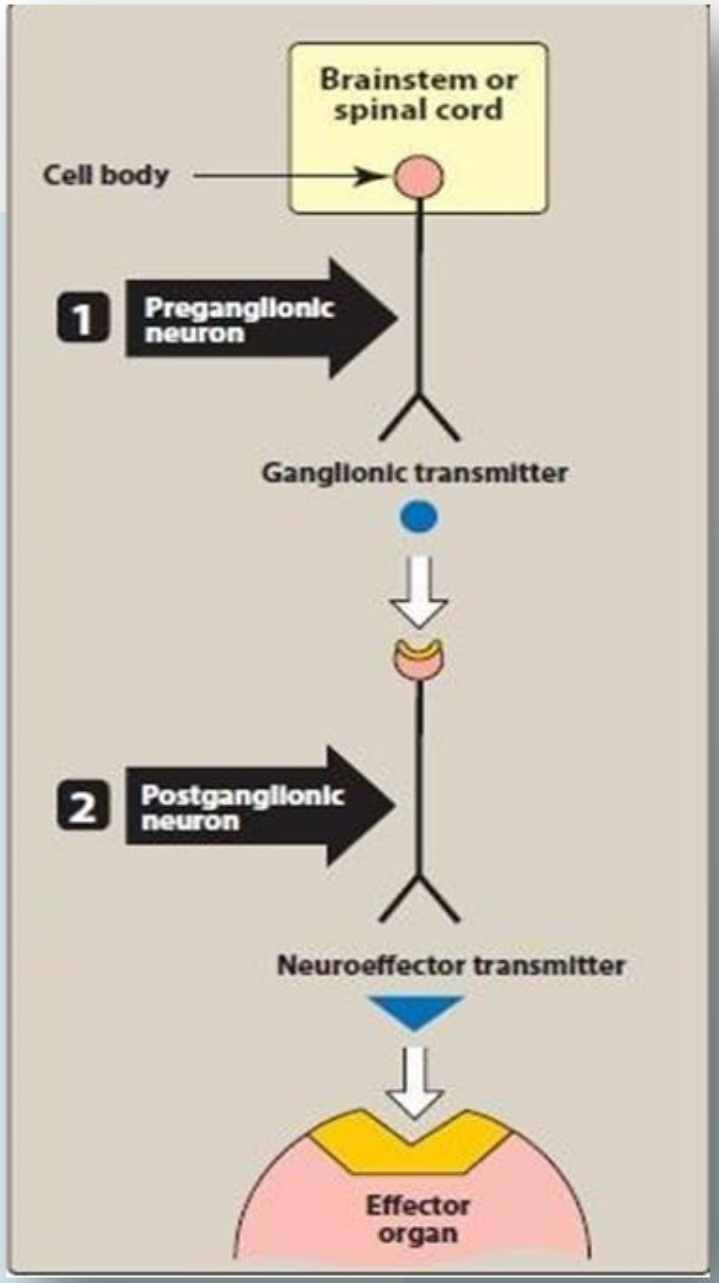
INTRODUCTION TO THE NERVOUS SYSTEM : The nervous system is divided into two anatomical divisions: the central nervous system (CNS), which is composed of the brain and spinal cord, and the peripheral nervous system, which includes neurons located outside the brain and spinal cord , The peripheral nervous system is subdivided into the efferent and afferent divisions. The efferent neurons carry signals away from the brain and spinal cord to the peripheral tissues, and the afferent neurons bring information from the periphery to the CNS. Afferent neurons provide sensory input to modulate the function of the efferent division through reflex arcs or neural pathways that mediate a reflex action. The ANS, conversely, regulates the everyday requirements of vital bodily functions without the conscious participation of the mind. Because of the involuntary nature of the ANS as well as its functions, it is also known as the visceral, or involuntary nervous system. It is composed of efferent neurons that innervate smooth muscle of the viscera, cardiac muscle, vasculature, and the exocrine glands, thereby controlling digestion, cardiac output, blood flow, and glandular secretions.



Anatomy of the ANS

1. Efferent neurons: 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 .

The cell body of the first nerve cell, the preganglionic neuron, is located within the CNS. The preganglionic neurons emerge from the brainstem or spinal cord and make a synaptic connection. in ganglia (an aggregation of nerve cell bodies located in the peripheral nervous system). The ganglia function as relay stations between the preganglionic neuron and the second nerve cell, the postganglionic neuron. The cell body of the postganglionic neuron originates in the ganglion. It is terminates on effector organs, such as smooth muscles of the viscera, cardiac muscle, and the exocrine glands.



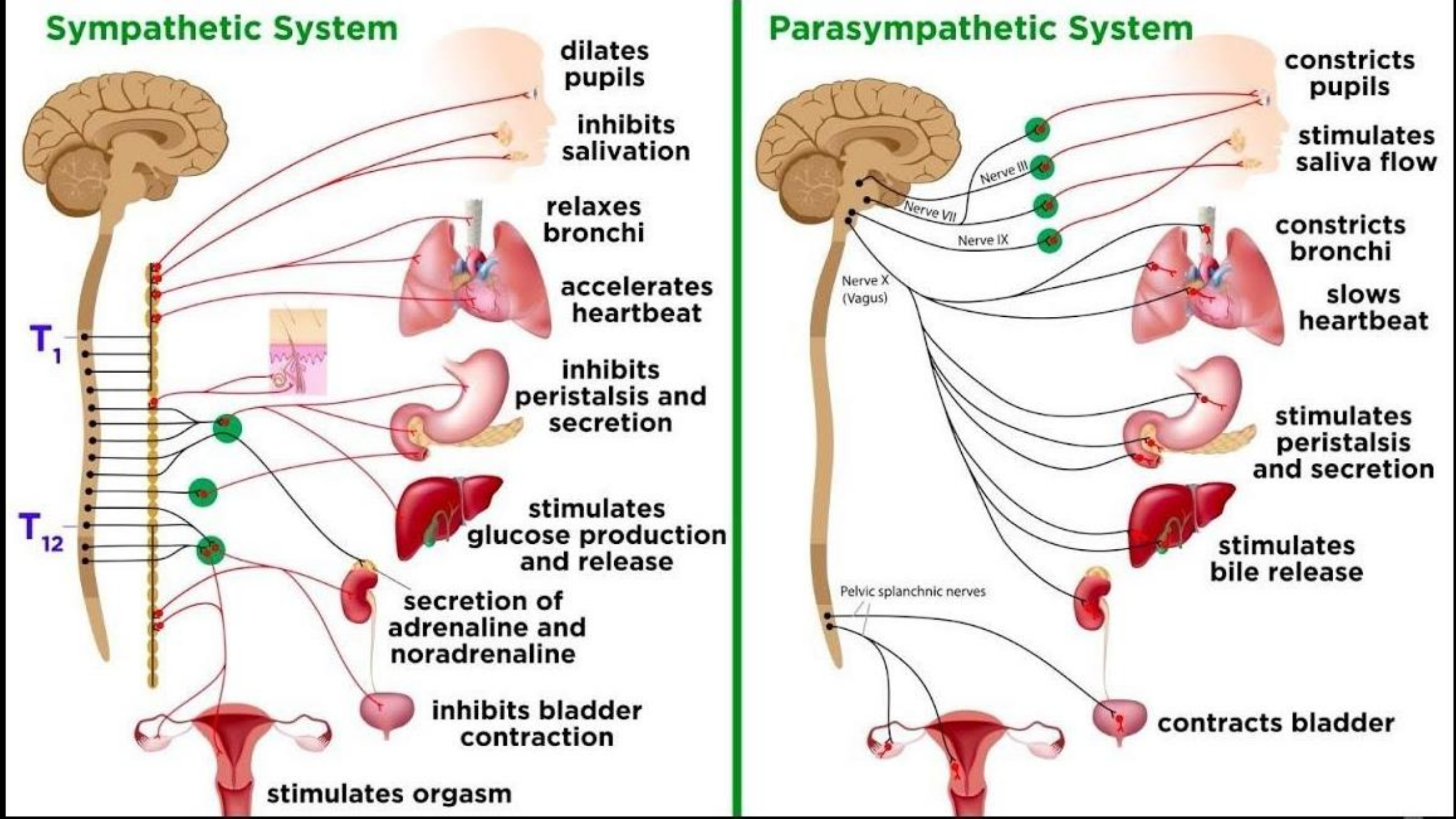
Afferent neurons: The afferent neurons (fibers) of the ANS are important in the reflex regulation of this system (for example, by sensing pressure in the carotid sinus and aortic arch) and in signaling the CNS to influence the efferent branch of the system to respond.

A- Functions of the sympathetic nervous system

Although continually active to some degree (for example, in maintaining the tone of vascular stressfulto responsein adjustingof propertythe has divisionsympatheticthebeds), situations, such as trauma, fear, hypoglycemia, cold, and exercise .

1. Effects of stimulation of the sympathetic division: The effect of sympathetic output is to increase heart rate and blood pressure, to mobilize energy stores of the body, and to increase blood flow to skeletal muscles and the heart while diverting flow from the skin and internal organs. Sympathetic stimulation results in dilation of the pupils and the bronchioles , It also affects GI motility and the function of the bladder and sexual organs.

2-Fight-or-flight response: The changes experienced by the body during emergencies are referred to as the “fight or 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 ,This system, with its diffuse distribution of postganglionic fibers, is involved in a wide array of physiologic activities. Although it is not essential for survival, it is nevertheless an important system that prepares the body to handle uncertain situations and unexpected stimuli.


Sympathetic System
dilates pupils
inhibits salivation
relaxes bronchi
accelerates heartbeat
T1
inhibits peristalsis and secretion
stimulates glucose production and release
T12
secretion of adrenaline and noradrenaline
inhibits bladder contraction
stimulates orgasm
Parasympathetic System
constricts pupils
stimulates saliva flow
Nerve III
Nerve VII
Nerve IX
Nerve X (Vagus)
constricts bronchi
slows heartbeat
stimulates peristalsis and secretion
stimulates bile release
Pelvic splanchnic nerves
contracts bladder

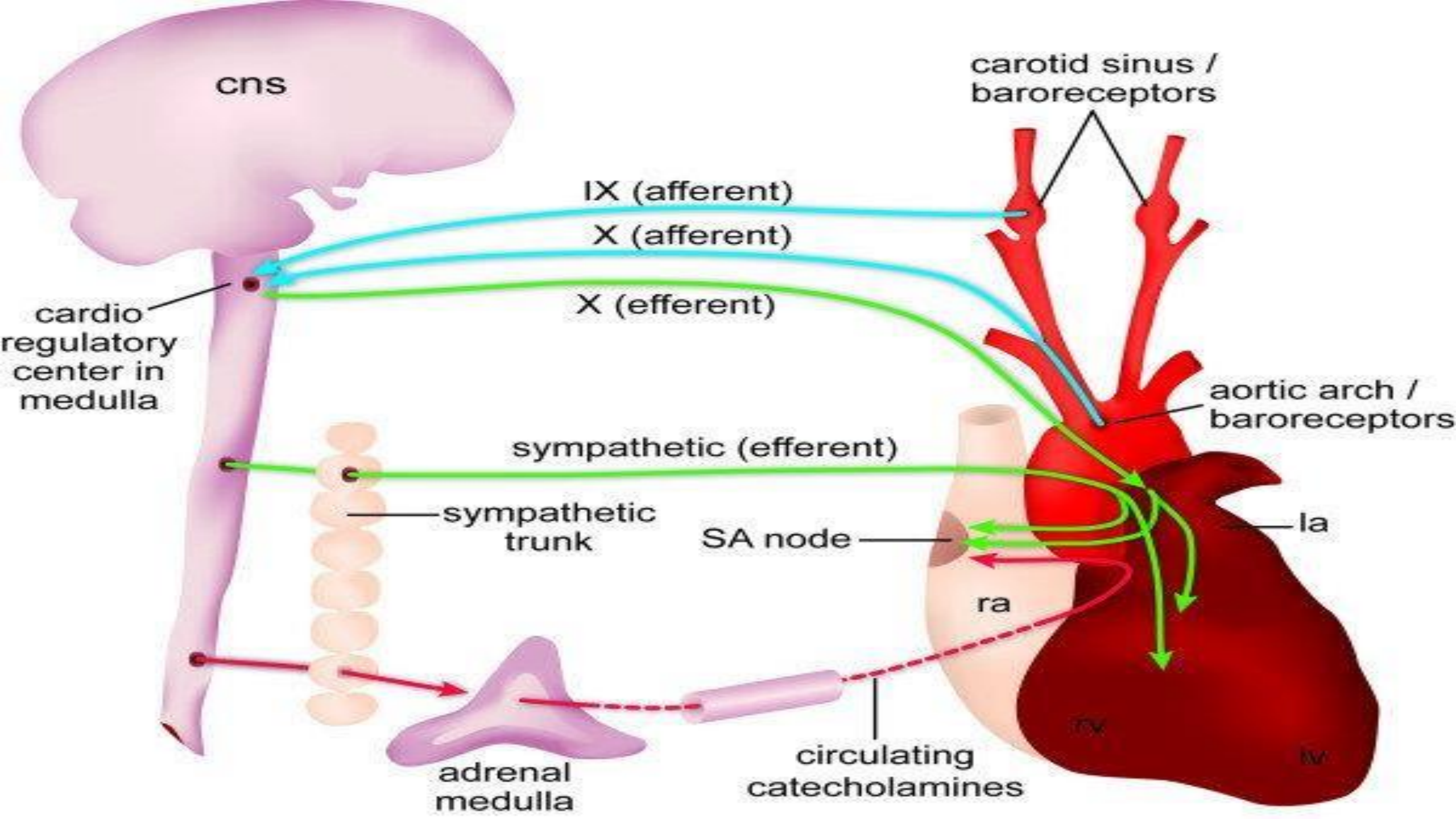
B- Functions of the parasympathetic nervous system : The parasympathetic division is involved with maintaining homeostasis within the body. It is required for life, since it maintains essential bodily functions, such as digestion and elimination of wastes, The parasympathetic division usually acts to 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 fibers innervating specific organs such as the gut, heart, or eye are activated separately, and the system functions to affect these organs individually.

C- Enteric neurons: It is a collection of nerve fibers that innervate the gastrointestinal (GI) tract, pancreas, and gallbladder, and it constitutes the "brain of the gut." This system functions independently of the CNS and controls the motility, exocrine and endocrine secretions, and microcirculation of the GI tract. It is modulated by both the sympathetic and parasympathetic nervous systems.

D- Somatic nervous system : The efferent somatic nervous system differs from the ANS in that a single myelinated motor neuron, originating in the CNS, travels directly to skeletal muscle without the mediation of ganglia. the somatic nervous system is under voluntary control, whereas the ANS is involuntary. Responses in the somatic division are generally faster than those in the ANS.

Reflex arcs: Most of the afferent impulses are involuntarily translated into reflex response. For example ,a fall in blood pressure causes pressure- sensitive neurons(**baroreceptors** in the heart, **vena cava**, **aortic arch**, and**carotid sinuses**)in send fewer impulses to cardiovascular centers 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 .

Organs receiving only sympathetic innervation: Although most tissues receive dual innervation, some effector organs, such as the adrenal medulla, kidney, pilomotor muscles, and sweat glands, receive innervation only from the sympathetic system


cns
carotid sinus /
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medulla
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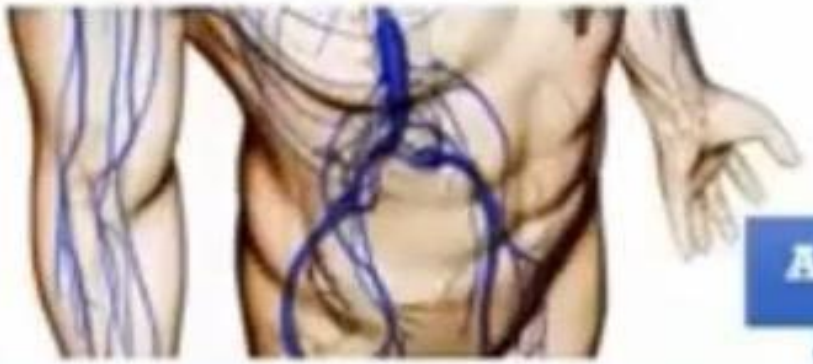
catecholamines



Somatic Nervous System

Autonomic Nervous System

- Supply cardiac muscle, smooth muscle and exocrine gland.
- ***Relay*** in autonomic ganglia (relay station) which consist of ***preganglionic*** & ***postganglionic*** fibers.

- ***Involuntary*** ⇨ under the control of CNS.

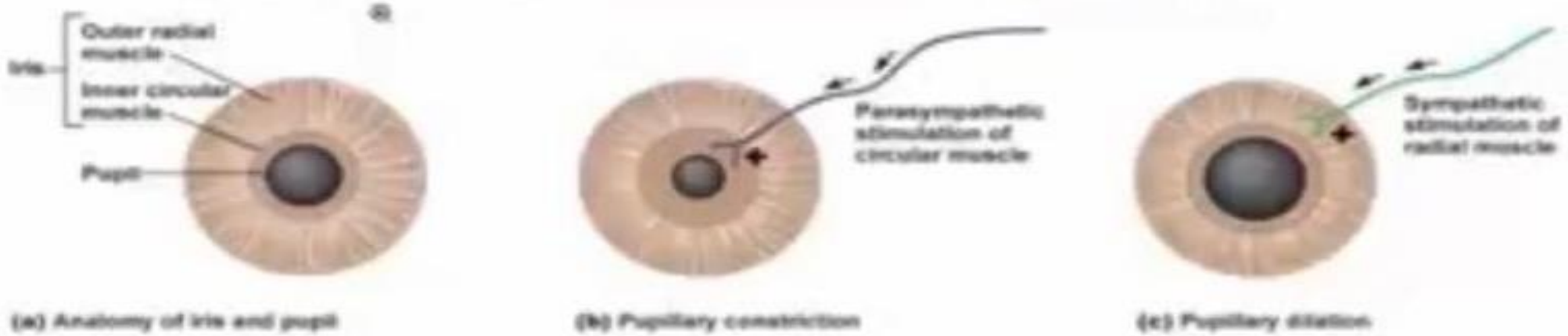
- Supply skeletal muscle.
- ***Don't relay*** *in ganglia.*
- ***Voluntary***.

Differences between sympathetic and parasympathetic nerves :

	SYMPATHETIC	PARASYMPATHETIC
Sites of origin	Thoracic and lumbar region of the spinal cord (thoracolumbar)	Brain and sacral area of the spinal cord (craniosacral)
Length of fibers	Short preganglionic Long postganglionic	Long preganglionic Short postganglionic
Location of ganglia	Close to the spinal cord	Within or near effector organs
Preganglionic fiber branching	Extensive	Minimal
Distribution	Wide	Limited
Type of response	Diffuse	Discrete

- **Some organs are supplied with one division of ANS:**

- **Iris sphincter (pupillary constrictor) muscle** *(Circular)* ⇨ Supplied by ***parasympathetic*** (M_3).
- **Iris dilator (pupillary dilator) muscle** *(Radial)* ⇨ Supplied by ***sympathetic*** (α_1).



- **Arrector pili muscle (pilomotor muscle)** ⇨ Supplied by sympathetic (α_1) ⇨ hair erection. The contraction of the muscle is therefore involuntary–stresses e.g. cold, fear (***Goosebumps***).

- **Thermoregulatory (Eccrine) sweat gland** ⇨ Supplied only by sympathetic fibers, but through cholinergic (parasympathetic) receptors (M_3).
- **Adrenal medulla** ⇨ Supplied only by sympathetic fibers, but through nicotinic (parasympathetic) receptors (N_N).
- **Ventricles of the heart and Kidney** ⇨ Supplied by both innervations but only sympathetic are active (β_1). Role of the parasympathetic innervation is still unclear.
- **Blood Vessels** ⇨ Vascular smooth muscle is innervated primarily by the sympathetic and indirectly non-innervated by the parasympathetic.

  I.e. ☛ ***Direct acting*** ⇨ ***innervated*** sympathetic ⇨ α_1 receptor (***Vasoconstriction***).

  ☛ ***Indirect acting*** ⇨ ***Non-innervated*** parasympathetic ⇨ M_3 receptors (***Vasodilatation***) via the nitric oxide (NO)/endothelium derived relaxing factor (no direct innervation).

Neurotransmitters

Communication between nerve cells, and between nerve cells and effector organs, occurs through the release of specific chemical signals (neurotransmitters) from the nerve terminals, This release is triggered by the arrival of the action potential at the nerve ending, leading to depolarization. An increase in intracellular Ca^{2+} initiates fusion of the synaptic vesicles with the presynaptic membrane and release of their contents. The neurotransmitters rapidly diffuse across the synaptic cleft, or space (synapse), between neurons and combine with specific receptors on the postsynaptic (target) cell.

Types of neurotransmitters:

Although over 50 signal molecules in the nervous system have been identified, norepinephrine (and the closely related epinephrine), acetylcholine, dopamine, serotonin, histamine, glutamate, and γ-aminobutyric acid are most commonly involved in the actions of therapeutically useful drugs. Each of these chemical signals binds to a specific family of receptors. Acetylcholine and norepinephrine are the primary chemical signals in the ANS .

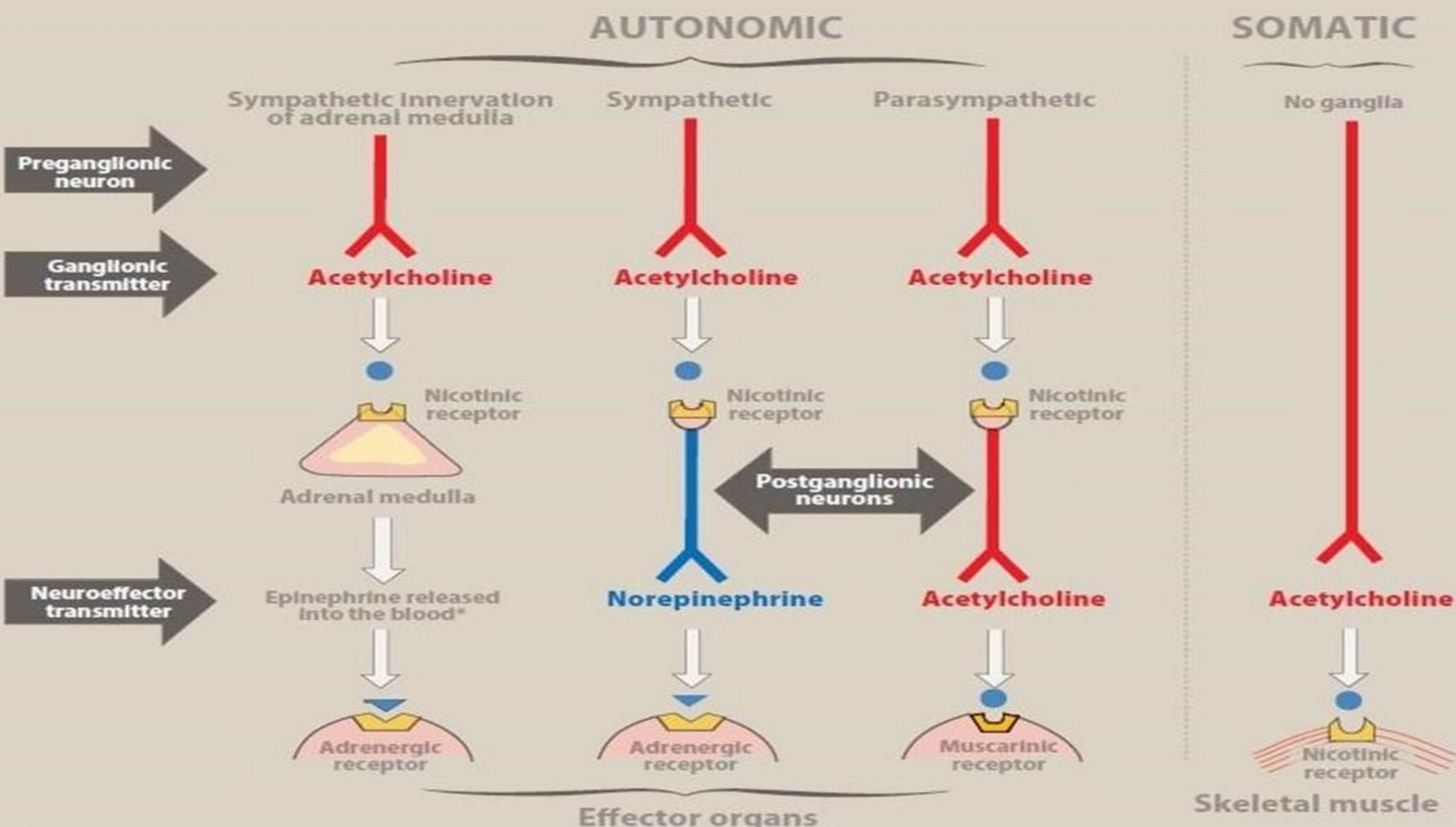
A. Acetylcholine: The autonomic nerve fibers can be divided into two groups based on the type of neurotransmitter released. If transmission is mediated by acetylcholine, the neuron is termed cholinergic , Acetylcholine mediates the transmission of nerve impulses across autonomic ganglia in both the sympathetic and parasympathetic nervous systems and Its the neurotransmitter at the adrenal medulla. Transmission from the autonomic postganglionic nerves to the effector organs in the parasympathetic system, involves the release of acetylcholine. also In the somatic nervous system, transmission at the neuromuscular junction (the junction of nerve fibers and voluntary muscles) .

B. Norepinephrine and epinephrine: When norepinephrine and epinephrine are the neurotransmitters, the fiber is termed adrenergic , In the sympathetic system, norepinephrine mediates the transmission of nerve impulses from autonomic postganglionic nerves to effector organs.

Comparison of Autonomic and Somatic Motor Systems

Cell bodies in central nervous system	Peripheral nervous system	Neurotransmitter at effector	Effector organs	Effect
SOMATIC NERVOUS SYSTEM	Single neuron from CNS to effector organs; Heavily myelinated axon	ACh	Skeletal muscle	+ Stimulatory
AUTONOMIC NERVOUS SYSTEM — SYMPATHETIC	Two-neuron chain from CNS to effector organs; Lightly myelinated preganglionic axons; ACh; Ganglion; Unmyelinated postganglionic axon; Epinephrine and norepinephrine; Adrenal medulla; Blood vessel	NE	Smooth muscle (e.g., in gut), glands, cardiac muscle	+ – Stimulatory or inhibitory, depending on neurotransmitter and receptors on effector organs
AUTONOMIC NERVOUS SYSTEM — PARASYMPATHETIC	Lightly myelinated preganglionic axon; ACh; Ganglion; Unmyelinated postganglionic axon	ACh		

▲ Acetylcholine (ACh) ● Norepinephrine (NE)


AUTONOMIC
SOMATIC
Sympathetic innervation of adrenal medulla
Sympathetic
Parasympathetic
No ganglia
Preganglionic neuron
Ganglionic transmitter
Neuroeffector transmitter
Acetylcholine
Acetylcholine
Acetylcholine
Nicotinic receptor
Nicotinic receptor
Nicotinic receptor
Adrenal medulla
Postganglionic neurons
Epinephrine released into the blood*
Norepinephrine
Acetylcholine
Acetylcholine
Adrenergic receptor
Adrenergic receptor
Muscarinic receptor
Nicotinic receptor
Effector organs
Skeletal muscle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PHARMACOLOGY

Adrenergic Agonists

Huda Nahi

M.Sc (pharmacology)

Adrenergic Agonists

The adrenergic drugs affect adrenergic receptors that are stimulated by norepinephrine (Noradrenaline) or epinephrine (adrenaline). Adrenergic drugs either act as sympathomimetics (activate the receptors) or sympatholytics (Block the receptors). sympathomimetics act either (direct-acting agonists), or (indirect-acting agonists) and that by enhancing release or blocking reuptake of norepinephrine, Adrenergic drugs act on adrenergic receptors in presynaptically neurons or postsynaptically neurons.

The Adrenergic Neuron: Adrenergic neurons release norepinephrine , These neurons are found in the central nervous system (CNS) and also in the sympathetic nervous system.

Neurotransmission at Adrenergic Neurons: Neurotransmission in adrenergic neurons resembles that described for the cholinergic neurons except that norepinephrine is the neurotransmitter. Neurotransmission involves (synthesis, storage, release, and receptor binding of norepinephrine, followed by removal of the neurotransmitter from the synaptic gap).

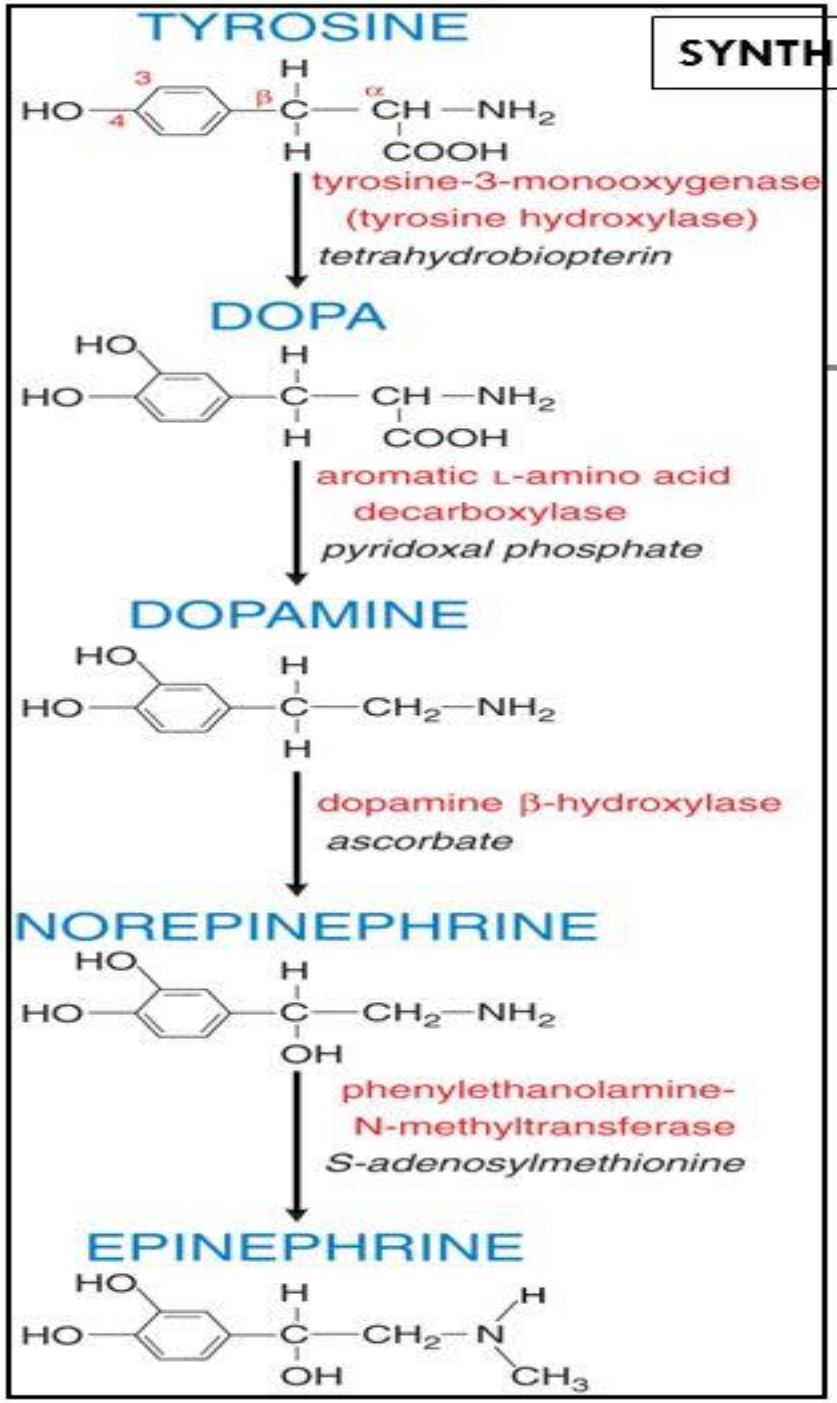
1- Synthesis of norepinephrine: Tyrosine is transported by a carrier into the adrenergic neuron, where it is hydroxylated to (DOPA) by tyrosine hydroxylase, DOPA is then decarboxylated to dopamine in the presynaptic neuron.

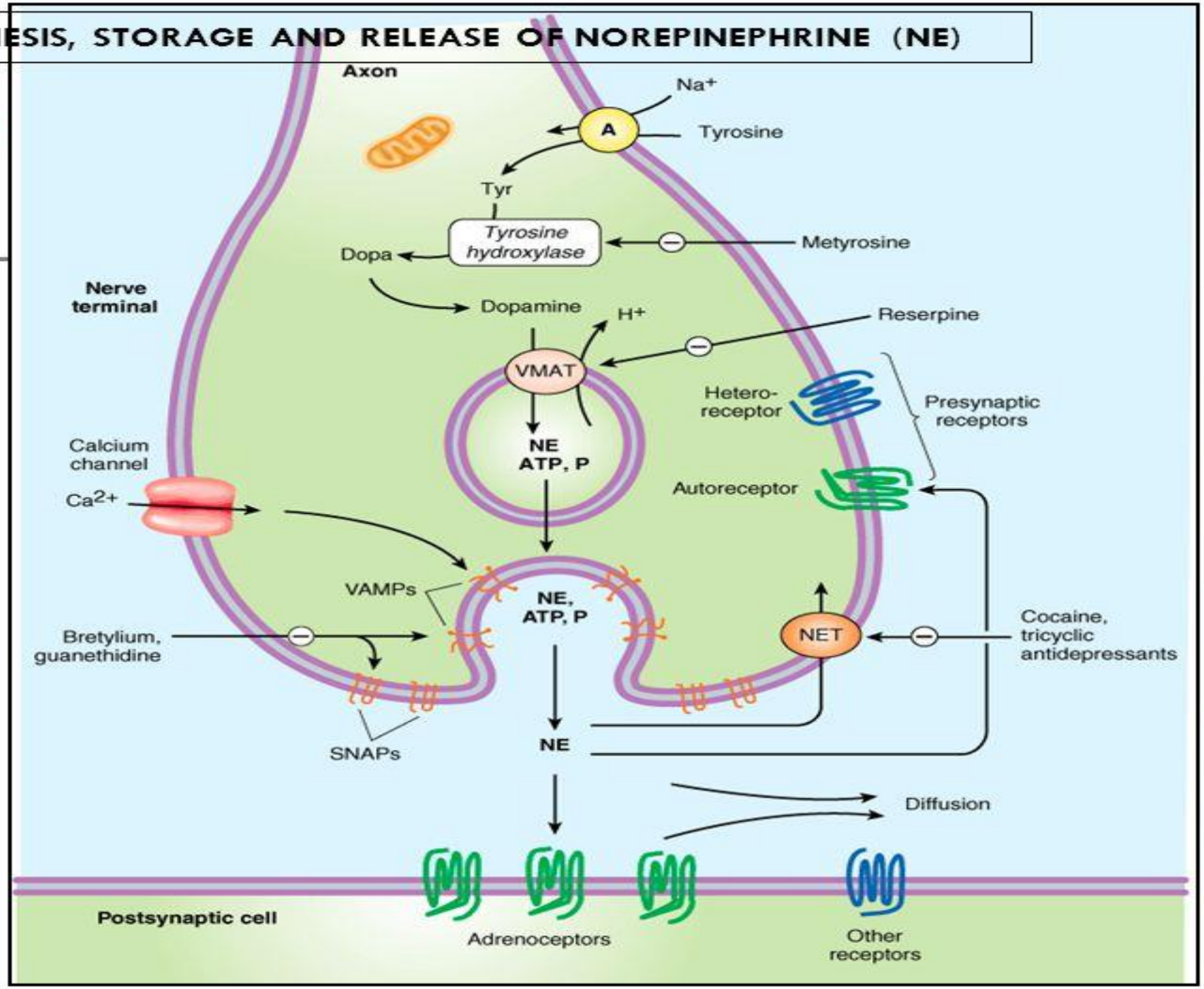
2- Storage of norepinephrine in vesicles: Dopamine is then transported into synaptic vesicles by an amine transporter system. This process blocked by reserpine, then Dopamine hydroxylated to norepinephrine.

3- 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. Drugs such as guanethidine block this release .....4- Binding to receptors: Norepinephrine released from the synaptic vesicles diffuses into the synaptic space and binds to postsynaptic receptors on the effector organ or to presynaptic receptors on the nerve ending.

This binding triggers a cascade of events within the cell, resulting in the formation of intracellular second messengers as (cyclic adenosine monophosphate (cAMP and the phosphatidylinositol) to transduce the signal into an effect. Norepinephrine also binds to presynaptic receptors (mainly α2 subtype) that modulate the release of the neurotransmitter.

SYNTHESIS, STORAGE AND RELEASE OF NOREPINEPHRINE (NE)





5- 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.

 The reuptake by the neuronal membrane involves a sodium-chloride (Na^+/Cl^-)-dependent norepinephrine transporter (NET) , that can be inhibited by tricyclic antidepressants (TCAs), such as imipramine, by serotonin–norepinephrine reuptake inhibitors such as duloxetine, or by cocaine

 Reuptake of norepinephrine into the presynaptic neuron is the primary mechanism for termination of its effects 6- Potential fates of recaptured norepinephrine: Once norepinephrine reenters the adrenergic neuron, it may be 1) taken up into synaptic vesicles via the amine transporter system and be sequestered for release by another action potential, or 2) Alternatively, norepinephrine can be oxidized by monoamine oxidase (MAO) present in neuronal mitochondria.

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). Each of these main receptor types has a number of specific receptor subtypes.

1- α-Adrenoceptors: The α-adrenoceptors show a weak response to isoproterenol, but show good response to (epinephrine and norepinephrine) ,affinity arranged as (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.

a- α1 Receptors:

1. Present on the postsynaptic membrane of the effector organs 2. Activation of α1 Receptors involving (constriction of smooth muscle). 3. Activation of α1 receptors initiates a series of reactions through the G protein activation of phospholipase C, ultimately resulting in the generation of second messengers inositol- 1,4,5- trisphosphate (IP3) and diacylglycerol (DAG). IP3 initiates the release of Ca^{2+} from the endoplasmic reticulum into the cytosol, and DAG turns on other proteins within the cell.

b- α2 Receptors: 1. Located primarily on sympathetic presynaptic nerve endings and control the release of norepinephrine.

2.When a sympathetic adrenergic nerve is stimulated, a portion of the released norepinephrine "circles back" and reacts with α2 receptors on the presynaptic membrane.

3.Stimulation of α2 receptors causes inhibition of further release of norepinephrine from the stimulated adrenergic neuron.

4.This inhibitory action serves as a local mechanism for modulating norepinephrine output when there is high sympathetic activity. (Its act as inhibitory autoreceptors)

5. α2 receptors are also found on presynaptic parasympathetic neurons. Norepinephrine released from a presynaptic sympathetic neuron can diffuse to and interact with these receptors, inhibiting acetylcholine release.

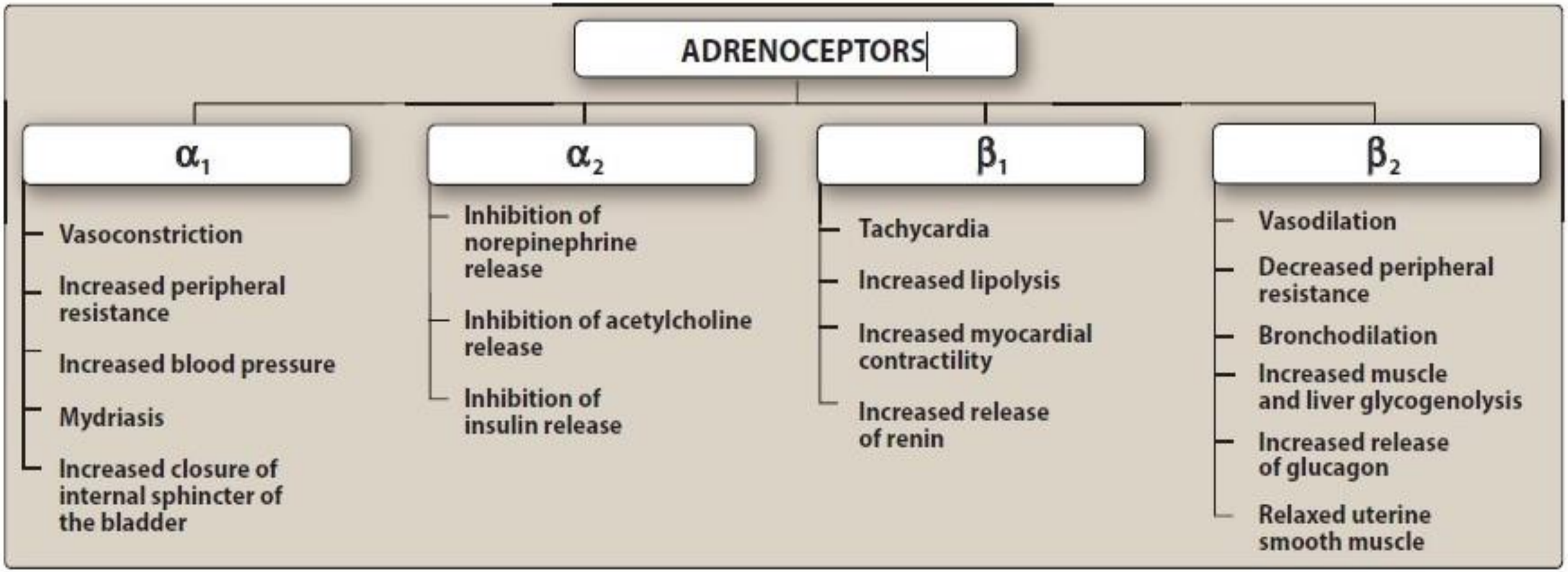
6. Activation of α2 receptors are mediated by inhibition of adenylyl cyclase and decrease in the levels of intracellular cAMP.

c- Further subdivisions: 1. α1 are further divided into α1A, α1B, α1C, and α1D 2.α2 are further divided into α2A, α2B, α2C. 3.This classification is necessary for understanding the selectivity of some drugs, For example, tamsulosin is a selective α1A antagonist which used in the treat benign prostatic hyperplasia.

The drug has fewer cardiovascular side effects because it targets α1A subtype receptors found primarily in the urinary tract and prostate gland and does not affect the α1B subtype found in the blood vessels.

2- β-Adrenoceptors: 1. β receptors shows a strong response to isoproterenol, with less sensitivity to epinephrine and norepinephrine , affinity arranged as(isoproterenol > epinephrine > norepinephrine). 2.The β-adrenoceptors subdivided into β1, β2, and β3, 3.β1 receptors have approximately equal affinities for epinephrine and norepinephrine. 4.β2 receptors have a higher affinity for epinephrine than for norepinephrine. Thus, tissues with a predominance of β2 receptors (such as the vasculature of skeletal muscle) are particularly responsive to the epinephrine that released by the adrenal medulla. 5.β3 receptors are involved in lipolysis and also have effects on the detrusor muscle of the bladder.

Activation of β receptors results in activation of adenylyl cyclase and increased concentrations of cAMP within the cell.



Distribution of receptors:

- Adrenergically innervated organs and tissues usually have a predominant type of receptor.
- As the vasculature of skeletal muscle have both α1 and β2 receptors, but β2 predominate.
- While heart contains predominantly β1 receptors.

Desensitization of receptors: Prolonged exposure to the catecholamines reduces the responsiveness of these receptors, (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) An inability to couple to G protein, because the receptor has been phosphorylated on the cytoplasmic side.

CHARACTERISTICS OF ADRENERGIC AGONISTS:

Most of the 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.

A. Catecholamines：

Sympathomimetic amines such as epinephrine, norepinephrine, isoproterenol, and dopamine) are called catecholamines. These compounds share the following properties: 1. High potency: Catecholamines (with –OH groups in the 3 and 4 positions on the benzene ring) show the highest potency in directly activating α or β receptors).

2. Rapid inactivation: Catecholamines are metabolized by COMT postsynaptically and by MAO intraneuronally, as well as 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 if 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.

B. Noncatecholamines: Compounds lacking the catechol hydroxyl groups have longer half lives, because they are not inactivated by COMT, These include phenylephrine, ephedrine, and amphetamine , These agents are poor substrates for MAO (an important route of metabolism) and, thus, show a prolonged duration of action. , Increased lipid solubility of many of the noncatecholamines (due to lack of polar hydroxyl groups) permits greater access to the CNS.

D. Mechanism of action of adrenergic agonists:

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 of direct-acting agonists include epinephrine, norepinephrine, isoproterenol, and phenylephrine.

2. Indirect-acting agonists: These agents act by 1) block the reuptake of norepinephrine or 2) cause the release of norepinephrine from the cytoplasmic pools or vesicles of the adrenergic neuron The norepinephrine then traverses the synapse and binds to α or β receptors. Examples of reuptake inhibitors and agents that cause norepinephrine release include cocaine and amphetamines, respectively.

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

Direct-Acting Adrenergic Agonists:

Direct-acting agonists 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 α and β receptors. (At low doses, β effects (vasodilation)) , whereas (at high doses, α effect (vasoconstriction)) . Actions:

1- Activation of α1 receptor : Cardiovascular: constricts arterioles in the skin, mucous membranes, and viscera. Activation of α2 receptor: feedback inhibition of adrenergic neurotransmitter release, decreased release of insulin.

2- Activation of β1 receptor : Cardiovascular: Increases cardiac output by, increase contractility of the myocardium (positive inotrope) and increases its rate of contraction (positive Chrono trope). Kidney: Induce renin release. Renin is an enzyme involved in the production of angiotensin II, a potent vasoconstrictor.

3- Activation of β2 receptor : Cardiovascular: Dilates vessels of liver and skeletal muscle, decreased in renal blood flow. Causing increase in systolic blood pressure, coupled with a slight decrease in diastolic pressure, vasodilation in the skeletal muscle vascular bed.

a- Respiratory : Bronchodilation, and inhibits the release of allergy mediators such as histamines from mast cells,

b- Metabolism : Hyperglycemic effect by (increased glycogenolysis in the liver, increased release of glucagon) a- Activation of β3 receptor: Initiates lipolysis of adipose tissue. Increased levels of cAMP stimulate a hormone-sensitive lipase, which hydrolyzes triglycerides to free fatty acids and glycerol.

- Total effect of epinephrine: increase BP. HR.CO. And coronary dilatation, decrease body secretion, decreases blood flow to splanchnic beds, bronchodilator, and increase glucose in blood.

Therapeutic uses:

1. Cardiogenic shock, cardiac arrest and sever hypotension.
2. its drug of choice for Sever bronchospasm (as in asthmatic patient) and anaphylactic shock
3. Nasal decongestant
4. Ophthalmic vasoconstrictor and mydriasis.
5. With local anesthesia to prolog anesthetic effect, which used at low concentrations (for example, 1:100,000 parts).

Adverse effects:

1.Can lead to myocardial ischemia or infarction, due to increase in cardiac work.
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,
5.Epinephrine increases the release of endogenous stores of glucose. In diabetic patients, dosages of insulin may have to be increased.

Contraindicated: in patients with- 1) coronary disease 2) glaucoma and 3) in pregnancy.
Metabolism: norepinephrine metabolite by MAO and COMT, resulting of metabolite are metanephrine and vanillylamandelic acid, which excreted by the urine
B. Norepinephrine: Its selectively activated α1, and β1 adrenergic receptors,(α1 > β1) with weak β2 .
α1: vascular smooth muscle contraction , mydrasis , hyperglycemia (hepatic glycogenolysis)
α2: feedback inhibition of adrenergic neurotransmitter release. β1: increase heart rate (+ve chronotropic), and force of contraction (+ve inotropic), increase lipolysis and renin release.

Total effect: peripheral vasoconstriction, increase in BP. And +ve inotropic effect.
Therapeutic uses: sever hypotension, shock (metaraminol favored), (not useful for asthma).
Side effects: myocardial ischemia or infarction and arrhythmias
Contraindication: in pregnancy and coronary diseases
Metabolism: inactivated by MAO and COMT, (not effective orally).

Isoproterenol: Is a direct-acting synthetic catecholamine that stimulates both β1- and β2-adrenergic receptors. it's not used therapeutically because of its non-selectivity
Therapeutic uses: can be used to stimulate the heart in emergency situations as (Atrioventricular block)
Metabolism: is a marginal substrate for COMT and its stale to MAO action. Side effect: adverse effects of isoproterenol are similar to those of Epinephrine.

D. Dopamine: Dopamine functions as a neurotransmitter in (CNS , basal ganglia, adrenal medulla) .The immediate metabolic precursor of norepinephrine.
Action: at high dose α1: vasoconstriction (increase peripheral resistance) . At low dose β1: increase in CO. and HR.
D1: renal and splanchnic vasodilation (increase renal perfusion and diuresis)

Therapeutic uses:

1.Dopamine is the drug of choice for cardiogenic and septic shock and is given by continuous infusion (dopamine is superior to norepinephrine, in the treatment of shock because norepinephrine diminishes blood supply to the kidney and may cause renal shutdown.

2. Used to treat hypotension and severe heart failure.

3. Enhance urination in patients with poor renal perfusion. Side effect: (arrhythmias, hypertension). Metabolism: dopamine inactivated by MAO and COMT.

Dobutamine: is a synthetic analogue of dopamine.

Action:

1. Activated of β1 and lesser extent β2 and α1 (causing increase in CO. and HR. with few vascular effect). 2. Net effect includes: increase in CO. and HR. with decrease in vascular smooth muscle resistance.

Therapeutic uses:

1.Acute management of CHF by increase of CO. 2.Support heart after cardiac surgery by increase HR.

Side effect: (Arrhythmias)

Metabolism: inactivated by MAO and COMT

Phenylephrine: is a direct-acting, synthetic adrenergic drug that binds primarily to α1 receptors (vascular smooth muscle contraction) causing rise in systolic and diastolic blood pressure , and reflex bradycardia,..

Therapeutic uses:

1. Nasal decongestant (topically or orally). 2.Mydriatic
3. For hypertension in hospitalized or surgical patients).

Side effect:

1.Prolonged uses of Phenylephrine as nasal decongestant may cause rebound mucosal swelling (Rhinitis medicamentosa) due to receptor desensitization or mucosal damage resulting from prolong vasoconstriction 2.(Large doses can cause hypertensive headache and cardiac irregularities)

Metabolism: it does not metabolize by COMT and thus has long duration of action.

Xylometazoline Oxymetazoline naphazoline:

These agents are α agonist, (used topically as nasal decongestant and for relief redness of eye that associated with swimming, cold or contact lens).

Fenoldopam:

It's an agonist of peripheral dopamine D1 receptors (causing rapid vasodilation of coronary, mesenteric and kidney arteries) , and some α1 and α2 antagonist activity. It is used as a rapid-acting vasodilator to treat severe hypertension in hospitalized patients.

Albuterol and terbutaline: Albuterol and terbutaline are short-acting β2agonists , used primarily as bronchodilators in asthmatic patients and patients with COPD , Terbutaline used as uterine relaxant to suppress premature labor. If given orally to patients with cardiac disease it may cause arrhythmia.

Salmeterol and formoterol: Salmeterol and formoterol are β2-adrenergic selective, long-acting bronchodilators. With duration over 12 hours, compared with less than 3 hours for albuterol. These agents used for treating nocturnal asthma in symptomatic patients taking other asthma medications.

Clonidine: Clonidine is a α2-agonist causing decrease in releasing of norepinephrine and in sympathetic outflow. Its uses as antihypertensive and in treatment of opioid withdrawals symptoms

INDIRECT-ACTING ADRENERGIC AGONISTS

These agents do not affect postsynaptic receptors directly , It cause release, inhibit reuptake, or inhibit the degradation of epinephrine or norepinephrine. They potentiate the effects of epinephrine or norepinephrine.

Amphetamine:

It's indirectly activated (vascular α1- receptors and cardiac β1-recptors causing elevation of BP.) through enhance release of storage catecholamine , blockage of norepinephrine reuptake and prevent degradation by inhibition of MAO ,At high dose Amphetamine increase release of dopamine and serotonin

Therapeutic uses:

1. ADHD (attention deficit hyperactivity disorder), it's a disease characterized by motor hyperactivity and decreased attention 2. Appetite control (suppression of appetite has been used to treat obesity 3. fatigue and treatment of depression (related to CNS stimulatory effects)

Side effects:

development of dependence (with high potential for addiction and abuse) Increase BP., arrhythmias, restlessness, anxiety, tremor.

Tyramine:

Its can enter the nerve terminal and displace storage NE. serotonin and less extent dopamine in the CNS (it's used for weight loss). 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. Normally, It is oxidized by MAO in the gastrointestinal tract, but, if the patient is taking MAOIs, it can precipitate serious vasopressor episodes.

Cocaine: its indirect adrenergic agonist causing enhancement of sympathetic activity and potentiating of the actions of epinephrine and norepinephrine by blocking of catecholamine reuptake at adrenergic nerve terminal through blocking the Na^+/K^+-activated ATPase (required for cellular uptake of norepinephrine)

Action:

CNS: general stimulation, euphoria, dysphoria following by depression and death in toxic level.

CVS: small dose: bradycardia (due to vagial stimulation)

Moderate dose: tachycardia and vasoconstriction

Local anesthesia: blocking of sodium ion channel causing decrease in nerve fiber conduction

pharmacology Therapeutic uses: as local anesthesia

Side effect: myocardial infarction, fetal arrhythmias and high potential for abuse (crack is a form of cocaine that can be smocked)

Metabolism: its degregate by all plasma esterase enzymes (its active by all route of administration)

Methylphenidate: is another agonist like amphetamine, and used to treat ADHA.

MIXED-ACTION ADRENERGIC AGONISTS

Action of these agents includes 1) enhance release of NEp 2) activated adrenergic receptors

Ephedrine, pseudoephedrine:

Mechanism of action:

o These agents act by enhance release of storage NEp from nerve ending, and directly stimulate (α and β) receptors.

Action:

o Ephedrine : increase systolic BP. and diastolic BP. (by vasoconstriction and cardiac stimulation) o Bronchodilator (used prophylactically , because they are less potent than EP.) o Mild CNS stimulating effect (increase alertness , prevent sleep)

Therapeutic uses: Nasal decongestant (relate to their ability to produce local vasoconstriction effect)

Side effects: (Hypertension, arrhythmias, insomnia).

Metabolism:

o They have along duration of action because they are not catechol, not inactivated by COMT and MAO. o Pseudoephedrine converts illegally to methamphetamine (it must be sale as behind the counter).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PHARMACOLOGY

Adrenergic Antagonists

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Adrenergic Antagonists

 Adrenergic agonists (adrenergic blocker or sympatholytics) binds with adrenergic agonist (reversibly or irreversibly) without triggering of intracellular response . Binding of adrenergic antagonists prevent binding of endogenous catecholamine Its classify according to their affinity to α- blocker and β- blocker Its useful clinically for treatment of disease associated with cardiovascular system

A-Adrenergic Blocking Agents:

1- Phentolamine: (it's a competitive block of α1 and α2 receptors with duration lasts for 4 hours after a single injection). Therapeutic uses: 1- short term management of pheochromocytoma (is a neuroendocrine tumor of the medulla of the adrenal glands , that secretes high amounts of catecholamines, mostly norepinephrine, plus epinephrine to a lesser extent). 2- For hypertension crisis resulting from (abrupt withdrawal of clonidine, or in patients that taking MAOIS with foods contain tyramine).

Side effect: arrhythmias and angina pain.

Contraindicated: in patients with coronary disease (related to tachycardia which mediated by baroreceptors reflex and blocking of α2 receptors).

2- Phenoxybenzamine: is nonselective, bind irreversibly to both α1 and α2 receptors with duration which last about 24 hours, is used in the treatment of pheochromocytoma.

3- Prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin: Prazosin, terazosin, doxazosin (it's a competitive blocker of α1 receptors) used for hypertension treatment, by decrease in peripheral vascular resistance with minimal change in CO. tamsulosin, and alfuzosin (it's a selective blocker of α1A blocker) used for benign prostatic hypertrophy .

Therapeutic uses:

 Hypertension (with less development of tolerance) , 1st dose produce postural hypotension , to overcome this problem (1/3) or (1/4) of dose given first , or given at bed time . For relief symptoms of benign prostatic hyperplasia.

Side effect:

 Orthostatic hypotension, dizziness, nasal congestion, headache, drowsiness, nightmare, sexual dysfunction. (Avoid using with other vasodilator agents as nitrate or PDE-5 inhibitors as sildenafil to avoid exaggerated antihypertensive action).

4- Yohimbine: It's a selective competitive α2-blocker. It used as a sexual stimulant (in the treatment of erectile dysfunction). It is contraindicated in cardiovascular disease, psychiatric conditions, and renal dysfunction because it may worsen these conditions.

β- Adrenergic Blocking Agents:

 All clinical available of β- blocker are competitive blocker , (the non-selective competitive β- antagonist block each β1 and β2 receptors) β1- blocker are cardioselective, while β2- blocker are not useful clinically.

 These blocker are :

1- different in their (CNS effect , blockage of sympathetic receptors , vasodilation and its pharmacokinetics)

2- Don't induce postural hypotension (less effect on α receptors).

3- Effective in treatment of (hypertension, angina, cardiac arrhythmia, myocardial infarction, hyperthyroidism and glaucoma).

4- Used prophylactically from migrant headache.

These agents can be categorized as:

1- Non-selective β- adrenergic antagonists : (Propranolol, Nadolol and Timolol)

2- Non-selective β1- and α1 adrenergic antagonists (nebivolol) 3- Non-selective β1- β2and α1 adrenergic antagonists (Carvedilol and Labetalol) 4- β- adrenergic partial agonist : (Pindolol) 5- β1- selective adrenergic antagonists: (Esmolol, Metoprolol , atenolol and Acebutolol).

DRUG	RECEPTOR SPECIFICITY	THERAPEUTIC USES
Propranolol	β_1, β_2	Hypertension Migraine Hyperthyroidism Angina pectoris Myocardial infarction
Nadolol *Pindolol*[1]	β_1, β_2	Hypertension
Timolol	β_1, β_2	Glaucoma, hypertension
Atenolol *Bisoprolol*[2] *Esmolol* *Metoprolol*[2]	β_1	Hypertension Angina Myocardial infarction
Acebutolol[1]	β_1	Hypertension
Nebivolol	β_1, NO ↑	Hypertension
Carvedilol[2] *Labetalol*	α_1, β_1, β_2	Hypertension


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CHOLINERGIC AGONISTS

The Cholinergic Neuron

This type of neurons used acetylcholine as neurotransmitter. Cholinergic neurons included (1- preganglionic fibers for sympathetic and parasympathetic 2- postganglionic fibers for parasympathetic 3- sympathetic fibers that innervate adrenal glands 4-postganglonic sympathetic fibers that innervate sweat glands 5- somatic fibers.

A. Neurotransmission at cholinergic neurons

Neurotransmission in cholinergic neurons involves sequential six steps.

1- **Synthesis of acetylcholine:** Choline is transported from the extra-cellular fluid into the cytoplasm of the cholinergic neuron by an energy- dependent carrier system that cotransports sodium and that can be inhibited by the drug hemicholinium. Choline acetyltransferase catalyzes the reaction of choline with acetyl coenzyme A (CoA) to form acetylcholine.

2- **Storage of acetylcholine in vesicles:** The acetylcholine is packaged into presynaptic vesicles The mature vesicle contains not only acetylcholine but also adenosine triphosphate (ATP) and proteoglycan, synaptic vesicles contain primary neurotransmitter(acetylcholine), with cotransmitter that will increase or decrease the effect of the primary neurotransmitter.

3- **Release of acetylcholine:** When an action potential propagated by the action of voltage-sensitive sodium channels arrives 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 release of their contents into the synaptic space. This release can be blocked by botulinum toxin. In contrast, the toxin in black widow spider venom causes all the acetylcholine stored in synaptic vesicles to empty into the synaptic gap.

4- **Binding to the receptor:** Acetylcholine released from the synaptic vesicles diffuses across the synaptic space, and it binds to either of two postsynaptic receptors on the target cell or to presynaptic receptors in the membrane of the neuron that released the acetylcholine. The postsynaptic cholinergic receptors on the surface of the effector organs are divided into (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 as mediated by second-messenger molecules.

5- **Degradation of acetylcholine:** The signal at the post junctional effector site is rapidly terminated, because acetylcholinesterase cleaves acetylcholine to choline and acetate in the synaptic cleft. 6- Recycling of choline: Choline may be back into the neuron by high- affinity uptake system that transports the molecule back into the neuron, where it is acetylated into acetylcholine that is stored until released by a subsequent action potential.

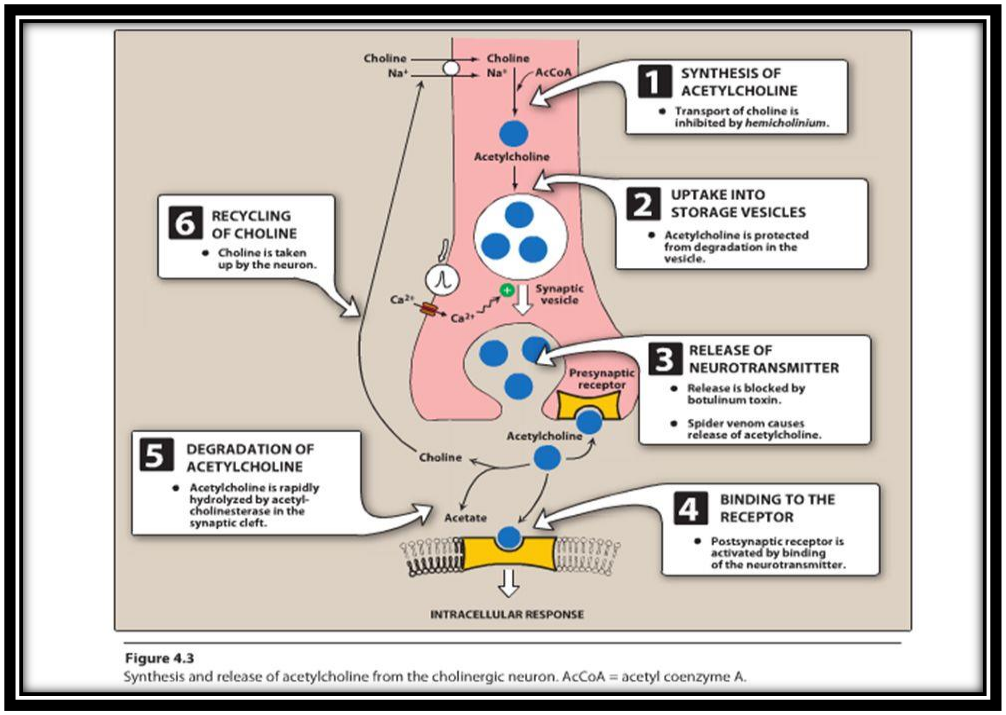
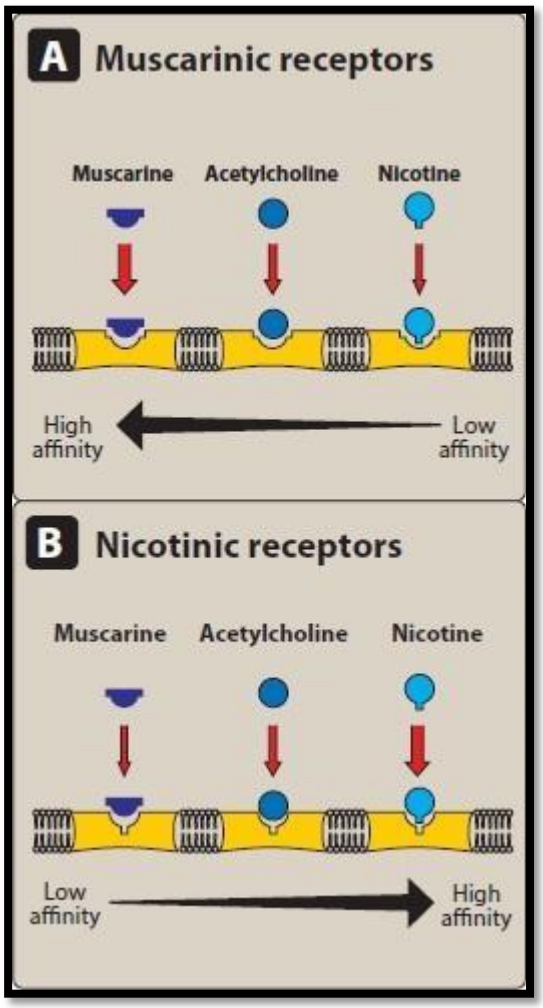


Figure 4.3
Synthesis and release of acetylcholine from the cholinergic neuron. AcCoA = acetyl coenzyme A.

III. Cholinergic Receptors (Cholinoceptors) : Two families of cholinoceptors, designated muscarinic and nicotinic receptors.



A. Muscarinic receptors : These receptors, in addition to binding acetylcholine, also recognize muscarine, an alkaloid that is present in certain poisonous mushrooms. By contrast, the muscarinic receptors show only a weak affinity for nicotine ,have distinguished five subclasses of muscarinic receptors: M1, M2, M3, M4, and M5. only M1, M2 and M3, receptors have been functionally characterized. Its belong to G-protein couple receptor type

Locations of muscarinic receptors: M1 receptors are found on gastric parietal cells, M2 receptors on cardiac cells and smooth muscle, and M3 receptors on the bladder, exocrine glands, and smooth muscle , Drugs with muscarinic actions preferentially stimulate muscarinic receptors on these tissues, but at high concentration they may show some activity at nicotinic receptors.

B . Nicotinic receptors:

 These receptors, in addition to binding acetylcholine, also recognize nicotine but show only a weak affinity for muscarine it functions as a ligand-gated ion channel , Binding of two acetylcholine molecules elicits a conformational change that allows the entry of sodium ions, resulting in the depolarization of the effector cell. Nicotine (or acetylcholine) initially stimulates and then blocks the receptor. Nicotinic receptors are located in the CNS, adrenal medulla, autonomic ganglia, and the neuromuscular junction. Those at the neuromuscular junction are sometimes designated NM and the others NN. The nicotinic receptors of autonomic ganglia differ from those of the neuromuscular junction.

Direct-Acting Cholinergic Agonists

Cholinergic agonists (also known as parasympathomimetics) mimic the effects of acetylcholine by binding directly to cholinoceptors. its classified into two groups:

a- Endogenous choline esters, which include (1- acetylcholine 2- synthetic esters of choline, as (carbachol and bethanechol) b- Naturally occurring alkaloids, as (pilocarpine and nicotine) . □ All of the direct-acting cholinergic drugs have (1-longer durations of action than acetylcholine 2- more therapeutically useful drugs) □ (pilocarpine and bethanechol) preferentially bind to muscarinic receptors and are sometimes referred to as muscarinic agents.

A. Acetylcholine

□ Acetylcholine is a quaternary ammonium compound that cannot penetrate membranes. □ Acetylcholine isn't important therapeutically because of 1-) multiplicity of its actions and 2-) rapid inactivation by the cholinesterases. □ Acetylcholine has both muscarinic and nicotinic activity.

Actions of Acetylcholine :

1- Decrease in heart rate and cardiac output: The actions of acetylcholine on the heart mimic the effects of vagal stimulation. if its injected intravenously, 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: Injection of acetylcholine causes vasodilation and lowering of blood pressure indirectly where, Acetylcholine activates M3 receptors found on endothelial cells lining the smooth muscles of blood vessels. This results in the production of nitric oxide from arginine. leading to hyperpolarization and smooth muscle relaxation. In the absence of administered cholinergic agents, Atropine blocks these muscarinic receptors and prevents acetylcholine from producing vasodilation.

Other actions:

1- ***In the gastrointestinal tract***, acetylcholine increases salivary secretion and stimulates intestinal secretions and motility.

2- ***In the respiratory tract*** acetylcholine enhance Bronchiolar secretions and bronchoconstriction

3- ***In the genitourinary tract,*** the tone of the bladder detrusor muscle is increased, causing expulsion of urine.
In the eye, acetylcholine cause constriction of the pupillae sphincter muscle, causing miosis.

Therapeutics uses of direct acting agonists:

1- ***Acetylcholine*** (1% solution) : is instilled into the anterior chamber of the eye to produce miosis during ophthalmic surgery.

2- ***bethanechol*** **:** It lacks nicotinic actions with strong muscarinic activity used to stimulate the atonic bladder, particularly in postpartum or postoperative, nonobstructive urinary retention and for megacolon.

3- ***Carbachol*** **:** has both muscarinic and nicotinic actions ; Because of its high potency, receptor non selectivity, and relatively long duration of action, carbachol is rarely used therapeutically except in the eye as a miotic agent by pupillary contraction and treat glaucoma by decrease intraocular pressure.

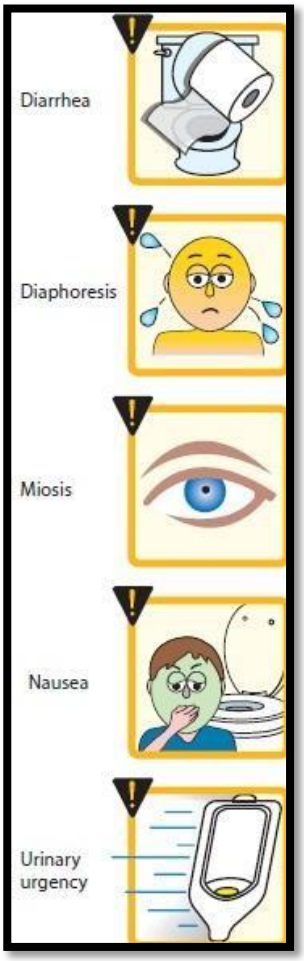
4- ***Pilocarpine*** **:** its exhibits muscarinic activity ,it's uncharged and can penetrate the CNS at therapeutic doses and ; is used primarily in ophthalmology (its consider as drug of choice for glaucoma treatment , its used for emergency needed lowering ocular pressure in glaucoma ; by opining of (trabicule meshwork of schlems cannel)

- Pilocarpine beneficial in promoting salivation in patients with xerostomia resulting from irradiation of the head and neck. Sjögren syndrome, which is characterized by dry mouth and lack of tears, (Sjögren syndrome ; an autoimmune disease in which the moisture – production glands of the body are affected causing mainly symptoms of dry eyes and mouth).

Adverse effect of acetylcholine and other cholinergic agonists:

This adverse effect resulting from generalized cholinergic stimulation as

1. Bronchospasm and increase bronchial secretion
2. Nausea vomiting and diarrhea
3. Miosis
4. Urinary urgency
5. Sweating (diaphoresis) and salivation
6. Pilocarpine ; cause CNS disturbance as blurred vision, night blindness (Poisoning with this agent is characterized by exaggeration of various parasympathetic effects, including profuse sweating (diaphoresis) and salivation.

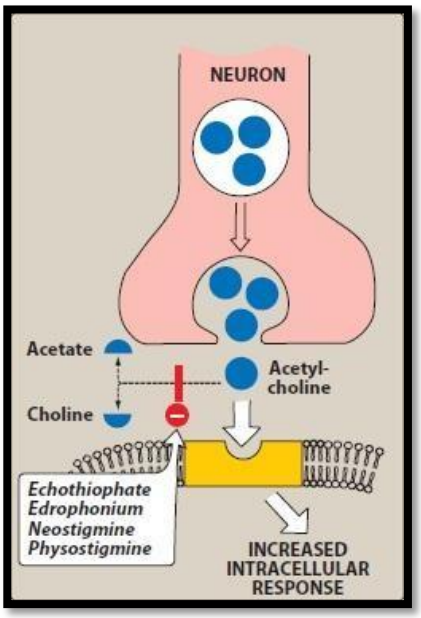


Indirect-Acting Cholinergic Agonists:

Anticholinesterase Agents (Reversible) :

AChE is an enzyme that specifically cleaves ACh to acetate and choline and, thus, terminates its actions. It is located both pre- and postsynaptically in the nerve terminal where it is membrane bound.

Inhibitors of AChE, its indirectly provide a cholinergic action by preventing the degradation of ACh. This results in an accumulation of ACh in the synaptic space , Therefore, 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)

A- Edrophonium:

- it's a short-acting AChE inhibitor (10 to 20 minutes).
- It is used in the diagnosis of myasthenia gravis, (an autoimmune disease caused by antibodies attack the nicotinic receptor at the NMJ), degradation it, making fewer receptors available for interaction with Ach
- excess drug may provoke a cholinergic crisis (atropine is the antidote).
- Used for reversing the effects of nondepolarizing neuromuscular blockers after surgery

B- Physostigmine:

- Its act on muscarinic and nicotinic sites of the ANS and nicotinic receptors of the NMJ.
- Its duration of action is about 30 minutes to 2 hours.
- Used in the treatment of overdoses of anticholinergic, such as atropine. Used for intestinal and bladder atony , by increase their motility, it can enter and stimulate the cholinergic sites in the CNS.

C- Neostigmine:

- Neostigmine it is more polar than physostigmine, duration of action, (30 minutes to 2 hours).
- used to manage symptoms of myasthenia gravis
- as an antidote for competitive neuromuscular-blocking agents.
- It is used to stimulate the bladder and GI tract
- Neostigmine does not cause CNS side effects and is not used to overcome toxicity of central-acting antimuscarinic agents such as atropine
- Neostigmine is contraindicated in intestinal or urinary bladder obstruction.

D- Pyridostigmine and ambenonium:

- Their durations of action are intermediate (3 to 6 hours and 4 to 8 hours, respectively)

  used in the chronic management of myasthenia gravis

E- Tacrine, donepezil, rivastigmine, and galantamine:

- Used for management the symptoms of Alzheimer's disease
- (Deficiency of cholinergic neurons in the CNS. Causing loss of cognitive function).
- Tacrine was the first to become available, but it has been replaced by others because of its hepatotoxicity.
- The ability of donepezil, rivastigmine, and galantamine to delay the progression of Alzheimer's disease none can stop its progression.

Adverse effect of acetylcholinesterase inhibitors (reversible):

- Adverse effects of neostigmine 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
- Bradycardia and a fall in cardiac output may also occur.

INDIRECT-ACTING CHOLINERGIC AGONISTS (ANTICHOLINESTERASE 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.

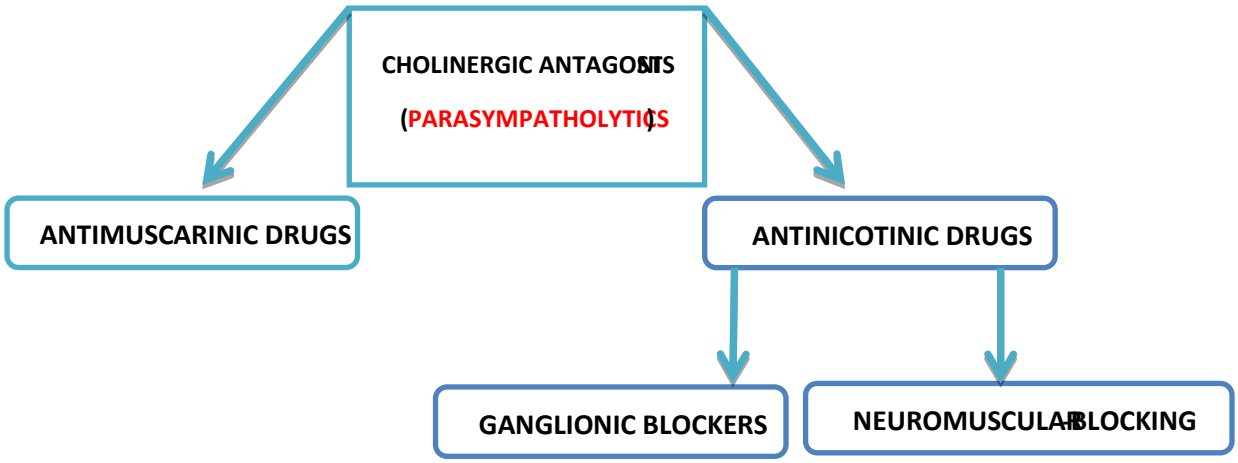
Treatment of organophosphorus posing : (pralidoxime) is an organophosphate compound antidote , it must be given directly before development of enzyme aging , symptoms can be overcome by using of atropine .

Therapeutic uses:

Echothiophate: A topical ophthalmic solution of the drug is available for the treatment of open-angle glaucoma (rarely used because cataract side effect).

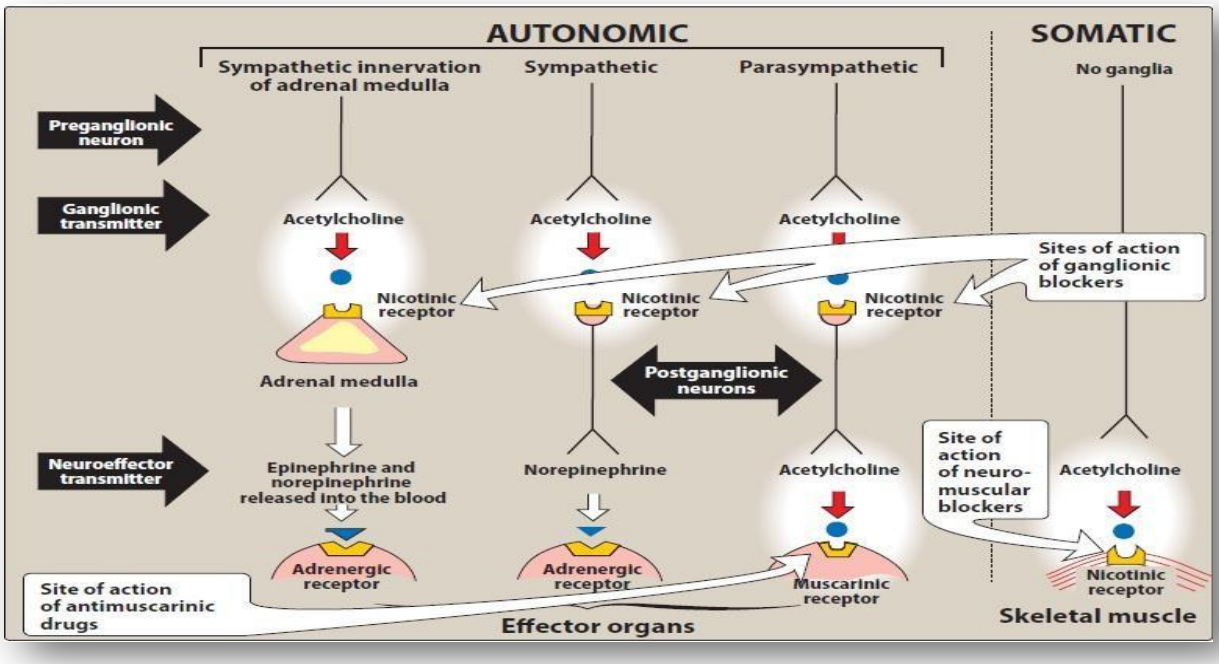
Adverse effect; including generalized cholinergic stimulation, paralysis of motor function (difficulty in breathing) and convulsion.

Cholinergic Antagonists



Antimuscarinic Agents (atropine and scopolamine) :

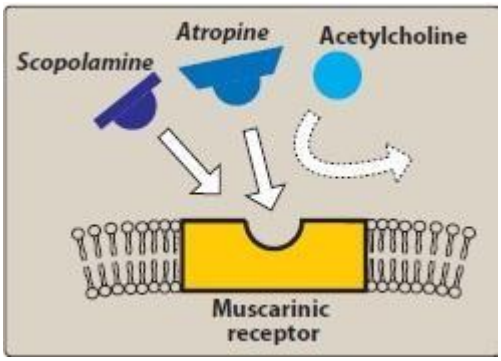
- **This agents inhibition of muscarinic function (also salivary and sweat gland)**
- **Less effect on autonomic ganglia and skeletal neuromuscular junction**



Atropine:

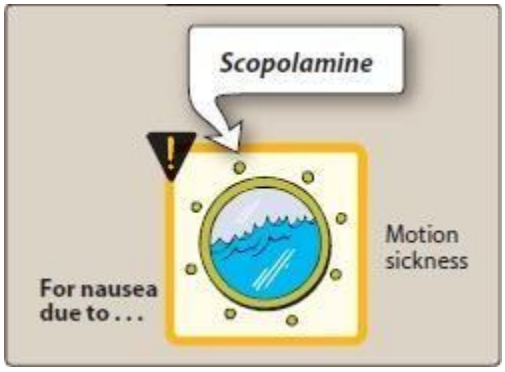
- **Its non-selective antagonists of muscarinic receptors (centrally and peripherally)**
- **Its duration (4 hr.) except topically (eye- last for days)**
- **Greatest inhibition effect of atropine are on bronchi, sweat and salivary glands.**

Organ	Effect / action	Therapeutic uses
Eye	**Mydriasis / caution in closed angle glaucoma**	**it permits the measurement of refractive errors without interference by the accommodative capacity of the eye.(replace by tropicamide) .**
G.I.T	**Decrease of G.I.T , not effective for peptic ulcer**	**Antispasmodic , and for treatment of diarrhea**
C.V.S	**At high dose (increase in heart rate ; blocking of M_2 on S.A node)**	**Treatment of bradycardia**
Antisecretory	**Dry mouth (xerostomia) , sweat and lacrimal glands also affected Cause elevation in body temperature**	**used for block secretions in the upper and lower respiratory tracts prior to surgery.**
Antidote for cholinergic agonists :	**1- For organophosphorus insecticide posing (central toxic effect)** **2- Overdose of AchE initiators reversible (Physostigmine)**	



Scopolamine: Have the same of atropine effect peripherally, but more effect centrally than atropine

Therapeutic uses: Limited to prevent of motion sickness and Prevent of postoperative nausea and vomiting



Ipratropium and tiotropium: Used as bronchodilator agents as a maintenance treatment of COPD, and in Acute managements of bronchospasm in asthma

Tropicamide and cyclopentolate: used as ophthalmic solutions for mydriasis and cycloplegia. Their duration of action is shorter than that of atropine

GANGLIONIC BLOCKERS:

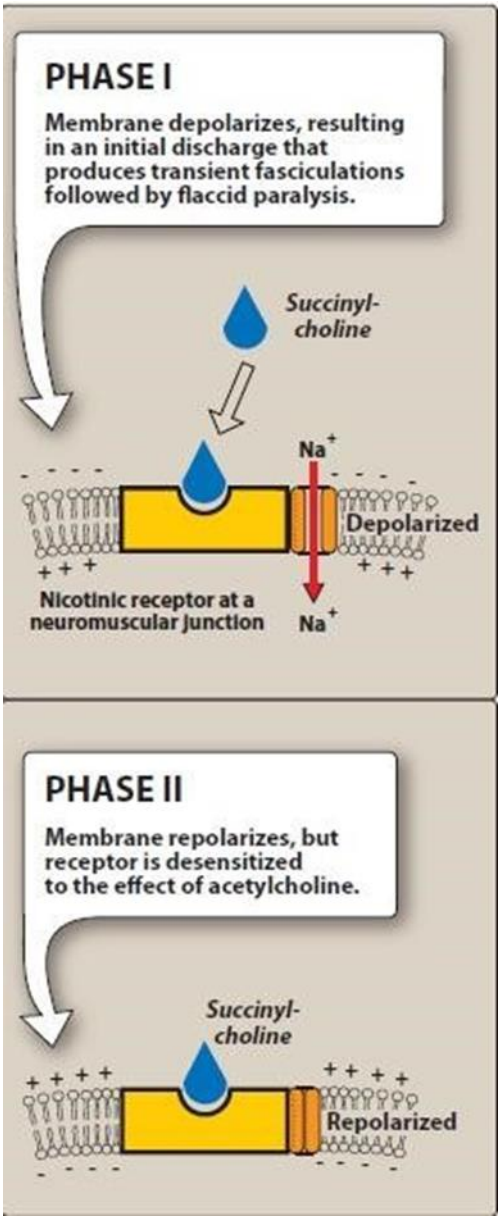
Nicotine:

Primary therapeutic uses of ganglionic blocker is in the treatment of nicotine dependence in people how try to get out smoking , by given the nicotine as nicotine gum , dermal patch or nasal spray , Ganglionic blockers are rarely used therapeutically .

Adverse effect:

- Increase blood pressure and heart rate (related to activation of adrenal medulla , epinephrine)
- Increase G.I.T motility Nausea and vomiting
- Induce skeletal muscle contraction (respiratory paralysis in toxic level)
- Carcinogenic

NEUROMUSCULAR-BLOCKING AGENTS:



Its blocking cholinergic transmission between motor nerve endings and the nicotinic receptors on the skeletal muscle.

They act either as antagonists (no depolarizing type) or as agonists (depolarizing type) at the receptors on the endplate of the NMJ.

Therapeutic uses:

it's useful during surgery to **1**) facilitate tracheal intubation **2**) provide complete muscle relaxation at lower anaesthetic doses, **3)** allowing rapid recovery from anaesthesia and **4)** reducing postoperative respiratory depression.

Nondepolarizing (competitive) blockers :

- These agents competitively block ACh at the nicotinic receptors, that is, they compete with ACh at the receptor without stimulating it. And prevent depolarization of the muscle cell membrane and inhibit muscular contraction as tubocurarine, pancuronium, and Vecuronium.
- Their competitive action can be overcome by administration of cholinesterase inhibitors, such as neostigmine and Edrophonium,

Tubocurarine : it's a toxic alkaloids ,which is used by American natives to hunt animals providing relaxation of skeletal muscle , its action increase if given with, aminoglycoside antibiotics (gentamycin) , and it action can be overcome by neostigmine.

Depolarizing agents (Succinylcholine):

•Its bind to Nm receptors and acts like acetylcholine , causing open of receptor channels and depolarize it , with more resistance to the action of acetylcholinesterase enzyme , causing persist depolarization producing continuous contraction eventually causing muscle paralysis (flaccid paralysis) , which mainly related to desensitization of Nm receptors .

- Its action depends on pseudo cholinesterase that diffusion from plasma
- Adverts effect (hyperthermia, Apnea and Hyperkalemia).

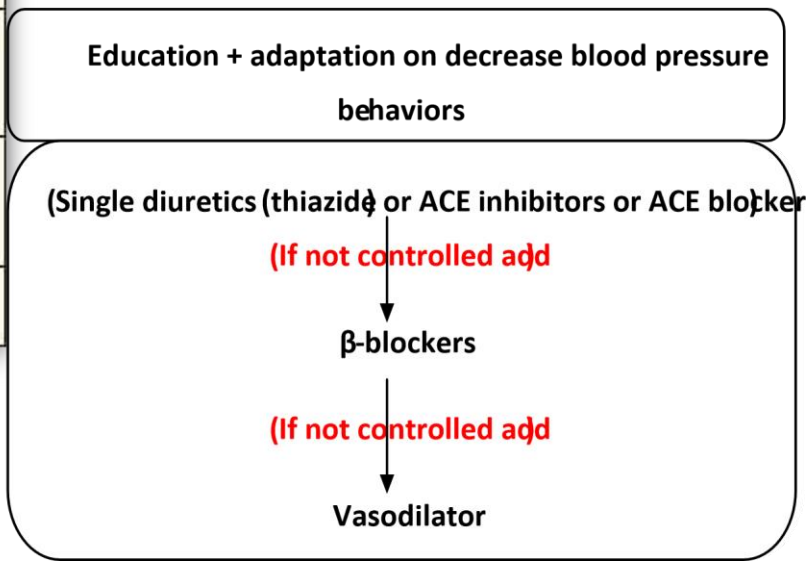
Huda Nahi. M.Sc. (Pharmacology & Toxicology)

Antihypertensive drugs

- Hypertension: is a sustained systolic blood pressure of greater than 140 mm Hg or a sustained diastolic blood pressure of greater than 90 mm Hg.
- Its results from increased peripheral vascular arteriolar smooth muscle tone (unknown cause), which leads to increased arteriolar resistance. • Chronic hypertension can lead to development of chronic kidney disease and heart failure.
- The incidence of morbidity and mortality significantly decreases when hypertension is diagnosed early and is properly treated.

Hypertension is classified into four categories for the purpose of treatment management

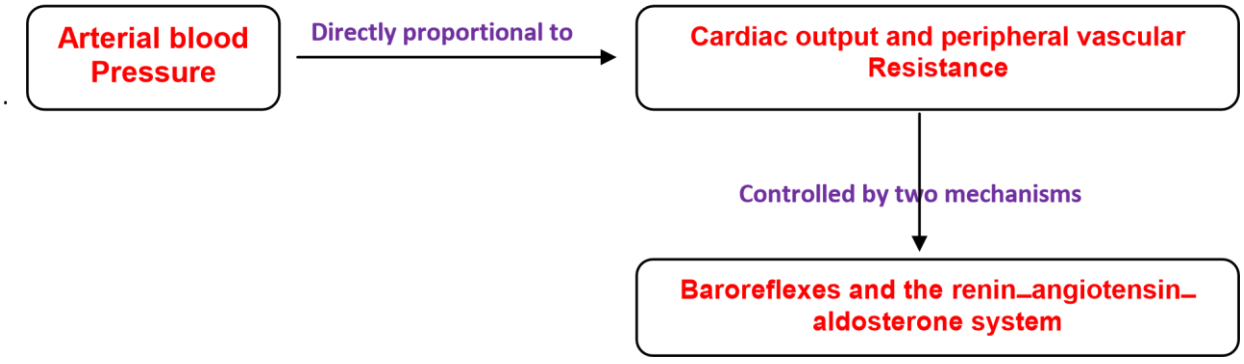
	Systolic mm Hg		Diastolic mm Hg
Normal	<120	and	<80
Prehyper-tension	120–139	or	80–89
Stage I	140–159	or	90–99
Stage II	≥160	or	≥100



Etiology of Hypertension:

- **Essential hypertension (primary hypertension)**: in more than 90% of patients have this type, which no specific causes can be found.
- **Secondary hypertension:** 10% of patients have this type; in which specific causes of hypertension can be established, such as pheochromocytoma, Cushing's disease.
- **Prevalence of hypertension** is increased with (family history and age) , and decreased with (education and income level)
- **Incidence of hypertension** increase with (diabetes mellitus, obesity, stressful lifestyle, increase Na intake and smoking).

- **Mechanisms For Controlling Blood Pressure:**
- Arterial blood pressure is regulated within a narrow range to (provide adequate perfusion of the tissues) (without causing damage to the vascular system).



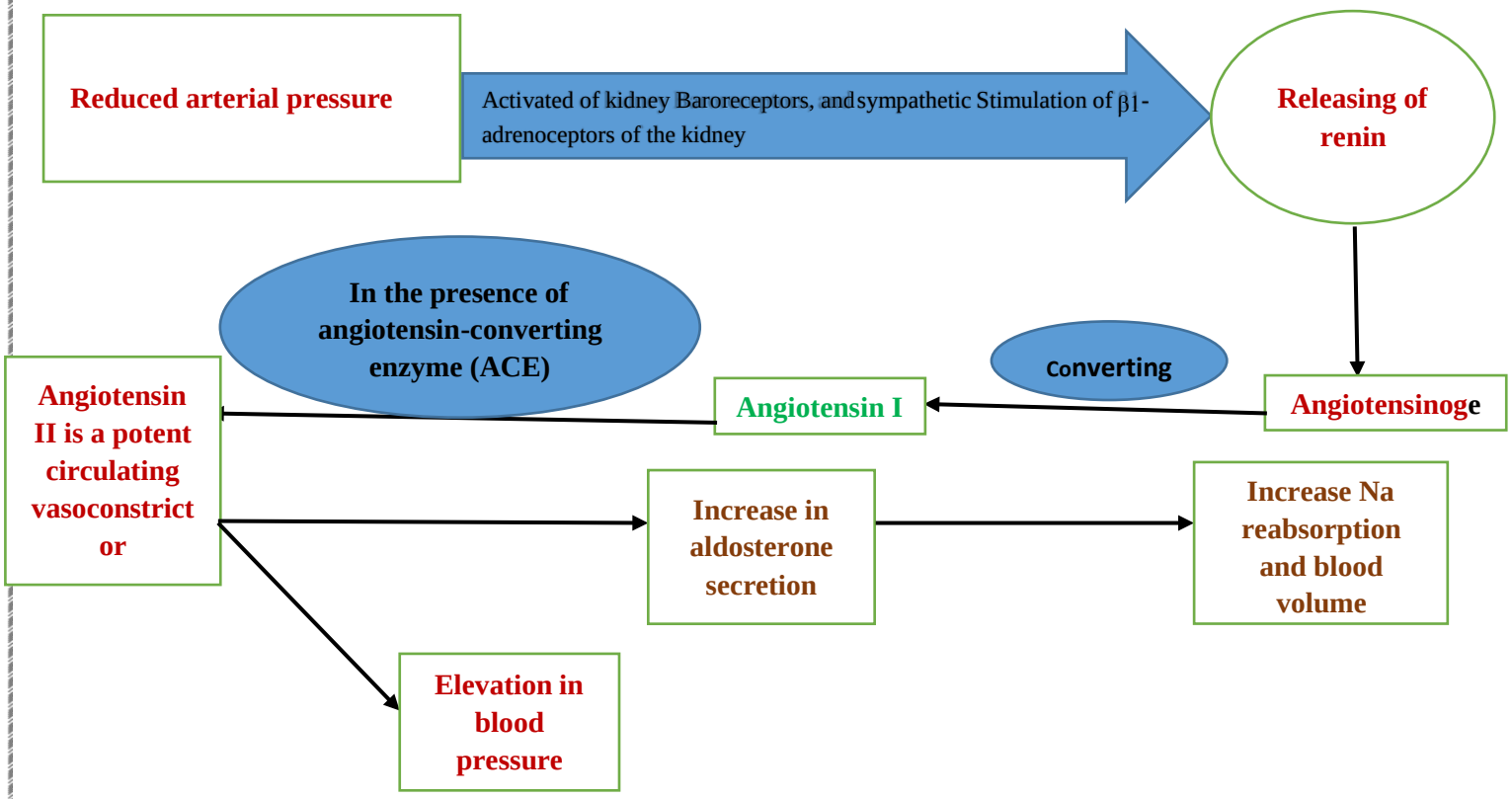
Most antihypertensive drugs lower blood pressure by reducing cardiac output and/or decreasing peripheral resistance.

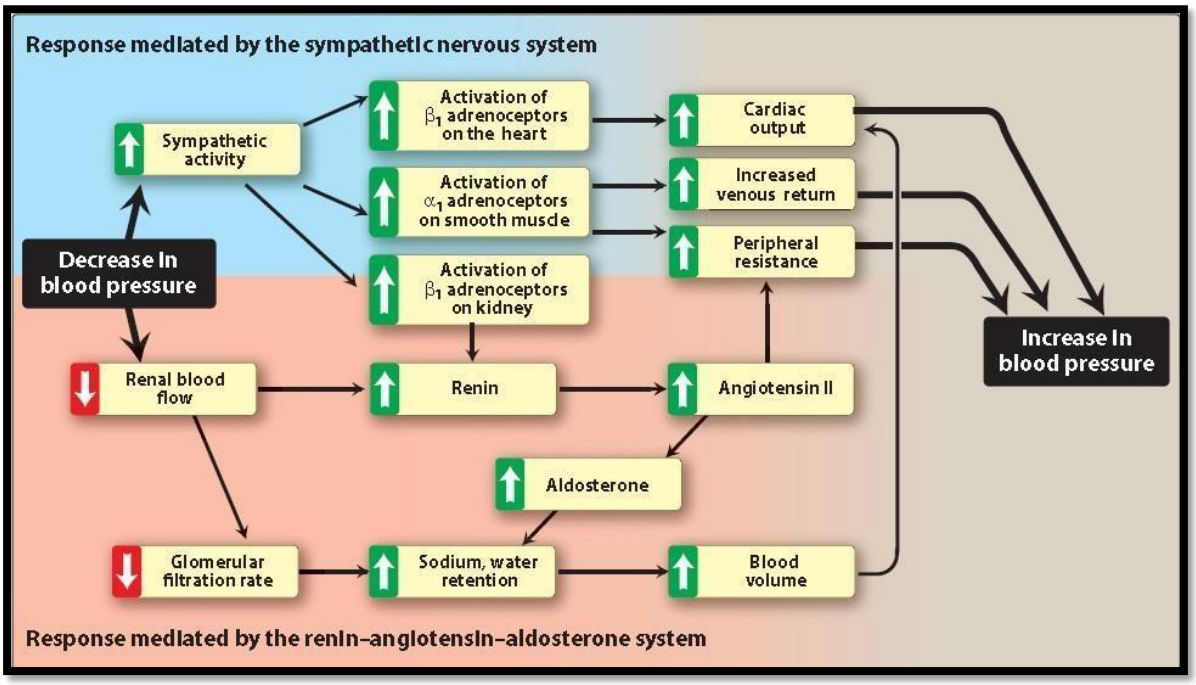
Baroreceptors and the sympathetic nervous system:

- It is responsible for the rapid, moment-to moment regulation of blood pressure.
- A fall in blood pressure causes pressure-sensitive neurons (baroreceptors in the aortic arch and carotid sinuses) to send fewer impulses to cardiovascular centers in the spinal cord. This prompts a reflex response of increased sympathetic and decreased parasympathetic output to the heart and vasculature, resulting in vasoconstriction and increased cardiac output.

Renin–angiotensin–aldosterone system:

- The kidney provides long-term control of blood pressure by altering the blood volume.


Reduced arterial pressure
Activated of kidney Baroreceptors, and sympathetic Stimulation of β1-adrenoceptors of the kidney
Releasing of renin
In the presence of angiotensin-converting enzyme (ACE)
Converting
Angiotensin II is a potent circulating vasoconstrictor
Angiotensin I
Angiotensinoge
Increase in aldosterone secretion
Increase Na reabsorption and blood volume
Elevation in blood pressure

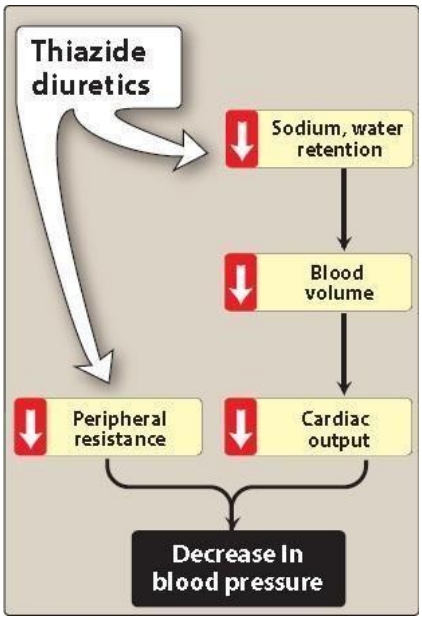


Treatment Strategies:

- Lowering of elevated blood pressure significantly reduces cardiovascular disease.
- Cretin hypertensive patients response better to specific drug class than others as

1. black peoples show (good response to diuretics and calcium channel blockers comparing with β-blockers and ACE inhibitors)
2. Elderly patients show (good response to calcium channel blockers, ACE inhibitors and diuretics comparing with β- blockers and α-antagonized).

Pharmacological basis of antihypertensive agents:



- All antihypertensive drugs act at one or more of the anatomic control sites, producing their effect by interfering with normal mechanism of blood pressure regulation
- These drugs classified according to the main regulatory sites which included the following **A- Diuretics:**
- These agents lowering blood pressure by depleting (body sodium and reduce blood volume).
- It's used as 1st line therapy (at low dose)
- It's effective in preventing myocardial infarction and congestive heart failure.
- Prefer in older patients than β- blockers.

A-1- Thiazide diuretics: (hydrochlorothiazide): Mechanism of action:

- Its decrease blood pressure initially by increase Na and water excretion lead to decrease in (cardiac output, peripheral resistance, renal blood flow and return plasma volume to normal value).
- Its act on distal convoluted tubules causing (hypokalemia, hypomagnesemia and hyperuricemia)
- Caution in patients with cardiac arrhythmias or patients that taken digitalis for cardiac arrhythmias **Therapeutic uses:**
- Its useful in combination therapy (used with other antihypertensive agents as β- blocker , ACE inhibitors , ACE blocker and potassium sparing diuretics)
- It's used for black and elderly patients , but not useful for patients with inadequate kidney function

A-2- Loop diuretics: (*furosemide*, *bumetanide*):

- Its act by decrease renal vascular resistance, and inhibit reabsorbing of Na / K / CL ions also causing hypokalemia , hypomagnesemia and hyperuricemia □ It's useful for treatment sever hypertensive.
- It's useful also for patients with poor renal perfusion and in patents that not response to thiazide and other diuretic

A-3- Potassium-sparing diuretics:

- As (Amiloride, triamterene) and aldosterone-receptor antagonists (spironolactone and eplerenone):
- its act by less K losing in the urine , and with other diuretics it enhance natriuretic effect and counteract K- depleting.
- Used for patients treated with digitalis, and diminish cardiac remodeling occur in heart failure.

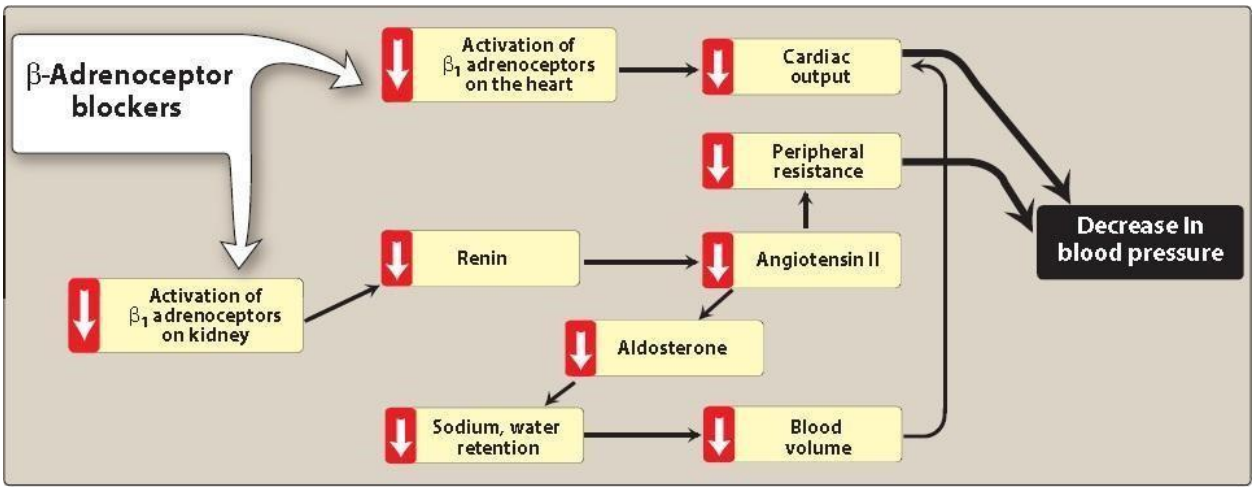
Side effect:

- Decrease in K level in the blood except (K-sparing diuretics)
- increase uric acid (hyperuricemia) and precipitate of gout
- Increase in serum lipid concentration (not used for hyperlipidemia and diabetes mellitus).

B- β- Adrenoceptor Blocking Agents (Propranolol, atenolol and Metoprolol):

Mechanism of action:

- Its act by blocking β- adrenergic receptors causing decrease (CO., sympathetic outflow from CNS and inhibition release of renin, by decrease the level of aldosterone, and angiotensin II).



Therapeutic uses:

- For hypertension that coexist with other conditions as (myocardial infarction , angina pectoris , chronic heart failure and migraine headache) ,
- Conditions that discourage the use of β-blockers (COPD, congestive heart failure, or peripheral vascular disease) which found in (elderly and diabetics patients)

Adverse effect: bradycardia, fatigue, insomnia, hypotension, decrease libido, impotence, decrease in HDL and increase in triglyceride level. (Propranolol is contraindicated in patients with asthma or COPD).

Drug withdrawal: abruptly withdrawal of β- blocker may induce (angina, myocardial infarction or sudden death in patients with ischemic heart disease), Therefore, the dose of these drugs must be tapered over 2 to 3 weeks in patients with hypertension and ischemic heart disease.

C- α- Adrenoceptor Blocking Agents (Prazosin, doxazosin and terazosin):

Mechanism of action: These drugs block α1- adrenergic receptors competitively causing decrease in peripheral vascular resistance with minimal change in CO.

Therapeutic uses: used for mild to moderate hypertension, used usually with Propranolol or diuretic for additive effect, tamsulosin used for benign prostatic hyperplasia.

D- Centrally Acting Adrenergic Drugs (α2 – agonist):

D-1- Clonidine:

Mechanism of action: its α2 agonist causing decrease of peripheral resistance and blood pressure by (diminish central adrenergic outflow).

Therapeutic uses:

- Useful for patents how not response to 2 or more of antihypertensive treatments and for patients with renal disease (not decrease renal blood flow)
- It's used for mild to moderate hypertension , often used with diuretics (because clonidine cause Na and water retention) **D-2- Methyldopa**:

- its α2 agonist causing decrease of peripheral resistance and blood pressure by (diminish central adrenergic outflow)(without decrease blood flow to vital organs specially kidney)

Therapeutic uses:

- for treatment of hypertensive patients with renal insufficiency
- for hypertensive pregnant patents

Side effect: (sedation and drowsiness due to inhibition of dopaminogenic neurons in the CNS)

E- Direct Vasodilators:

They act by **1)** direct – acting smooth muscle relaxant, causing decrease in vascular resistance and blood pressure with reflex tachycardia; **2)** they increase plasma renin concentration with increase in Na and water retention.

E-1- Hydralazine:

- Used for moderate to severe hypertension
- Used with β- blocker (for balanced reflex tachycardia) and with diuretics (for decrease Na retention) Used as monotherapy for controlling of pregnancy induce hypertension **E-2- Minoxidil:**
- Its act by opining of K channels
- Used only for severe to malignant hypertension that is refractory to other drugs.
- Minoxidil may induce Reflex tachycardia and fluid retention which require concomitant use of a loop diuretic and β-blocker.
- It causes hypertrichosis (the growth of body hair). This drug is now used topically to treat male pattern baldness.

E-3- Sodium nitroprusside: • Is administered intravenously and causes vasodilation with reflex tachycardia.

- It is capable of reducing blood pressure in all patients regardless of the cause of hypertension Its requires continuous infusion to maintain its hypertensive action (short t1/2)
- **Adverse effect:**

- Hypotension, accumulation of cyanide and metabolic acidosis.

F- Calcium-Channel Blockers:

- It's used when 1st line agents are contraindicated or ineffective
- Its effective for patients with angina or hypertensive
- Avoid high dose because of increase risk of myocardial infarction (related to reflex cardiac stimulation)
- Its class including (Verapamil, Diltiazem and Nifedipine , Amlodipine)

Intracellular calcium play a role in maintenance of (the tone of smooth muscle and contraction of myocardium), calcium inter the muscle by (special voltage Ca channels) triggering release of Ca from sarcoplasmic reticulum, causing elevate in Ca level in the cytoplasm of muscular cells

Mechanism of action:

Calcium-Channel Blockers binds with Ca channels of the heart and smooth muscle of coronary and peripheral vascular causing block inward movement of calcium producing the following effect:

1. Blocking of Vascular smooth muscle cause (**vasodilation**)
2. Blocking of cardiac smooth muscle cause (**reduce force of heart contractility**)

3. Slow down conducting of heart electrical activity causing (**decrease in heart rate**)
4. Direct reducing of aldosterone production play a role (**decrease in blood pressure**)

Therapeutic uses:

- It's used for management hypertensive patients who have (asthma, diabetes, angina and peripheral vascular disease).
- They have antihypertensive, antianginal, antiarrhythmics (diltiazem and verapamil) .

F-1- **Verapamil**: has more cardiac effect.

F-2- **Diltazim**: effect on both cardiac and vascular smooth muscle

F-3- **Nifidipim, amoldipin**: has more vascular effect **Side effect:**

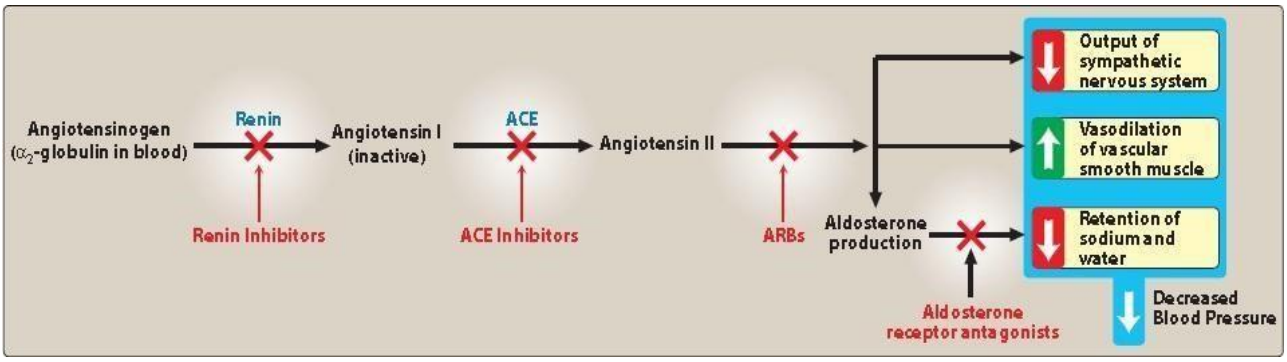
- Should be avoided in patients with congestive heart failure or with atrioventricular block due to its negative inotropic (verapamil).
- Dizziness, headache, and fatigue.
- Nifidipim may cause gingival hyperplasia

G- Angiotensin converting enzyme inhibitors (*Enalapril, Lisinopril)*:

Mechanism of action:

- Its reduce blood pressure by decrease peripheral resistance without reflex cardiac output or rate

- ***They act by blocking of ACE causing*** **1)** decrease in conversion of angiotensin I to angiotensin II (potent vasoconstrictor) **2)** decrease breakdown of bradykinin **3)** decrease in the secretion of aldosterone causing decrease in Na and water retention



Therapeutic uses:

1. Used when 1st line agents (diuretics or β- blocker) are contraindicated or ineffective
2. They slow the progression of diabetic nephropathy and decrease albumin urea
3. effective for patients with heart failure and myocardial infarction

Adverse effect:

- dry cough, rash, fever, altered taste, hypotension

- Hypotension and hyperkalemia (avoid potassium supplement and potassium sparing diuretics) may induce 1st dose angioedema or syncope (must give under supervision)
  Avoid in pregnancy (Fetus toxic). □

H- Angiotensin II Receptor Blockers (losartan, irbesartan, valsartan, candesartan, telmisartan):

Mechanism of action: 1- they block Angiotensin II-receptors competitively 2- Its effect is more specific on Angiotensin II-receptors with less or no effect on bradykinin production.

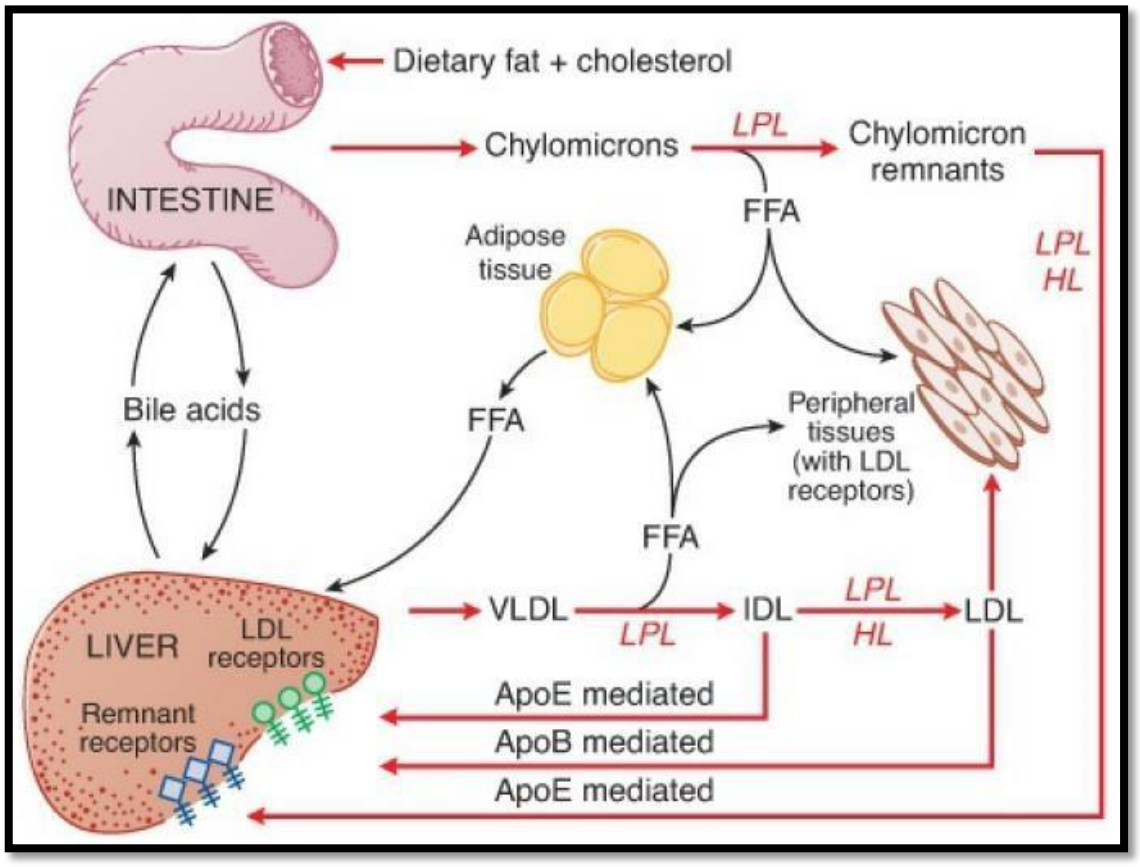
Therapeutic uses: Its clinical uses are similar to the ACE inhibitors. They have advantage above ACE inhibitors of not causing cough and angioedema which resulting from the effect of bradykinin accumulation.

Adverse effect and toxicity: similar to ACE inhibitors but not cause cough and angioedema.

Huda Nahi. M.Sc. (Pharmacology & Toxicology)

Drugs for Hyperlipidemia

- **Coronary heart disease (CHD) is the leading cause of death worldwide**
- **The development of coronary heart diseases (atherosclerosis) correlated with (1- elevated the level of LDL cholesterol, bad cholesterol, 2- elevation in the level of triglyceride, 3- decrease in the level of HDL cholesterol, good cholesterol**
- **Other risk factors included: (cigarettes smoking, hypertension, obesity, diabetes mellitus and life style factors as lack of exercise or diet containing excess saturated fats**
- **Hyperlipidemia can result from inherited defect in lipoprotein metabolism or more commonly from combination of (genetics and lifestyle factors)**
- **Appropriate lifestyle changes and drugs can lead to reduction in 30 – 40 % of coronary heart diseases**.



Treatments goals:

- **Plasma lipid consists mostly of lipoprotein (complex of lipid) and specific protein (apolipoproteins).**
- **The important type of lipoprotein that correlated clinically with incidence of atherosclerosis is (LDL, VLDL, chylomicrons and HDL)**
- **Occurrence of CHD positively associated with increase in the level of cholesterol and more to the level of LDL –c, while the level of HDL associated with the risk of heart diseases**
- **Primary therapy of lowering cholesterol therapy is reduction of LDL, its useful for population of high risk of**
  (Atherosclerosis cardiovascular disease) ASCVD.

Treatment options of hypercholesterolemia:

1. **Life style change as (diet, exercise and weight reduction) , can lead to moderate (reduction in LDL and elevation of HDL) , but it's not sufficient for significant reduction in LDL and HDL .**
2. **Drugs therapy may be required, by treatment with HMG Co. A reductase inhibitors (statin) which found as four main groups, it's the primary options for hypercholesterolemia (treatment with statin started in patients with LDL level more than 160 mg /dl or in patients with hypertension, diabetes mellitus and smoking**

Treatment options of hypertriglyceridemia:

Elevation in the level of triglyceride is independently associated with high risk of CHD, exercise is the primary treatments of hypertriglyceridemia, but if not sufficient, the following drugs indicated

- **niacin and fabric acid (its most effective for lowering triglyceride level)**
- **omega -3 (its beneficial also)**
- **Statins (secondary benefit, but primary benefit for lowering LDL level).**

Drugs of hyperlipidemia:

- **Included (statins, niacin, fibrates, bile acid binding –resins and omega-3- fatty acid) .**
- **this medication used either alone or in combination**
- **It should be accompanied by lifestyle modification as exercise and diet low fats.**

A. HMG CoA Reductase inhibitor (Simvastatin, Lovastatin, Atorvastatin, Rosuvastatin, Fluvastatin, Pitavastatin).

- **3-hydroxy-3-methylglutaryl coenzyme – A reductase inhibitor, lowering elevated level of LDL –C level, resulting in substantial reduction in CHD and death from CHD**
- **Its 1st line for patients with high risk of atherosclerosis coronary heart disease**
- **Its act by plaque stabilization, inhibition of thrombus formation, improvement of coronary endothelial function and anti-inflammatory.**

Mechanism of action:

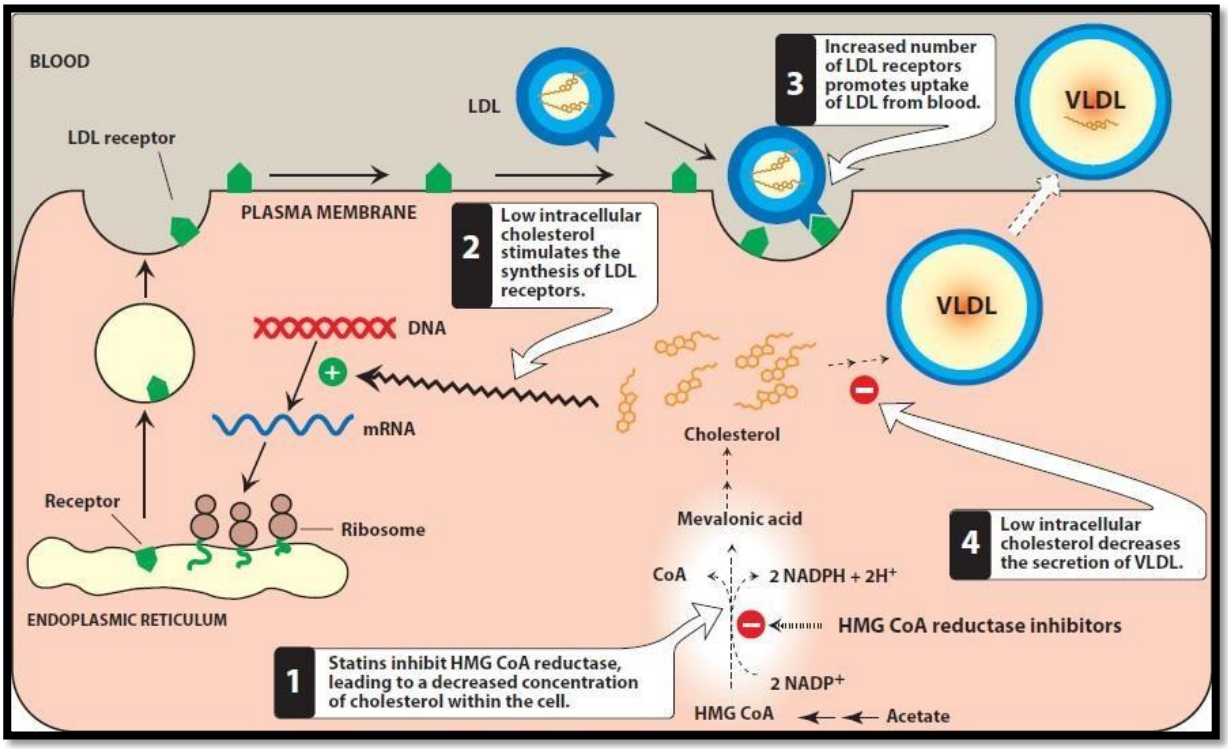
It is competitively inhibition of HMG Co- A reductase enzyme causing

1. **Inhibition of cholesterol synthesis (depletion of intracellular supply of cholesterol).**
2. **Increase in the number of liver cell surface LDL – receptors (internalized circulating LDL)**

Thus, decrease cholesterol level by inhibition its synthesis and increase catalyzed of LDL

3. **Also decrease triglyceride level**
4. **May increase HDL level in some patients**

Therapeutic uses: this medication effective to decrease plasma cholesterol level in all types of hyperlipidemia



Adverse effect:

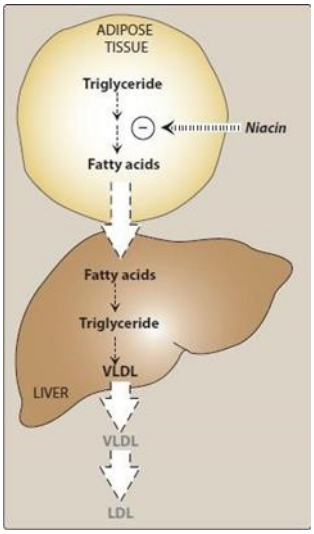
1. Elevation in the liver enzyme (liver function test must be monitored)

2. Myopathy and rhabdomyolysis (degradation of skeletal muscle), it is rare but increase risk of rhabdomyolysis occur if taken with drugs that inhibition 3A4 cyp450 isoenzymes. 3. HMG Co-A reductase inhibitors drugs may increase the effect of warfarin (must evaluated the level of INR)

4. Contraindicated in pregnancy

B. Niacin (Nicotinic acid): It can reduce LDL and T.G with elevation in HDL; it is used in combination with statin drugs as (Lovastatin + Niacin).

Mechanism of action: niacin act by inhibition of lipolysis in adipose tissue causing decrease in free fatty acid that used by liver to synthesis T.G, causing decrease in the level of liver T.G, also decrease in the level of hepatic VLDL and consequently decrease in the level of LDL in the plasma.



Therapeutic uses: by its ability to decrease the level of cholesterol and T.G, niacin is useful for familial hyperlipidemia, sever hypercholesterolemia and

Hypertriglyceridemia,

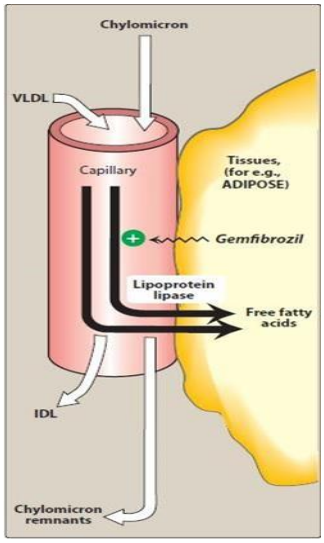
Adverse effect:

a. Cutaneous flush and pruritus (aspirin can minimize this adverse effect)

b. Nausea and vomiting

c. Inhibition uric acid secretion (precipitate hyperuricemia and gout)

d. Should be avoid in hepatic disease.



C. Fibrates (Fenofibrate and Gemfibrozil): It is act by decrease the level of T.G and elevate the level of HDL.

Mechanism of action:

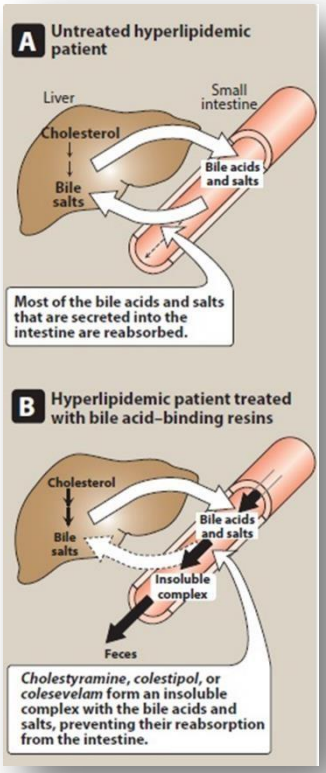
Peroxisome proliferator–activated receptors are nuclear receptor that regulates lipid metabolism. These receptors activated upon binding to (fatty acids or eicosanoids) or antihyperlipidemic drugs, Activated of these receptors lead to decreased triglyceride concentrations by (1- increased expression of lipoprotein lipase, 2- decreasing apolipoproteins (apo) CII concentration.

Fibrates also increase the level of HDL cholesterol by increasing the expression of apo AI and apo AII.

Therapeutic uses: **useful for patients with hypertriglyceridemia. (Avoid in patients with renal or hepatic disease)**

Adverse effect:

- **G.I.T disturbance**
- **Increase incidence of gallstone because increasing in biliary cholesterol excretion**
- **Fibrate may increase the level of warfarin, INR should be monitoring**
- **Myopathy and rhabdomyolysis**



D. Bile acid-binding resins (Cholestyramine, Colestipol and Colesevelam):

It has ability to lowering LDL cholesterol, with less significant than statins

Mechanism of action: **its anion – exchange resins that bind with negative charge (bile acids and bile salts) in small intestine formed a complex that excreted in the faces causing decrease in bile acid concentration leading to increase in hepatocyte to conversion of cholesterol to bile acid , eventually causing decrease in the intracellular cholesterol concentration and increase in hepatic uptake of cholesterol contain LDL , leading to decrease in LDL concentration in the plasma .**

Therapeutic uses: **it is used as 2nd line therapy for**

a. **Hyperlipidemia (given with diet or niacin)**
b. **It's not effective for patients with hyperlipidemia have lacking in LDL receptors**
c. **Colesevelam indicated for type 2 diabetes mellitus due to its glucose-lowering effects**

Adverse effects:

a. **GI disturbances, as constipation, nausea, and flatulence.**
b. **May impair the absorption of the fat-soluble vitamins (A, D, E, and K), and they interfere with the absorption of many drugs (for example, digoxin, warfarin, and thyroid hormone). Therefore, other drugs should be taken at least 1 to 2 hours before, or 4 to 6 hours after, the bile acid– binding resins.**
c. **These agents may raise triglyceride levels and are contra-indicated in patients with significant hypertriglyceridemia (≥400 mg/dL).**

E. Cholesterol absorption inhibitor:

1- Ezetimibe:

- **its selectively inhibition the absorption of dietary biliary cholesterol in small intestine causing decrease in cholesterol delivery to the liver leading to decrease in hepatic cholesterol stores causing increase in clearance of cholesterol from the blood.**
- **It is used for hypercholesterolemia as adjunct to statins therapy (due to modest lowering of LDL level).**

F. Omega-3 fatty acids:

- **Its polyunsaturated fatty acid, found in marine source, tuna and salmon**
- **Its act by lowering T.G level through inhibition synthesis of T.G in the liver, with small elevation in the LDL and HDL level**
- **Using of fish oil capsule (because of difficulty to consume enough content of omega - 3 from dietary source**

G- Orlistat (Xenical): its act by inhibition of G.I.T lipase that interferes with T.G digestion to free fatty acid, it's not used for hyperlipidemia but for obesity.

Combination therapy:

- **As using of statins with bile acid binding drugs (very effective for lowering LDL-C).**
- **In addition, the combination of (simvastatin + Ezetimibe) and (simvastatin + niacin) used for lowering LDL-C level.**
- **Maximizing statin dose plus niacin or fibrate used only in patients with persist elevation in T.G (more than 500 mg/dl) or decrease in the level of HDL below than 40 mg/dl.**
- **(Combination drug therapy is not without risks), Liver and muscle toxicity occurs more frequently with lipid-lowering drug combinations**

Heart Failure

Heart Failure: its complex progressive disorder in which the heart unable to pump sufficient blood to meet the needs of the body (by impaired ability of the heart to adequately fill with and or/ eject blood with abnormal elevation in blood volume and interstial fluid.

Signs and symptoms of heart failure: dyspnea (which worse with exercise), fatigue and fluid retention,

Causes of heart failure: atherosclerosis heart disease, myocardial infarction, hypertensive heart disease, valvular heart disease, dilated cardiomyopathy, congenital heart disease.

Heart failure can be classified as:

1. **Systolic heart failure:** its more common type of heart failure, cause by unable of ventricles to pump blood effectively, it's affected the left side of the heart.
2. **Diastolic heart failure**: it's characterized by inability of the ventricles to relax and accept blood related to structural changes such as hypertrophy. The thickening of the ventricular wall and subsequent decrease in ventricular volume decrease the ability of heart muscle to relax.

Other classification included:

1. **Left side heart failure:** fluid accumulation in the lung (pulmonary edemas).
2. **Right side heart failure:** fluid accumulation in the body (leg, feet, abdomen **…).**

Compensatory physiological responses in HF: The failing heart activates three major compensatory mechanisms to enhance cardiac output, although initially beneficial, *these alterations ultimately result in further deterioration of cardiac function.* **These mechanisms included:**

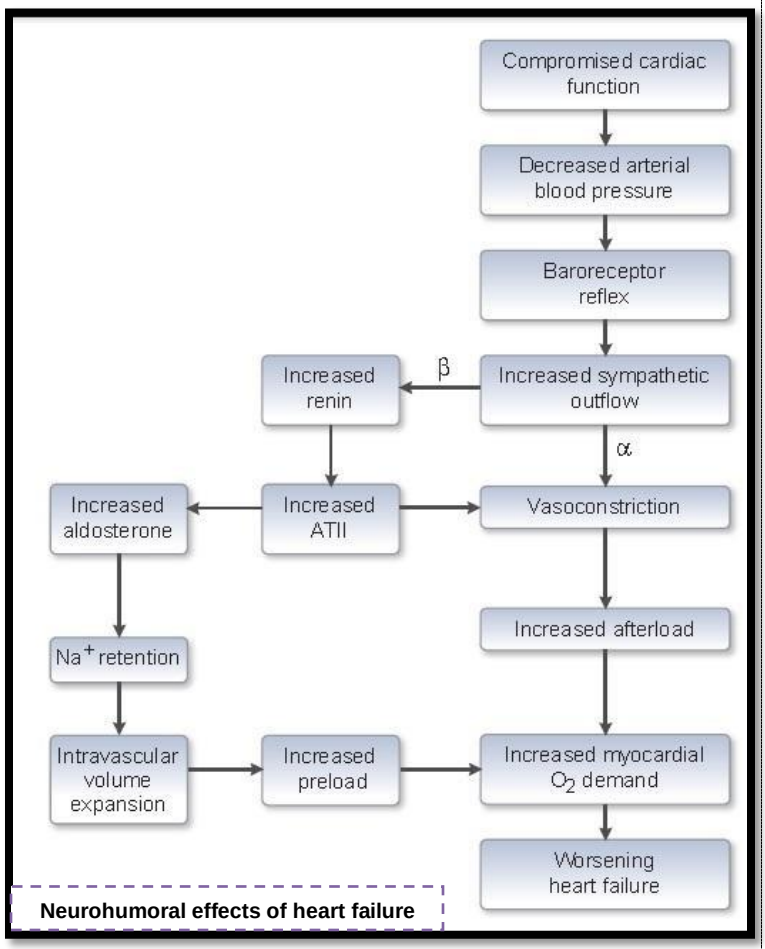
1. **Increased sympathetic activity.**
2. **Activation of the renin–angiotensin–aldosterone system.**
3. **Myocardial hypertrophy.**

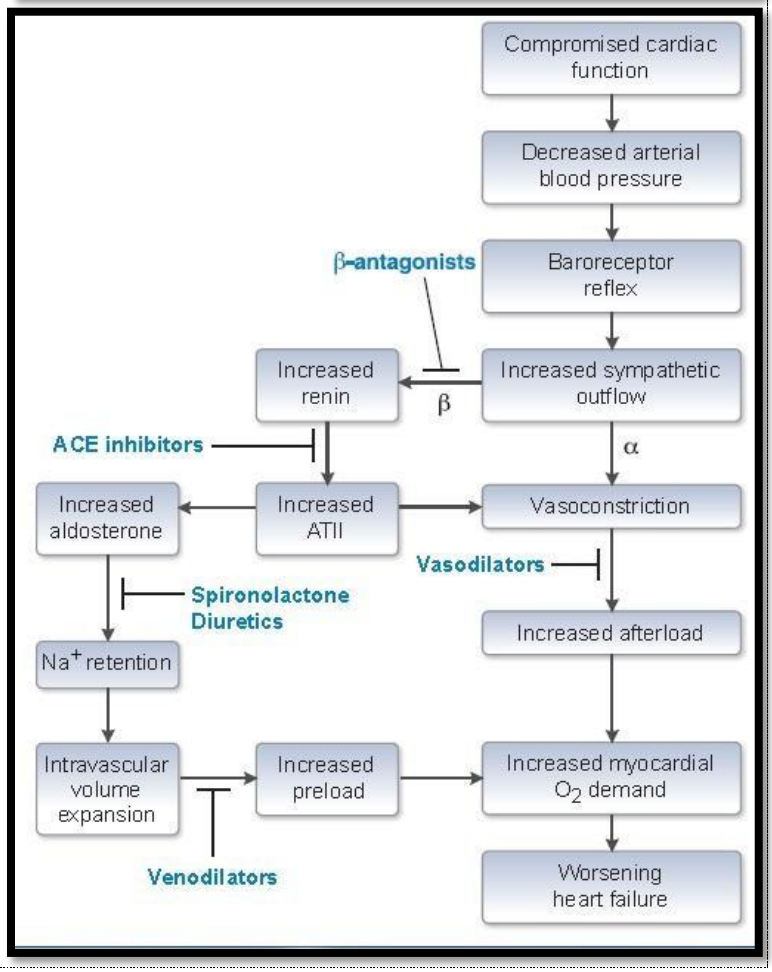
Diagnosis:

- case history , physical examination
- **Ejection fraction** (is the percentage of blood that pumping out of the heart per beat) , its considerate as the key indicator for heart failure diagnosis
- (chest X ray , blood test , electrocardiogram (ECG), (echocardiogram, Echo) and angiogram (blood vessels X-ray).

Therapeutic strategies in HF:

- That is for prolongation of the life, prevention of acute decompensation reduction of symptoms, and enhance the activity.
- Chronic HF is typically managed by (*fluid limitations, low dietary intake of sodium, Treatment of comorbid conditions;* and use of (*diuretics, inhibitors of the renin–angiotensin– aldosterone system, and inhibitors of the sympathetic nervous system)*.
- **Inotropic agents** are reserved for acute HF signs and symptoms.
- **this medication use for :**
  1. **Decrease myocardial work load**
  2. **Decrease extra cellular fluid volume**
  3. **Improve cardiac contractility**
  4. **Decrease rate of cardiac remodeling**
- Drugs that may exacerbate HF, (nonsteroidal anti-inflammatory drugs (NSAIDs), alcohol, nondihydropyridine calcium channel blockers verapamil, diltiazem and some antiarrhythmic drugs).

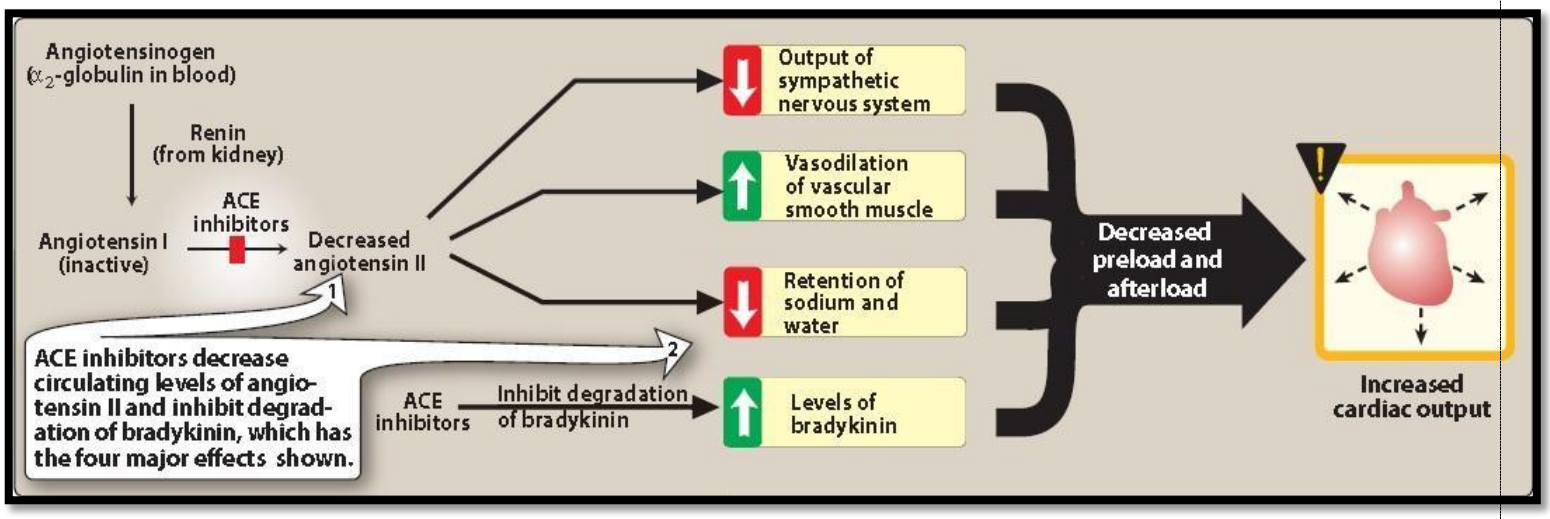




A- INHIBITORS OF THE RENIN–ANGIOTENSIN– ALDOSTERONE SYSTEM

Its 1st line therapy for heart failure, its act by relaxation of blood vessels, decreases of blood volume and reduce both preload and afterload on the heart, including the following groups.

1. **Angiotensin-converting enzyme inhibitors (Lisinopril, Enalapril).**
2. **Angiotensin-converting enzyme blockers (losartan, candesartan).**
3. **Aldosterone antagonists (spironolactone, eplerenone).**



B- β-Blockers (bisoprolol, carvedilol and Metoprolol):

These agents decrease heart rate and inhibit release of renin in the kidneys. In addition, β-blockers prevent the deleterious effects of norepinephrine on the cardiac muscle fibers, decreasing remodeling, hypertrophy, and cell death.

C- Diuretics (furosemide):

- Diuretics relieve pulmonary congestion and peripheral edema. These agents are also useful in reducing the symptoms of volume overload, including orthopnea and paroxysmal nocturnal dyspnea.
- Diuretics decrease plasma volume and, subsequently, decrease venous return to the heart (preload). This decreases cardiac workload and oxygen demand. Diuretics may also decrease afterload by reducing plasma volume, thereby decreasing blood pressure.
- Loop diuretics are the most commonly used diuretics in HF. These agents are used for patients who require extensive diuresis and those with renal insufficiency.

D- Vaso- And Vasodilators (Nitroglycerin, Hydralazine):

- Its act by Dilation of venous blood vessels leads to a decrease in cardiac preload by increasing venous capacitance.
- Nitrates are commonly used venous dilators to reduce preload for patients with chronic HF.
- Arterial dilators, such as *Hydralazine,* reduce systemic arteriolar resistance and decrease afterload.
- It's used for patient that cannot be tolerate the action of ACE inhibitors or β-blockers,

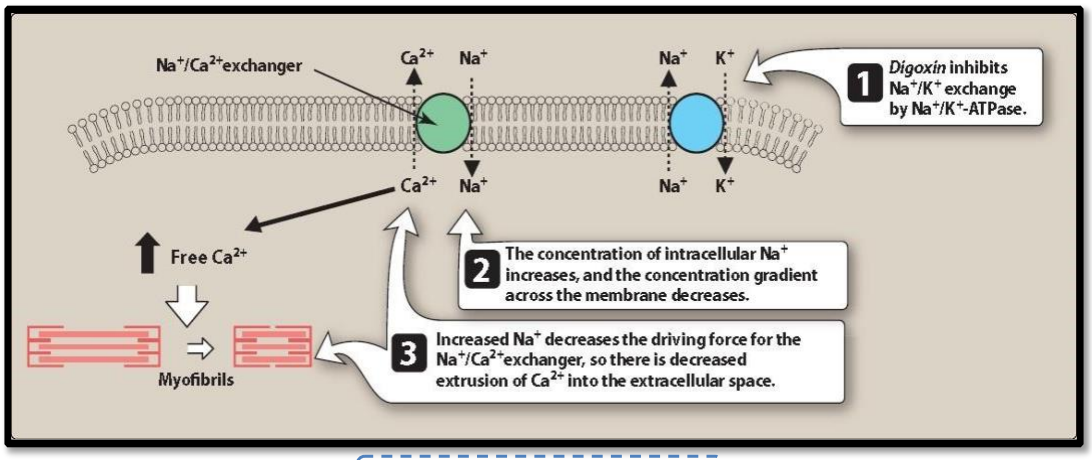
E- Inotropic Drugs :

- Positive inotropic agents enhance cardiac contractility and cardiac output
- These drugs act by a mechanism included increase cytoplasmic calcium concentration that enhance contractility of cardiac muscle
- All positive inotropic agents (except digoxin) used for a short periods because it's associated with reduced survival of the patients have (heart failure with reduce ejection fraction) due to coronary disease.

E-1- Digitalis glycosides (digoxin, *Digitoxin*):

- Often called digitalis, because it's come from digitalis (foxgloves) plant.
- Its can increase the contractility of the heart muscle; therefore it's used for treatment of heart failure.
- Digitalis glycoside has a low therapeutic index.

Mechanism of action: Digitalis Regulation the cytosolic calcium concentration**,** by inhibiting the Na+/K+-adenosine triphosphatase (ATPase) enzyme, *digoxin* reduces the ability of the myocyte to actively pump Na+ from the cell (Figure 19.8). This decreases the Na+ concentration gradient and, consequently, the ability of the Na+/ Ca2+-exchanger to move calcium out of the cell. Further, the higher cellular Na+ is exchanged for extracellular Ca2+ by the Na+/Ca2+-exchanger, increasing intracellular Ca2+. A small but physiologically important increase occurs in free Ca2+ that is available at the next contraction cycle of the cardiac muscle, thereby increasing cardiac contractility.



Mechanism of action of *digoxin*

Therapeutic uses:

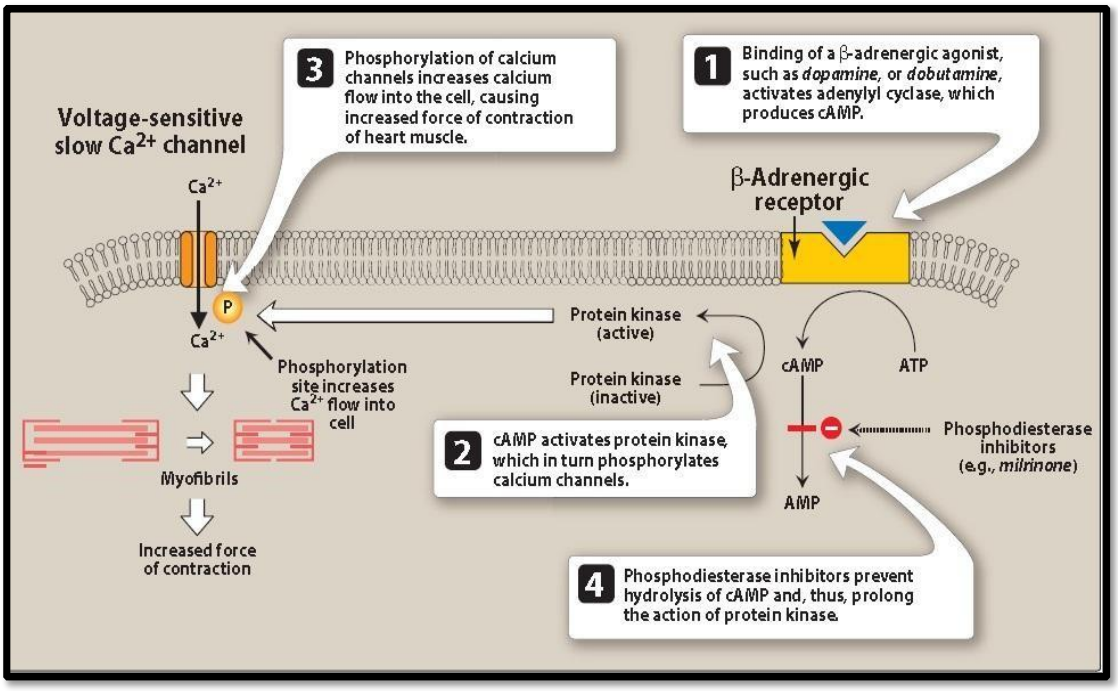
- low serum concentration of *digoxin* used for patients with severe HF after initiation of ACE inhibitor, β-blocker, and diuretic therapy , At this level, patients may see a reduction in HF admissions, along with improved survival
- *Digoxin* is not indicated in patients with diastolic or right sided HF unless the patient has concomitant atrial fibrillation.

Toxicity:

- digoxin has a very narrow therapeutic index, *digoxin* toxicity needs hospitalization,
- Initial symptoms that indicated of toxicity (Anorexia, nausea, and vomiting) Patients may also experience (blurred vision, yellowish vision (xanthopsia), and various cardiac arrhythmias).
- Toxicity can often managed by discontinuing *digoxin*, determining serum potassium levels, and, if indicated, replenishing potassium. Decreased levels of serum potassium (hypokalemia) predispose a patient to *digoxin* toxicity, since *digoxin* normally competes with potassium for the same binding site on the Na+/K+-ATPase pump)as thiazide or loop diuretics because of hypokalemia
- Severe toxicity resulting in ventricular tachycardia may require administration of antiarrhythmic drugs and the use of antibodies to *digoxin* (*digoxin immune Fab*), which bind and inactivate the drug.

E-2- B. β-Adrenergic agonists (*dobutamine, dopamine*):

- Improve cardiac performance by causing positive inotropic effects and vasodilation.
- Its act by increase intracellular (cAMP), which results in the activation of protein kinase. Protein kinase then phosphorylates slow calcium channels, thereby increasing entry of calcium ions into the myocardial cells and enhancing contraction.



E-3- Phosphodiesterase inhibitors (Milrinone):

- is a phosphodiesterase inhibitor that increases the intracellular concentration of cAMP
- Like β-adrenergic agonists, this results in an increase of intracellular calcium and, therefore, cardiac contractility.

Note:

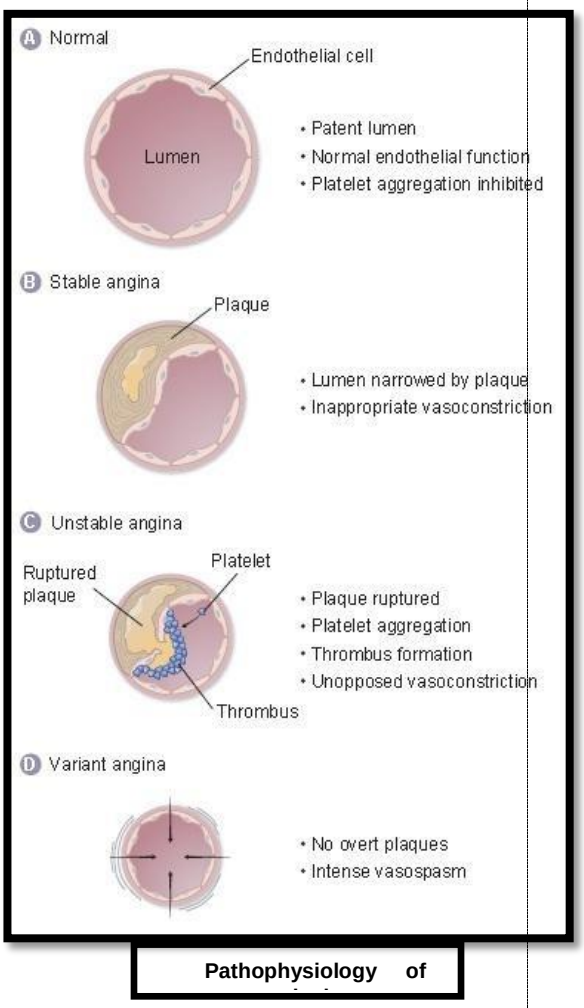
Calcium channel blocker not used for treatment of heart failure, because depressant effect on the heart may worsen the heart failure.

Antianginal Drugs

Angina pectoris: A sudden, severe, crushing chest pain may radiate to the neck, jaw, back, and arms. Patients may also present with dyspnea or indigestion, nausea, vomiting, or diaphoresis. **Caused by:** insufficient coronary blood flow that provide oxygen to myocardium leading to ischemia **during excise:** there is imbalance between oxygen delivery and oxygen utilization resulting from either (1- obstruction of blood vessels cause by atherosclerosis; 2- spasm of vascular smooth muscle).

THESES TRANSIENT EPISODES (LAST FROM 15 SEC TO 15 MIN OF MYOCARDIAL ISCHEMIA, DON'T CAUSE CELLULAR DEATH)

Types of angina: *Have 3 overlapping patterns*



Pathophysiology of

1. **Stable angina, effort-induced angina, classic or typical angina:**

- Its characterized by burning , heavy squeeze feeling in the chest
- Its caused by decrease of coronary perfusion due to fixed obstruction of coronary artery caused by atherosclerosis
- Heart became vulnerable to ischemia whenever increasing in demand of oxygen as in (physical activity and emotional excitements)
- Relief by rest or using of nitroglycerin (vasodilator)

2. **Unstable angina:**

- It's a type of angina lies between (stable angina and myocardial infarction)
- Chest pain experiences either acceleration in frequency or severity of chest pain.
- Not response to rest or nitroglycerin , but its required hospital admission and more aggressive therapy for prevent death or myocardial infarction

3. **Prinzmetal, variant, vasospastic, or rest angina:**

- Its occurs at rest , duo to coronary artery spasm causing decrease blood flow to the heart producing the symptoms
- Angina attack at this type are unrelated to physical activity , heart rate and blood pressure.(with significant atherosclerosis)

- Its response to coronary vasodilators as nitroglycerin or calcium channel blockers, β-blocker is contraindicated.

(This class of drugs used for angina pectoris, used either alone or in combination)

β-blockers, calcium channel blockers, organic nitrates, and the sodium channel–blocking drug, ranolazine

These drugs act by decrease oxygen demand of the heart by

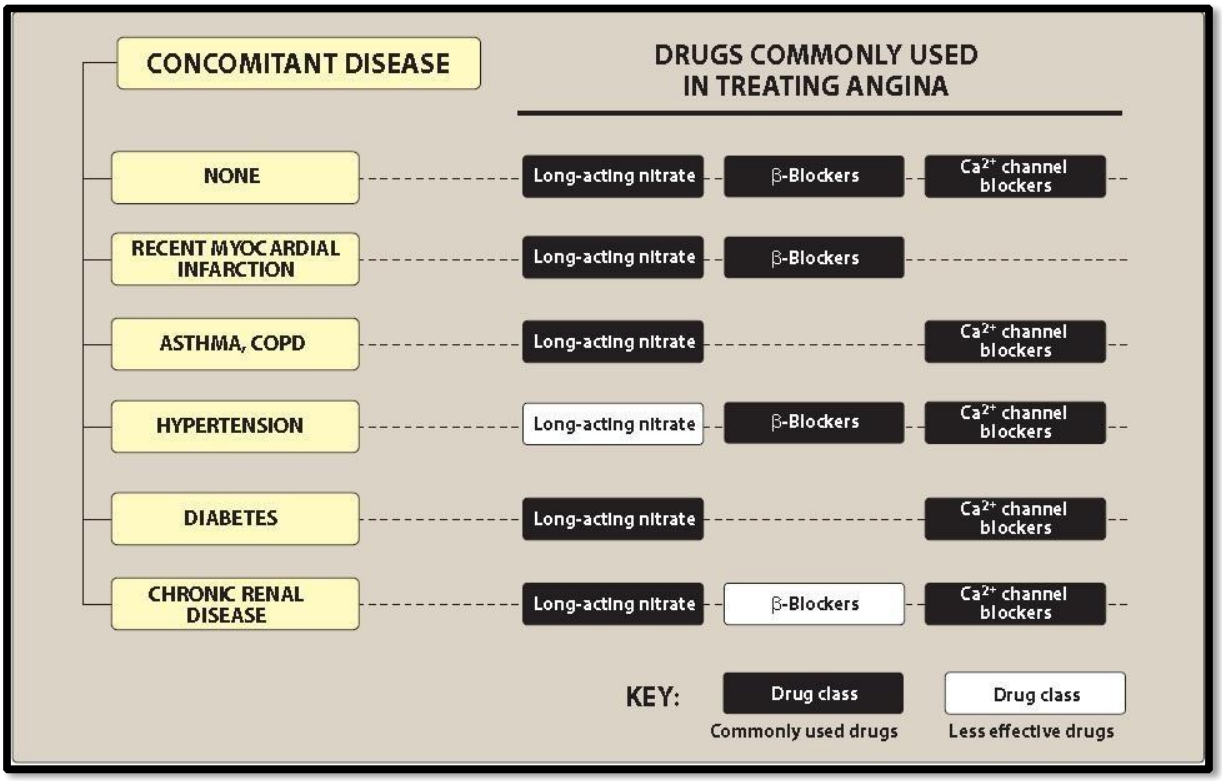
1) Decrease blood pressure
2) Decrease venous return
3) Decrease heart rate
4) Decrease contractility.

Non-pharmacological treatment included: 1) life style and risk factors modification as cessation of smoking, 2) surgical treatment included angioplasty, and coronary artery bypass surgery.

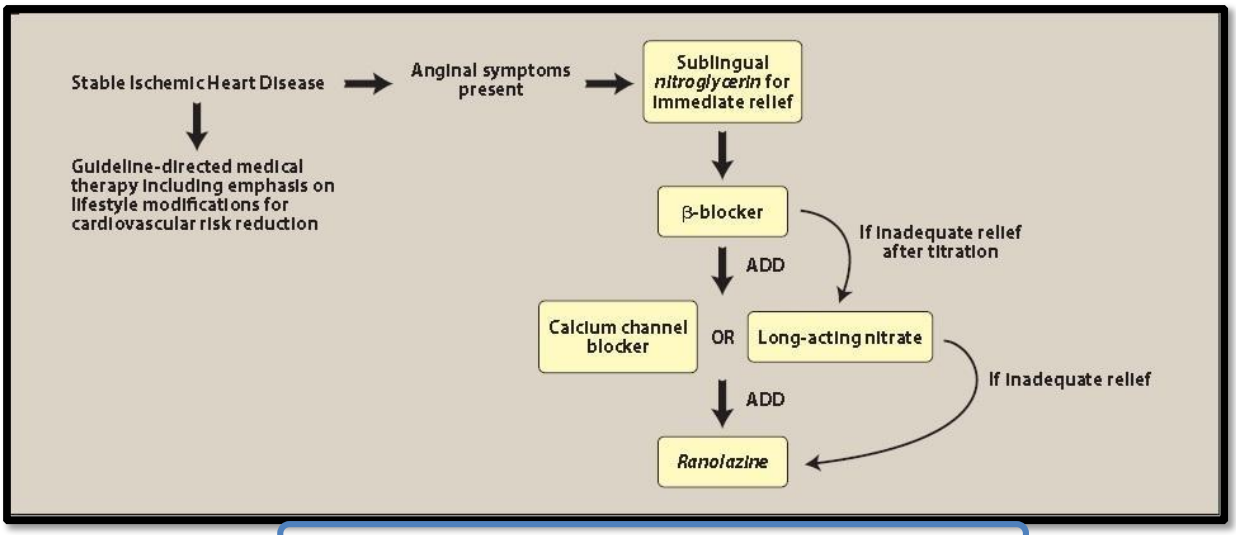
Diagnosis:

Angina should be suspected in people presenting with tight, dull or heavy chest discomfort as the following:

1. Pressure , squeezing , burning , or tightness in the chest
2. Left side , radiation to the left arm , neck , jaw or back
3. Associated with excretion or emotional stress and relived within several minutes by rest (stable angina)
4. Precipitate by cold weather or a meal
5. It may feel like indigestion.



Treatment of angina in patients with concomitant diseases



Treatment algorithm for improving symptoms in patients with

1- β-Adrenergic Blockers: (prophylaxis)

- Its suppress the activity of heart by blocking β1-heart receptors , causing decrease in heart rate , contractility , cardiac output and blood pressure , producing decrease oxygen demand by the myocardium during exertion and at rest .
- 1-selective Blockers (cardioselective as Metoprolol, atenolol) prefer than non-selective ones as Propranolol.
- Agents with intrinsic sympathetic activity (partial agonist) Pindolol, less effective and should be avoided.

Therapeutic uses:

- It's used for reduce frequency and severity of angina attack
- It's useful for patients with myocardial infarction
- Used with nitrate to increase exercise duration and tolerance **Contraindication:**
- In patients with asthmas, diabetes mellitus, sever bradycardia, peripheral vascular resistance and COPD.

2- Calcium channel blockers: (prophylaxis)

- Calcium channel blocker act by inhibition the entrance of calcium into the cardiac and smooth muscle cells of coronary and systemic arterial beds, producing decrease in smooth muscle tone vascular resistance.
- Clinically theses agents affected the resistance of vascular smooth muscle and the myocardium.
- verapamil : mainly affected myocardium
- Nifidipim: has greater effect on smooth muscle in the peripheral vascular.
- Diltiazem: affected both.

Dihydropyridine calcium channel blockers (nifidipim, amlodipine):

- They act as arterioles vasodilator , with less effect on heart rate or cardiac output
- Used for variant angina (that caused by spontaneous coronary spasm)

Side effect: Flushing, headache, hypotension, peripheral edema and constipation (it should be avoid in coronary artery disease, because reflex tachycardia if peripheral vasodilator is marked)

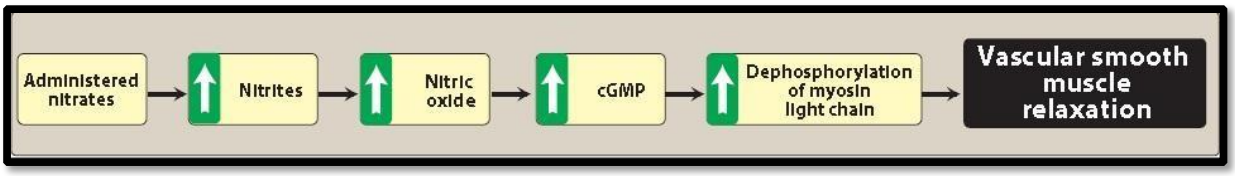
Nondihydropyridine calcium channel blockers:

A- Verapamil:

- act by slow cardiac Atrioventricular conducting directly , causing decrease in heart rate , contractility , blood pressure and oxygen demand
- (it's a weaker vasodilator)
- Should be used with caution in patients taking digoxin (because verapamil increase digoxin level)
- **B- Diltiazem :**
- Its act by reduce heart rate to lesser extent than verapamil with decrease in blood pressure Its useful for variant angina because of its ability to relief coronary artery spasm
- Should be used with caution in patients taking digoxin.

3- Organic Nitrates (for immediate relief of angina)

- Used for treatment of angina pectoris, its mainstay therapy for immediate relief of angina. Its act by relax veins causing decrease preload and myocardial oxygen consumption
- Inside the cell nitroglycerin convert to nitrite ions and then to nitro oxide, then in turn it activates guanylyl cyclase and increase cGMP, (elevate it ultimately lead to dephosphorylation of myosin light chain, result vascular smooth muscle relaxation.



Effect of cardio vascular system:

- Organic nitrate included (nitroglycerin, Isosorbide dinitrate, Isosorbide mononitrate) these agent are different in onset and duration of action.
- These agents (especially spray or sublingual form) have ability to relief attack of angina that precipitates by excises or emotional stress). Nitroglycerin has 2 major effect

1- dilatation of large vein (pooling of blood in vein) , diminish preload , reduce heart work and decrease in myocardial oxygen consumption
2- Dilated coronary vasculature, causing increase blood supply to heart muscle

Kinetics:

- onset of action varies from 1min (nitroglycerin) to 1hr. Isosorbide mononitrate
- these agents used commonly as sublingual or via transdermal to avoid 1st pass metabolism (specially nitroglycerin) , while Isosorbide mononitrate has an important boiavilibilty (stable for hepatic breakdown) with long duration of action
- Isosorbide dinitrate undergo to denitration into two (mononitrate) each one has antianginal effect

Adverse effect:

- The most common side effect is headache (occur with 30 -60%) of patients that receiving intermediate long acting therapy, at high dose it produce (postural hypotension, facial flushing and tachycardia).
- Combination with sildenafil is contraindication because of dangerous hypertension that producing.

Tolerance:

- Tolerance of blood vessels to the action of nitrates occurs rapidly by (desensitization of the receptors).
- Tolerance can be overcome by (daily nitrate – free – intervals) to restore sensitivity of receptors to the drugs, interval typically about (10-12) hr. especially at night While dermal patch worn for 12 hr. and removed for 12 hr.

Drugs for Diabetes

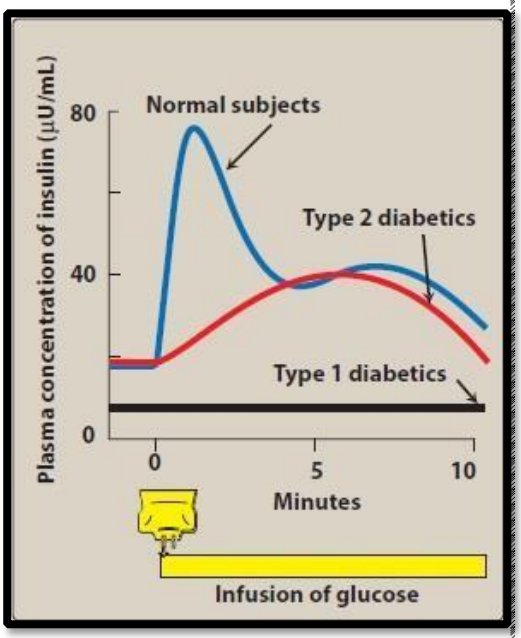
- **Pancreas produces insulin (β cells), glucagon (α cells) and somatostatin (δ cells).**
- **theses hormones regulate metabolic activity of the body (glucose haemostasis)**
- **in diabetes mellitus there is relatively or absolutely lack of insulin causing serious hyperglycemia**
- **if hyperglycemia left untreated can cause retinopathy , nephropathy , neuropathy and cardiovascular complication**

Diabetes Mellitus: it's a disease characterized by elevation of blood glucose attributed to a relatively or absolutely deficiency of insulin, it's categorized to four types:

	Type 1	Type 2
Age of onset	Usually during childhood or puberty	Commonly over age 35
Nutritional status at time of onset	Commonly undernourished	Obesity usually present
Prevalence	5% to 10% of diagnosed diabetics	90% to 95% of diagnosed diabetics
Genetic predisposition	Moderate	Very strong
Defect or deficiency	β cells are destroyed, eliminating the production of insulin	Inability of β cells to produce appropriate quantities of insulin; insulin resistance; other defects

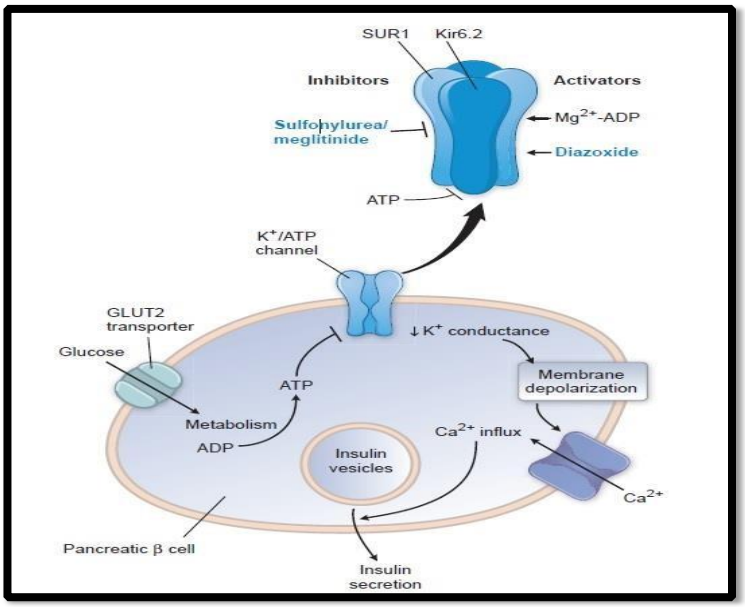
1. **Type 1 diabetes : its most commonly in young patients , its characterized by absolute deficiency of insulin , patients with this type of diabetes must be rely on exogenous insulin to control (hyperglycemia , ketoacidosis, and to maintenance acceptable formation of glycosylated Hb (Hb A_{1c})**
2. **Type 2 diabetes : this type of diabetes influence by genetic , aging , obesity and peripheral insulin resistance , its cause by lack sensitivity of insulin target and insufficient insulin to maintenance glucose hemostasis , its treated by oral lowering agent with weight reduction , exercise and dietary modification to prevent long term complication**
3. **Gestational diabetes : its cause by placental hormones cause insulin resistance cause occur in last trimester , it produce fetal macrosomia, shoulder dystocia and neonatal hypoglycemia , can be treated by insulin administration**
4. **Diabetes due to other causes: such as genetic defects or medications.**

- **Level of the glucose is change at various time in the day , at fasting in normal healthy person is about 80 – 110 mg/dl , elevation of glucose level above than 126 mg/dl indicated hyperglycemia , while a constant decrease in the level of glucose below than 70 mg/dl indicated hypoglycemia .**
- **Hypoglycemic agents: found as (1- insulin, given S/C and 2- oral hypoglycemic agents).**



A- Insulin:

- **it's a polypeptide hormones, synthesis as precursor (proinsulin) which undergo cleavage to insulin and C-peptide chain ,**
- **insulin undergo hepatic and renal extraction , while C- reactive chain which consider as better index for insulin level insulin production regulated by the level of (glucose , certain amino acids , other hormones and autonomic mediators)**



Insulin secretion: at high level of glucose it transport to the β- cells of pancreas , then phosphorylated by glucokinase, and enter to the mitochondrial respiratory chain , which generate ATP that block K channel's and open calcium channels causing exocytosis of insulin

Insulin degradation: insulin depredated rapidly by insulinase enzyme in the liver and kidney with a circulating half-life of 6- min.

Effect of insulin at target tissue:

- **Although virtually all tissue expresses insulin receptors, energy storage tissue (liver, muscle and adipose tissue) express high level of insulin receptors.**
- **Type of insulin receptors is tyrosine kinase receptor**
- **Insulin is the classic anabolic (energy storing) hormone , it promote the storage of fat as well as glucose with specialized target cell and influence cell growth and metabolic function with wide different tissue**

1. **In liver : insulin storage glucose in the liver as glycogen , glycolysis and fatty acid synthesis**
2. **In muscle : insulin facilitate movement of glucose , increase amino acid uptake ,and promote glycogen synthesis and storage**
3. **In adipose tissue: insulin promotes expression of lipoprotein lipase enzyme, and that hydrolysis of triglyceride and lipoproteins, and storage of fat and glucose inside fat cell as triglyceride.**

Pharmacokinetics:

- **Human insulin produced by recombinant DNA technology (by using strain of E.coli contain gene for human insulin**
- **Modification of amino acid sequences of insulin produce insulin with different pharmacokinetics properties (onset and duration) , which affected also by site of injection , blood supply , temperature and physical activity**

  Usually insulin given s/c , but in hyperglycemic emergency regular insulin is given by I.V route or by continuous I.V insulin infusion device (insulin pump)

Four principle types of injected insulin are available

1. **Rapid - acting with vary fast onset and shorter duration (aspart , lispro and glulisine)**
2. **Short – acting with rapid onset of action (regular insulin)**
3. **Intermediate action (neutral protamine hagdron NPH)**
4. **Long – acting with slow onset of action (insulin glargine and insulin detemir)**

Insulin combination:

Various premixed combinations of human insulins are found, as (70% NPH, plus 30% regular) or 50% of each of these.

Side effects:

1. **Hypoglycemia : which cause autonomic hyperactivity , sympathetic (tachycardia , palpitation , sweating and tremor), while parasympathetic (nausea , may progress to convulsion and coma if not treated)**
2. **Weight gain**
3. **lipodystrophy**
4. **Diabetic patients with renal insufficiency may require to decrease in insulin dose.**

B- Oral hypoglycemic agents:

• These agents used for patients with type 2 diabetes mellitus

• It is used for patients who developed diabetes after age 40 and had diabetes less than 5 years

Four categories of oral antidiabetics' drugs are now available:

1- Insulin secretagogues agents:

• Sulfonylureas: (1st generation included tolbutamide, chlorpropamide and tolazamide), while (2nd generation included glyburide, glipizide and glimepiride) Theses medication promote secretion of insulin from β-cells of pancreas

• The sulfonylureas in current use are the second-generation drugs glyburide, glipizide and glimepiride).

Mechanism of action: these medication act by stimulation of insulin release from β- cells in pancreas by blocking ATP-sensitive K channel (causing depolarization) , Ca influx and insulin exocytosis

Therapeutic uses: for type II diabetes mellitus

Side effect:

- **including (weight gain , hyperinsulinemia and hypoglycemia)**
- **used in caution in patients with hepatic or renal insufficiency**

Glyburide duration of action may increase in patients with renal impairments (while (glipizide and glimepiride) are safer option

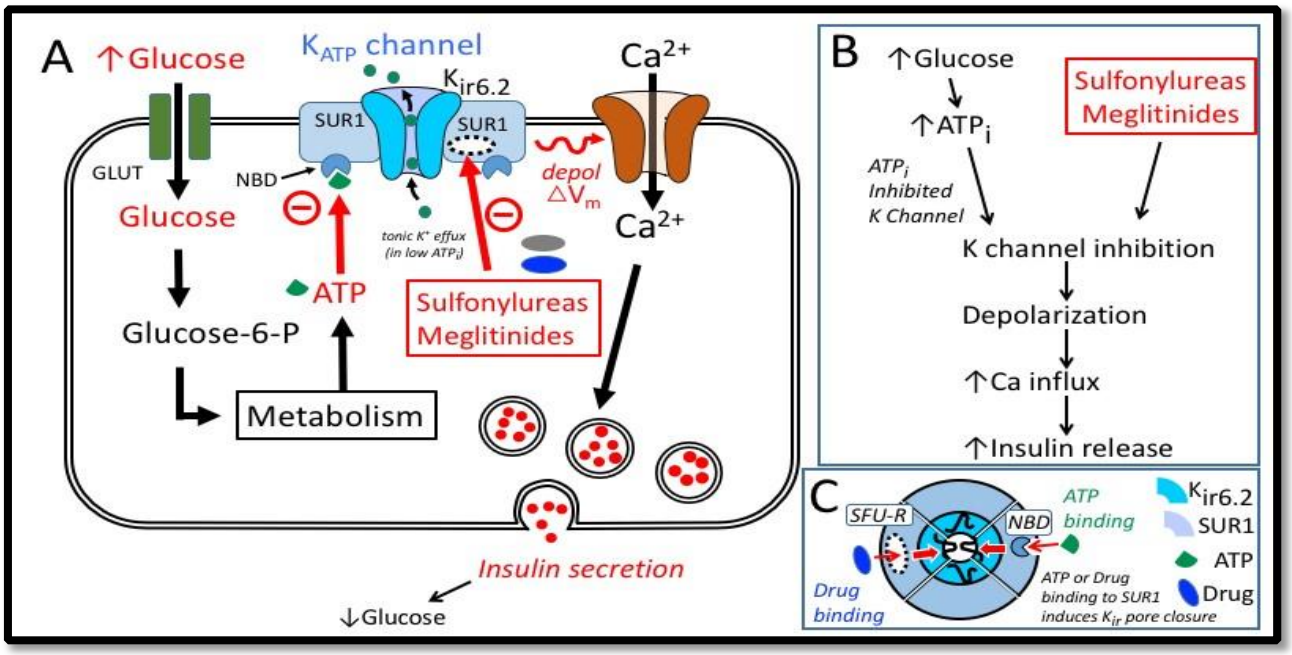
A- Meglitinide (repaginate and nateglinide): (its insulin secretagogues agents)

Mechanism of action:

- **its act as sulfonylurea by stimulate secretion of insulin by closed ATP – sensitive K channel and initiate a series of reaction result in release of insulin**
- **they varies from sulfonylurea by rapid onset and shorter duration of action**
- **must not be used in combination with sulfonylurea to avoid risk of serous hypoglycemia**

Therapeutic uses: For diabetes, mellitus type II (3rd line agent)

Side effect: hypoglycemia, weight gain (with less degree than sulfonylurea)



2- Biguanides (Metformin):

- **its act as insulin sensitizer (by increase insulin uptake and used by target tissue) therapy decrease of insulin resistance**
- **hypoglycemia is less incidence with metformin as compare with sulfonylurea**

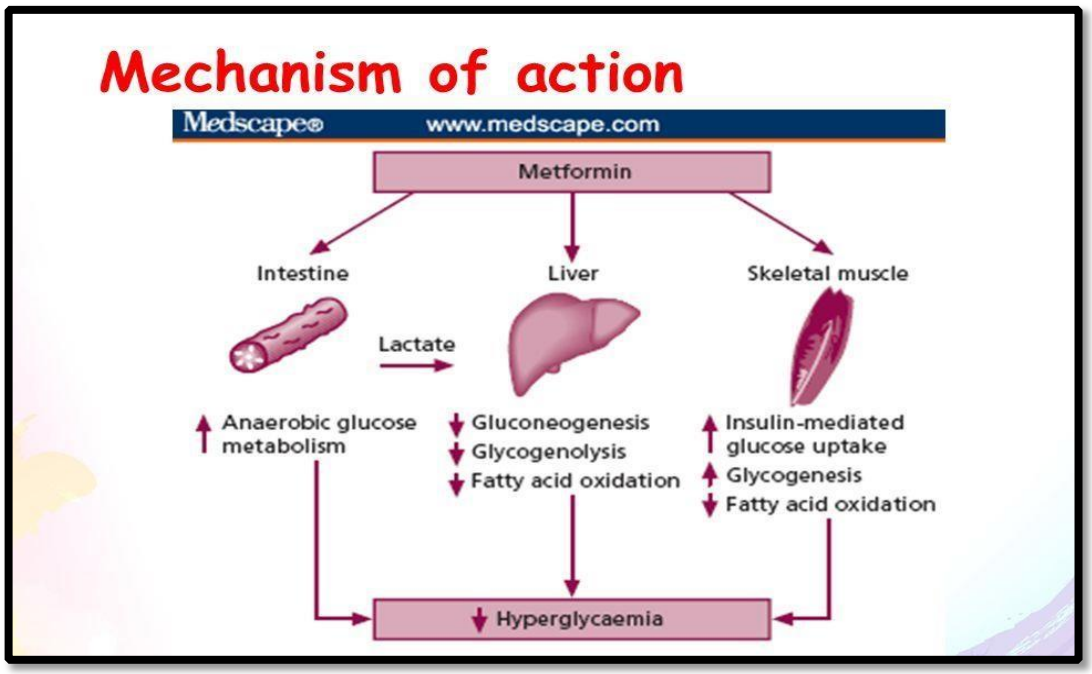
Mechanism of action: metformin act by

- **reduce hepatic gluconeogenesis**
- **slows intestinal absorption of sugar**
- **improve peripheral glucose uptake and utilized**
- **weight loss occur due to loss of appetite**

Side effects: (gastrointestinal distress, lactic acidosis (rarely) and interfere with vit B12 absorption) .

Contraindication: metformin is contraindicated in patients with

1- renal dysfunction , due to risk of lactic acidosis 2- heart failure 3- renal failure 4- over 80 years (with heart failure) 5- alcohol abuse.



B- Thiazolidinedione's (pioglitazone and rosiglitazone): it's an insulin sensitizer, with low risk of hyperinsulinemia, because it don't promote insulin release

Mechanism of action:

- **TZDs lower insulin resistance by acting as agonist for (peroxisome proliferator–activated receptor-γ (PPARγ) , it's a nuclear hormone receptor , activation of (PPARγ) regulate transcription of insulin responsive gene , resulting in increase in insulin sensitivity in adipose tissue , liver and skeletal muscle**
- **Rosiglitazone cause increase in LDL , T.G and HDL level while pioglitazone decrease T.G and increase in HDL**
- **Dose of TZDs should be lower if use with insulin**

Therapeutic uses: for type II of diabetes mellitus, also used for polycystic over syndrome in premenstrual women

Adverse effect:

- **Weight gain , by increase subcutaneous fat and fluid retention**
- **Avoid in patients with severe heart failure because of fluid retention**
- **Osteopenia and increase risk of fracture**
- **Liver toxicity**
- **Pioglitazone increase risk of bladder cancer**

α-Glucosidase inhibitors (Acarbose and miglitol):

- **Mechanism Of Action: these medication act by inhibition of α-Glucosidase enzyme that found in intestinal border , which responsible for enzymatic breakdown of carbohydrate into glucose that can be absorption by the intestine**
- **Therapeutic uses: For diabetes, mellitus type II (3rd line therapy).**
- **Adverse uses: diarrhea, abdominal cramp and flatulence, this medication should be avoided in patients with irritable bowel disease and colonic ulceration and intestinal abstraction.**

Huda Nahi. MSc.. (Pharmacology &

Anti-inflammatory, Antipyretic, and Analgesic Agents 16

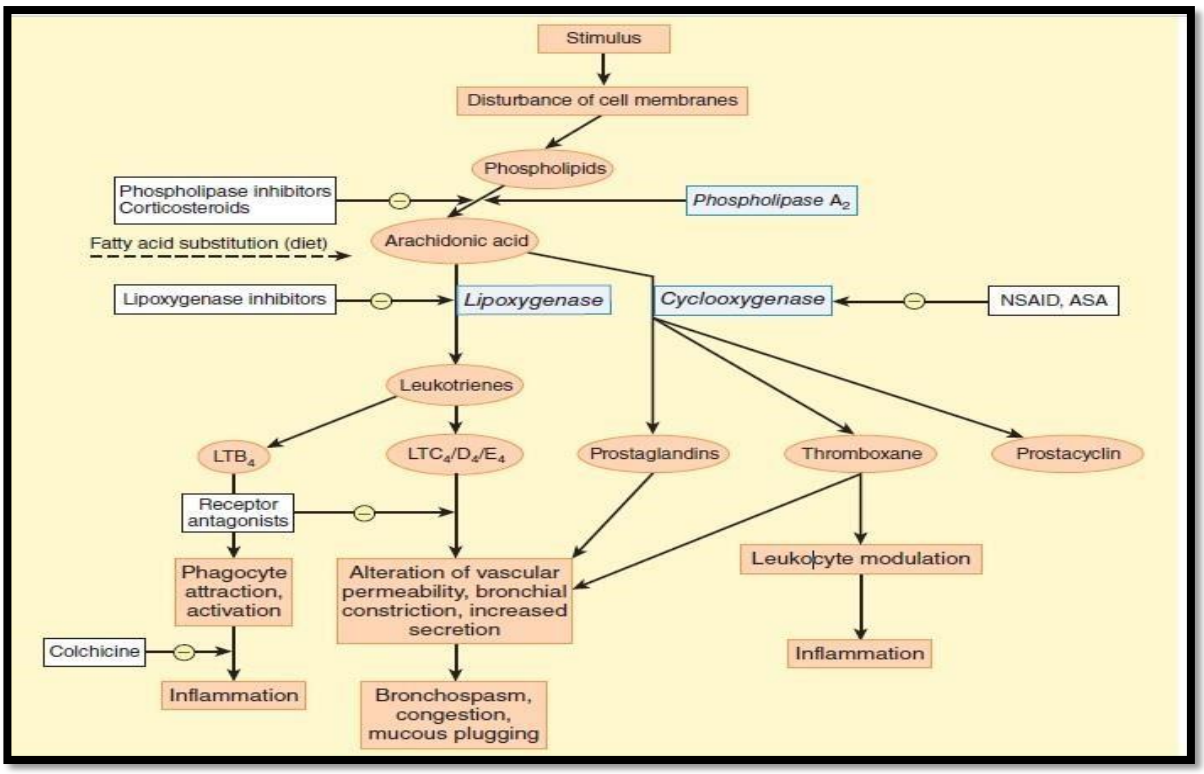
- Inflammation is a normal, protective response to tissue injury caused by physical trauma, noxious chemicals, or microbiologic agents.
- Inflammation is the body's effort to inactivate or destroy invading organisms, remove irritants, and set the stage for tissue repair.
- When healing is complete, the inflammatory process usually subsides. However, inappropriate activation of the immune system can result in inflammation, leading to immunemediated diseases such as rheumatoid arthritis (RA).

PROSTAGLANDINS

- The NSAIDs act by inhibiting the synthesis of prostaglandins.
- Understanding of NSAIDs requires comprehension of the actions and biosynthesis of prostaglandins.

Role of prostaglandins as local mediators

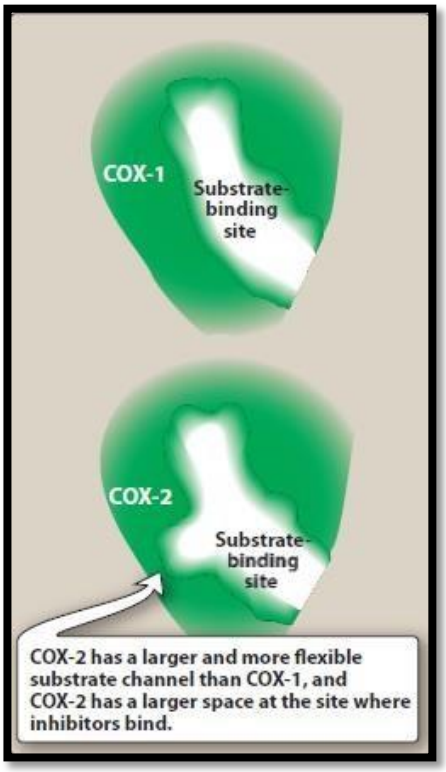
- Prostaglandins and related compounds are produced virtually in all tissues.
- They generally act locally on the tissues in which they are synthesized and inactive at their sites of action.
- Thromboxanes and leukotrienes are related lipids that are synthesized from the same precursors as the prostaglandins.



Synthesis of prostaglandins

- Arachidonic acid is the primary precursor of the prostaglandins and related compounds.
- Arachidonic acid is present as a component of the phospholipids of cell membranes.
- Free arachidonic acid is released from tissue phospholipids by the action of phospholipase A2 via a process controlled by hormones and other stimuli.
- There are two major pathways in the synthesis of the eicosanoids from arachidonic acid, the cyclooxygenase and the lipoxygenase pathways

Cyclooxygenase pathway:

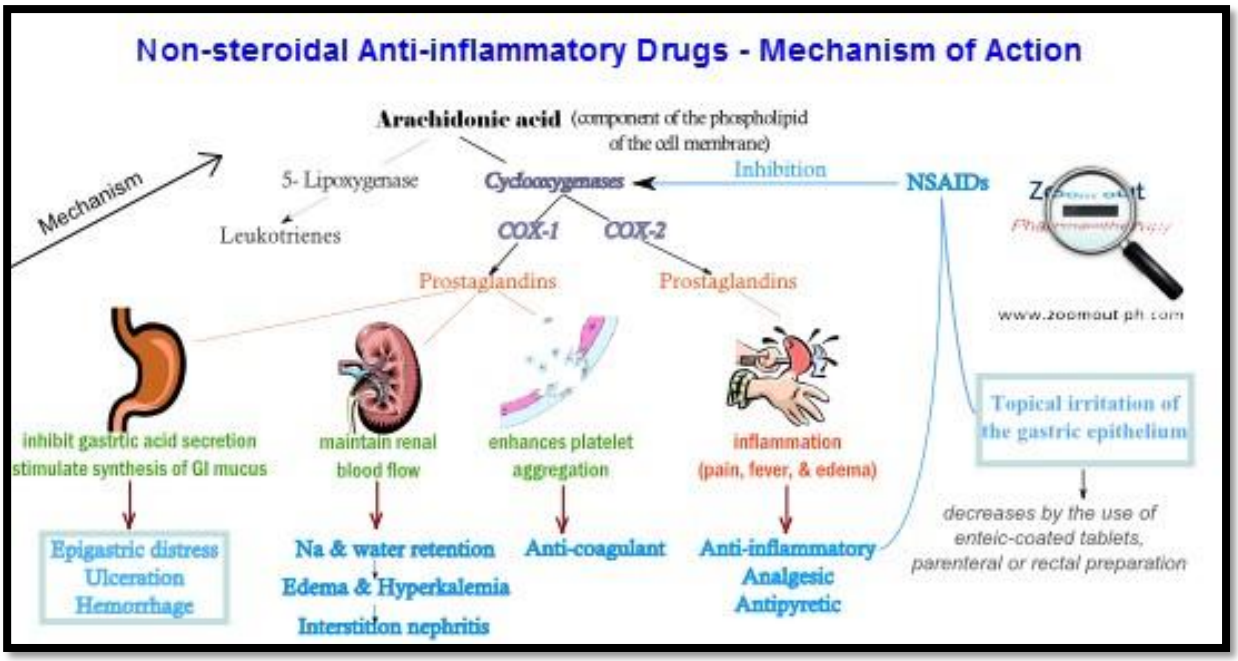


- Prostaglandins, thromboxanes, and prostacyclins) are synthesized via the cyclooxygenase pathway.
- Two related isoforms of the cyclooxygenase enzymes have been described. Cyclooxygenase-1 (COX-1) is responsible for the physiologic production of prostanoids, (COX-1 is a constitutive enzyme that regulates normal cellular processes, such as gastric cytoprotection, vascular homeostasis, platelet aggregation, and reproductive) And kidney functions
- Cyclooxygenase-2 (COX-2) causes the elevated production of prostanoids that occurs in sites of chronic disease and inflammation
- Differences in binding site shape have permitted the development of selective COX-2 inhibitors .glucocorticoids antiinflammatory effect contributed to inhibition of COX-2

Lipoxygenase pathway: Alternatively, several lipoxygenases can act on arachidonic acid to form leukotrienes, Antileukotriene drugs, such as *zileuton*, *zafirlukast*, and *montelukast*, are treatment options for asthma.

Actions of prostaglandins

- Many of the actions of prostaglandins are mediated by their binding to a wide variety of distinct cell membrane receptors that operate via G-coupled proteins.
- Prostaglandins and their metabolites, produced endogenously in tissues , Their functions vary widely, depending on the tissue and the specific enzymes within the pathway that are available at that particular site
- (For example, the release of thromboxane A2 (TXA2) from platelets during tissue injury triggers the recruitment of new platelets for aggregation, as well as local vasoconstriction. However, prostacyclin (PGI2), produced by endothelial cells, has opposite effects, inhibiting platelet aggregation and producing vasodilation. The net effect on platelets and blood vessels depends on the balance of these two prostanoids.



Therapeutic uses of prostaglandins

Prostaglandins have a major role in modulating pain, inflammation, and fever. They also control many physiological functions, such as acid secretion and mucus production in the gastrointestinal (GI) tract, uterine contractions, and renal blood flow and in allergic and inflammatory processes.

A- Lubiprostone

It's a PGE1 derivative indicated for the treatment of chronic idiopathic constipation, opioid-induced constipation, and irritable bowel syndrome with constipation. It stimulates chloride channels in the luminal cells of the intestinal epithelium, thereby increasing intestinal fluid secretion.

B- Misoprostol

- It a PGE1 analog, is used to protect the mucosal lining of the stomach during chronic NSAID treatment. *Misoprostol* interacts with prostaglandin receptors on parietal cells within the stomach, reducing gastric acid secretion.
- Misoprostol has a GI cytoprotective effect by stimulating mucus and bicarbonate production. This combination of effects decreases the incidence of gastric ulcers caused by NSAIDs.
- Misoprostol is for labor induction, since it increases uterine contractions by interacting with prostaglandin receptors in the uterus. Misoprostol has the potential risk to induce abortion in pregnant women.
- The drug is contraindicated during pregnancy.

Nonsteroidal Anti-Inflammatory Drugs

The NSAIDs are a group of chemically dissimilar agents that differ in their antipyretic, analgesic, and anti-inflammatory activities. The class includes derivatives of

1. **salicylic acid** (*aspirin , diflunisal , salsalate*)
2. **propionic acid** (ibuprofen , fenoprofen , flurbiprofen , ketoprofen , naproxen , oxaprozin*)* ,
3. **acetic acid** (diclofenac , etodolac , indomethacin , ketorolac , nabumetone , sulindac , tolmetin)
4. **enolic acid** (meloxicam , piroxicam, fenamates (mefenamic acid, meclofenamate)
5. **Selective COX-2 inhibitor** (celecoxib, they act primarily by inhibiting the cyclooxygenase enzymes that catalyze the first step in prostanoids biosynthesis. This leads to decreased prostaglandin synthesis with both beneficial and unwanted effects.

- Differences in safety and efficacy of the NSAIDs may be explained by relative selectivity for the COX-1 or COX-2 enzyme. Inhibition of COX-2 is thought to lead to the anti- inflammatory and analgesic actions of NSAIDs, while inhibition of COX-1 is responsible for prevention of cardiovascular events and most adverse events.

Aspirin and other NSAIDs

- Aspirin can be thought of as a traditional NSAID,
- It acts as anti-inflammatory activity only at relatively high doses that are rarely used.
- At lower doses its use for the prevention of cardiovascular events such as stroke and myocardial infarction (MI).
- Aspirin is often differentiated from other NSAIDs, since it is an irreversible inhibitor of cyclooxygenase activity.

1. Mechanism of action:

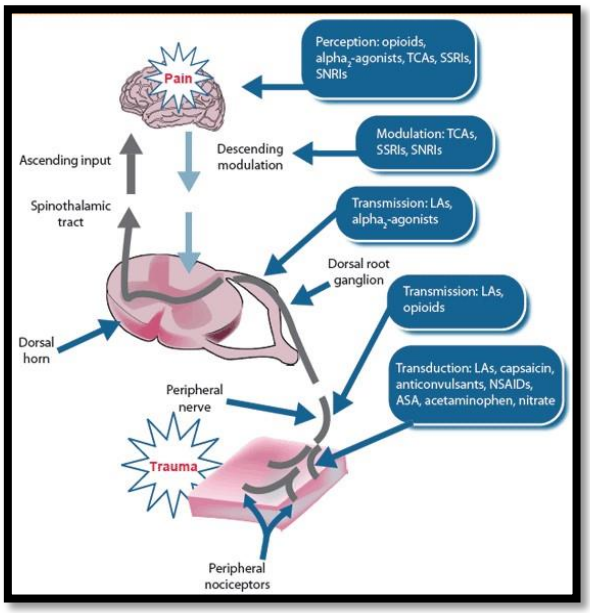
- Aspirin irreversibly inactivates cyclooxygenase enzyme, while the other NSAIDs are reversible inhibitors of cyclooxygenase.
- NSAIDs, including *aspirin*, have three major therapeutic actions: they reduce inflammation (anti-inflammatory), pain (analgesic effect), and fever (antipyretic effect

a. Anti-inflammatory actions:

- Cyclooxygenase inhibition diminishes the formation of prostaglandins and, thus, modulates aspects of inflammation in which prostaglandins act as mediators.
- NSAIDs inhibit inflammation in arthritis, but they neither arrest the progression of the disease nor induce remission.

b. Analgesic action:

- PGE2 is thought to sensitize nerve endings to the action of bradykinin, histamine, and other chemical mediators released locally by the inflammatory process. Causing decrease in pain sensation
- As COX-2 is expressed during times of inflammation and injury, it is thought that inhibition of this enzyme is responsible for the analgesic activity of NSAIDs.
- All agents of NSAIDs are generally considered to have equivalent efficacy.
- The NSAIDs are used mainly for the management of mild to moderate pain arising from musculoskeletal disorders. Except ketorolac, this can be used for more severe pain but for only a short duration.



c. Antipyretic action:

- Fever occurs when the set-point of the anterior hypothalamic thermoregulatory center is elevated. This can be caused by PGE2 synthesis, which is stimulated when endogenous fever-producing agents (pyrogens), such as cytokines, are released from WBCs that are activated by infection, hypersensitivity, malignancy, or inflammation.
- The NSAIDs lower body temperature in patients with fever by impeding PGE2 synthesis and release. These agents essentially reset the "thermostat toward normal by increasing heat dissipation as a result of peripheral vasodilation and sweating.

Therapeutic uses:

a. Anti-inflammatory and analgesic uses:

- NSAIDs are used in the treatment of osteoarthritis, gout, and RA. also used to treat (headache, arthralgia, myalgia, and dysmenorrhea)
- Combinations of opioids and NSAIDs may be effective in treating pain caused by malignancy.
- The addition of NSAIDs may lead to an opioid-sparing effect, allowing for lower doses of opioids to be utilized.
- The salicylates exhibit analgesic activity at lower doses. Only at higher doses do these drugs show anti-inflammatory activity as example, (two 325-mg *aspirin* tablets administered four times daily produce analgesia, whereas 12 to 20 tablets per day produce both analgesic and anti-inflammatory activity).

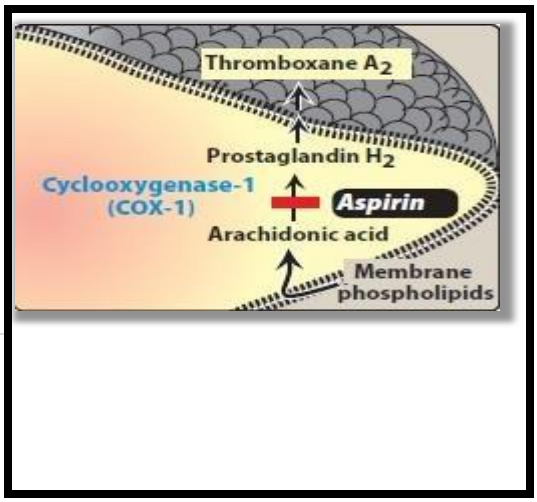
b. Antipyretic uses:

- Aspirin, ibuprofen, and naproxen may be used to treat fever.

- [Note: Aspirin should be avoided in patients less than 20 years old with viral infections, such as varicella (chickenpox) or influenza, to prevent Reye syndrome (a syndrome that can cause fulminating hepatitis with cerebral edema, often leading to death).

c. Cardiovascular applications:

Aspirin is used to inhibit platelet aggregation.



- Low-dose aspirin inhibits COX-1–mediated production of TXA2, thereby reducing TXA2-mediated vasoconstriction and platelet aggregation and the subsequent risk of cardiovascular events (At dose 81 mg)
- aspirin used prophylactically to

1) Reduce the risk of recurrent cardiovascular events and/or death in patients with previous MI or unstable angina pectoris,
2) reduce the risk of recurring transient ischemic attacks (TIAs) and stroke or death in those who have had a prior TIA or stroke, and
3) Reduce the risk of cardiovascular events or death in high-risk patients such as those with chronic stable angina or diabetes.

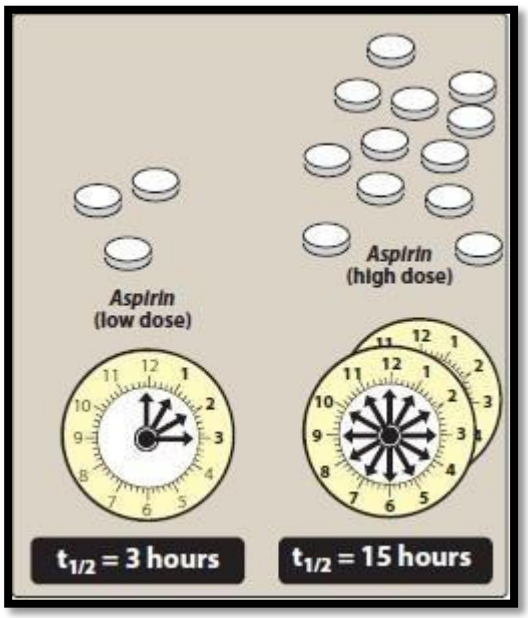
- As aspirin irreversibly inhibitsCOX-1, the antiplatelet effects persist for the life of the platelet. Chronic use of low doses allows for continued inhibition as new platelets are generated.

d. External applications:

- Salicylic acid is used topically to treat acne, corns, calluses, and warts.
- Methyl salicylate is used externally as a cutaneous counterirritant in liniments, such as arthritis creams and sports rubs.

Pharmacokinetics:

- After oral administration, aspirin is passively absorbed mostly from the upper small
- Salicylates cross both the blood– brain barrier and the placenta and are absorbed through intact skin (especially methyl salicylate).
- At anti-inflammatory dosages (more than 4 g/day), the hepatic metabolic pathway becomes saturated, and zeroorder kinetics are observed, leading to a half-life of 15 hours or more
- Salicylate is secreted into the urine and can affect uric acid excretion.
- At low doses of aspirin (less than 2 g/day), uric acid secretion is decreased, whereas at high doses, uric acid secretion may be unchanged or increased. Therefore, aspirin is avoided in gout or in patients taking probenecid.



Adverse events: Because of the associated adverse events below, it is preferable to use NSAIDs at the lowest effective dose for the shortest duration possible.

a. Gastrointestinal:

- The most common adverse effects of NSAIDs are GI related, ranging from dyspepsia to bleeding. Normally, production of prostacyclin (PGI2) inhibits gastric acid secretion, and PGE2 and PGF2α stimulate synthesis of protective mucus in both the stomach and small intestine.
- Agents that inhibit COX-1 reduce beneficial levels of these prostaglandins, resulting in increased gastric acid secretion, diminished mucus protection, and increased risk for GI bleeding and ulceration.
- Agents with a higher relative selectivity for COX-1 may have a higher risk for GI events compared to those with a lower relative selectivity for COX-1 (that is, higher COX-2 selectivity). NSAIDs should be taken with food or fluids to diminish GI upset.
- If NSAIDs are used in patients with a high risk for GI events, proton pump inhibitors or *misoprostol* should be used concomitantly to prevent NSAID-induced ulcers.

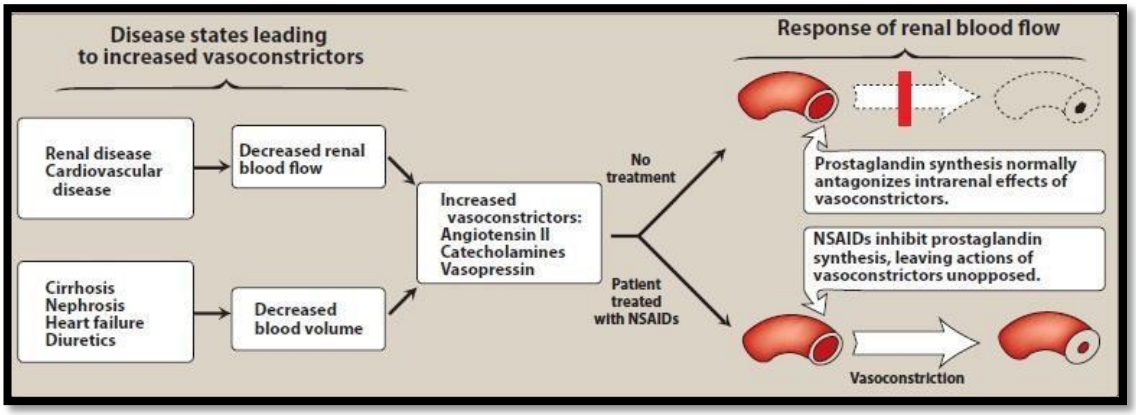
b. Increased risk of bleeding (antiplatelet effect):

- TXA2 enhances platelet aggregation; Aspirin irreversibly inhibits COX-1–mediated TXA2 formation, while other NSAIDs reversibly inhibit the production of TXA2.
- Because platelets lack nuclei, they cannot synthesize new enzyme when inhibited by aspirin, and the lack of thromboxane persists for the lifetime of the platelet (3 to 7 days).

- Because of the decrease in TXA2 production, platelet aggregation (the first step in thrombus formation) is reduced, producing an antiplatelet effect with a prolonged bleeding time. For this reason, aspirin is often held, or not given, at least 1 week prior to surgery.
- NSAIDs other than aspirin are not utilized for their antiplatelet effect but can still prolong bleeding time.
- NSAIDs can also block aspirin binding to cyclooxygenase when used concomitantly. Patients who take aspirin for cardioprotection should avoid concomitant NSAID use if possible.

c. Actions on the kidney:

- NSAIDs prevent the synthesis of PGE2 and PGI2, prostaglandins that are responsible for maintaining renal blood flow
- Decreased synthesis of prostaglandins can result in retention of sodium and water and may cause edema in some patients.
- Patients with a history of heart failure or kidney disease are at particularly high risk. These effects can also mitigate the beneficial effects of antihypertensive medications.



d. Cardiac effects:

- Agents such as aspirin, with a very high degree of COX-1 selectivity, have shown a cardiovascular protective effect thought to be due to a reduction in the production of TXA2.
- Agents with higher relative COX-2 selectivity have been associated with an increased risk for cardiovascular events, possibly by decreasing PGI2 production mediated by COX-2.
- An increased risk for cardiovascular events, including MI and stroke, has been associated with all NSAIDs except aspirin.
- Use of NSAIDs, other than aspirin, is discouraged in patients with established cardiovascular disease. For patients with cardiovascular disease in whom NSAID treatment cannot be avoided, naproxen appears to be the least likely to be harmful.

e. Other side effects:

- NSAIDs should be used with caution in patients with asthma, as inhibition of prostaglandin synthesis can cause a shift toward leukotriene production and, therefore, increase the risk of exacerbations of asthma.

f. Drug interactions:

- Salicylate is roughly 80% to 90% plasma protein bound (albumin) and can be displaced from protein binding sites, resulting in increased concentration of free salicylate. Alternatively, *aspirin* can displace other highly protein-bound drugs, such as *warfarin*, *phenytoin*, or *valproic acid*, resulting in higher free concentrations of these agents

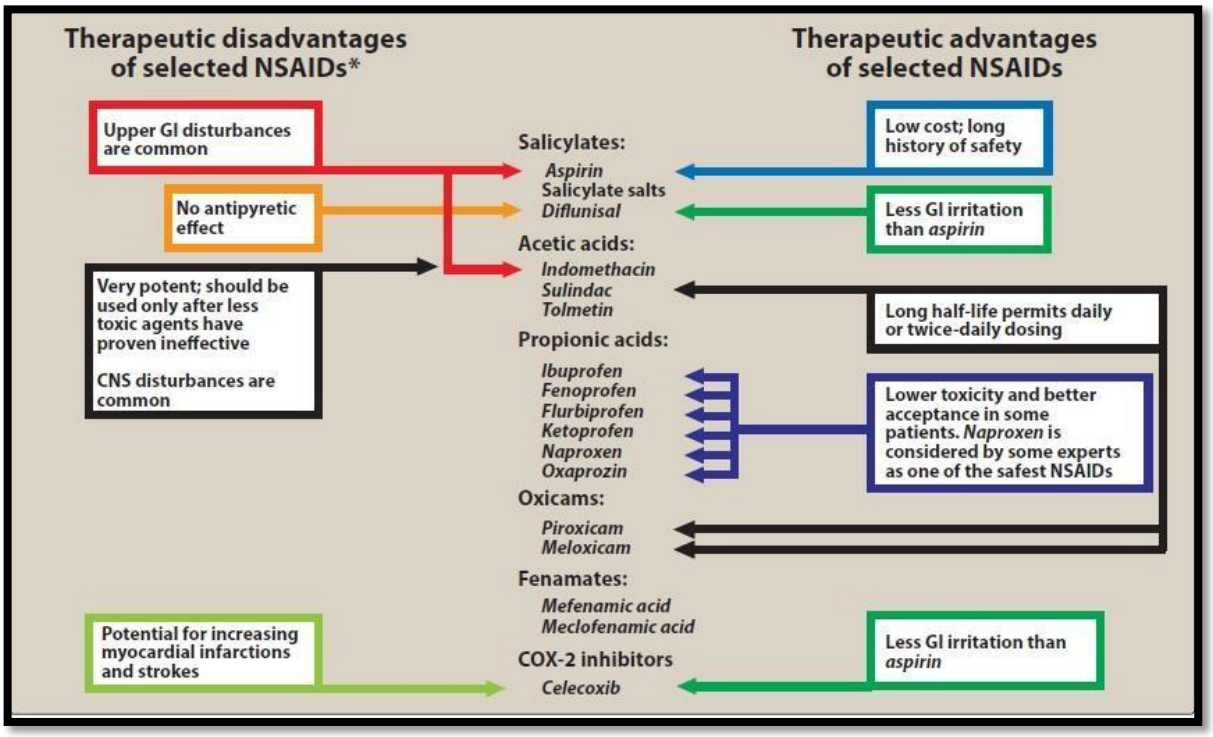
g. Toxicity:

- Salicylate intoxication may be mild or severe.
- The mild form characterized by nausea, vomiting, marked hyperventilation, headache, mental confusion, dizziness, and tinnitus
- When large doses of salicylate are administered, severe salicylate intoxication may result, Restlessness, delirium, hallucinations, convulsions, coma, respiratory and metabolic acidosis, and death from respiratory failure may occur.
- Children are particularly prone to salicylate intoxication. Ingestion of as little as 10 g of *aspirin* can cause death in children.

h. Pregnancy:

- Most NSAIDs are pregnancy risk category C in the first two trimesters.
- In the third trimester, NSAIDs should generally be avoided due to the risk of premature closure of the ductus arteriosus.

- Acetaminophen is preferred if analgesic or antipyretic effects are needed during pregnancy.



(Celecoxib)

- a selective reversible COX-2 inhibitor, is significantly more selective for inhibition of COX-2 than COX-1

1. Therapeutic uses:

- *Celecoxib* is approved for the treatment of RA, osteoarthritis, and acute mild to moderate pain. *Celecoxib* has similar efficacy to NSAIDs in the treatment of pain.

2. Pharmacokinetics:

- Celecoxib is readily absorbed after oral administration. It is extensively metabolized in the liver by cytochrome P450 (CYP2C9) , (Inhibitors of CYP2C9, such as fluconazole and fluvastatin, may increase serum levels of celecoxib)
- The half-life is about 11 hours, and the drug may be dosed once or twice daily. The dosage should be reduced in those with moderate hepatic impairment, Celecoxib should be avoided in patients with severe hepatic or renal disease.

3. Adverse effects:

- Headache, dyspepsia, diarrhea, and abdominal pain are the most common adverse effects.
- Celecoxib, less induce of GI bleeding and dyspepsia

- As all NSAIDs Celecoxib has a similar risk of cardiovascular events.
- Celecoxib should be used with caution in patients who are allergic to sulfonamides.

Acetaminophen

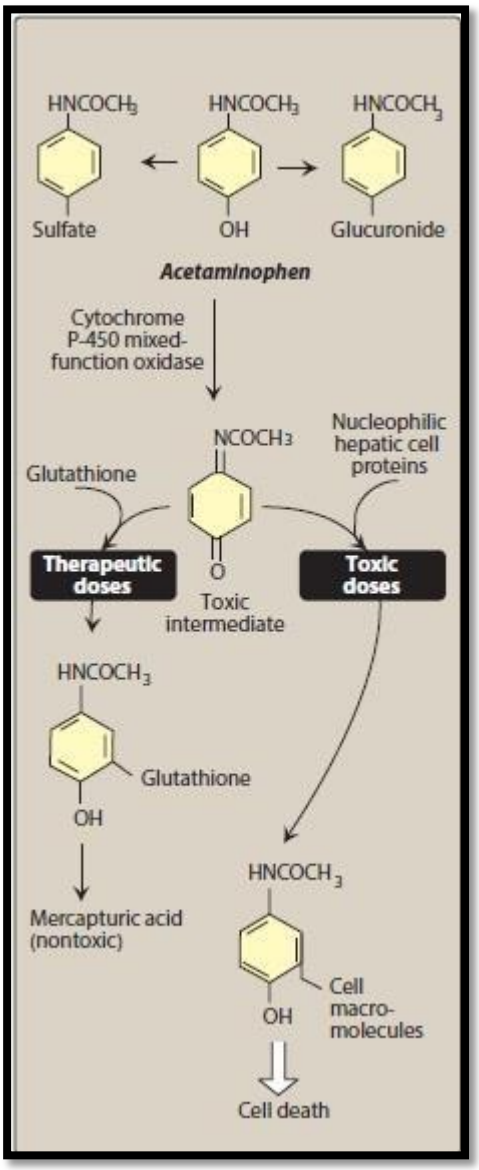
- Acetaminophen inhibits prostaglandin synthesis in the CNS.
- This explains its antipyretic and analgesic properties.
- Acetaminophen has less effect on cyclooxygenase in peripheral tissues (due to peripheral inactivation), which accounts for its weak anti-inflammatory activity.
- Acetaminophen does not affect platelet function or increase bleeding time.

A. Therapeutic uses

- Acetaminophen is a suitable substitute for the analgesic and antipyretic effects of NSAIDs for those patients with
- gastric complaints/ risks,
- in patients whom a prolongation of bleeding time is not desirable,
- In patients who do not require the anti-inflammatory action of NSAIDs. Acetaminophen is the analgesic/antipyretic of choice for children with viral infections or chickenpox (due to the risk of Reye syndrome with aspirin).

B. Pharmacokinetics

- Acetaminophen is rapidly absorbed from the GI tract.
- Acetaminophen is conjugated in the liver to form inactive glucuronidated or sulfated metabolites. A portion of acetaminophen is hydroxylated to form N-acetyl-pbenzoquinoneimine, or **NAPQI**, a highly reactive metabolite that can react with sulfhydryl groups and cause liver damage.
- At normal doses of acetaminophen, NAPQI reacts with the sulfhydryl group of glutathione, which is produced by the liver, forming a nontoxic substance
- Acetaminophen and its metabolites are excreted in urine. The drug is also available in intravenous and rectal formulations.



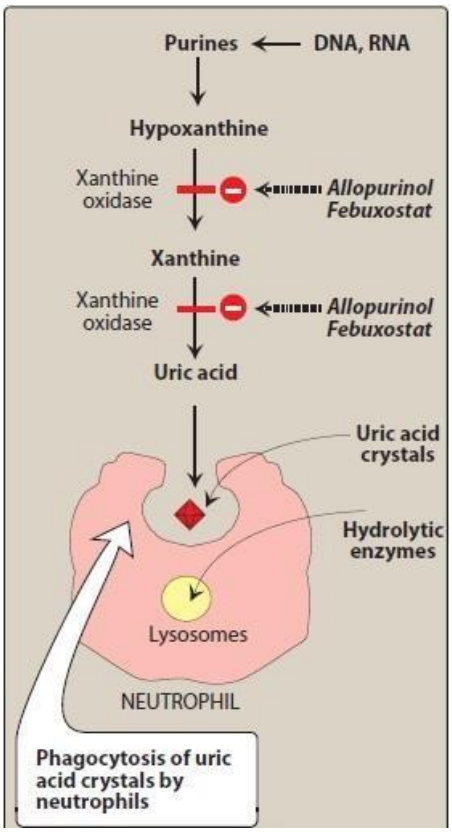
C. Adverse effects

- At normal therapeutic doses, acetaminophen is virtually free of significant adverse effects.
- With large doses of acetaminophen, the available glutathione in the liver becomes depleted, and NAPQI reacts with the sulfhydryl groups of hepatic proteins, forming covalent bonds Hepatic necrosis, a very serious and potentially life threatening condition, can result. Patients with hepatic disease, viral hepatitis, or a history of alcoholism are at higher risk of acetaminophen induced hepatotoxicity.
- N-acetylcysteine, which contains sulfhydryl groups to which the toxic metabolite can bind, is an antidote

Drugs used for treatment of gout

* Gout is a metabolic disorder characterized by high levels of uric acid in the blood (hyperuricemia). * Hyperuricemia can lead to deposition of sodium urate crystals in tissues, especially the joints and kidney. * The deposition of urate crystals initiates an inflammatory process involving the infiltration of granulocytes that phagocytize the urate crystals * The cause of hyperuricemia is an imbalance between overproduction of uric acid and the inability of the patient to excrete it via renal elimination. * Most therapeutic strategies for gout involve lowering the uric acid level below the saturation point (6 mg/dL), thus preventing the deposition of urate crystals. This can be accomplished by interfering with uric acid synthesis or increasing uric acid excretion.

A. Treatment of acute gout



 Acute gout attacks can result from a number of conditions, including

1. excessive alcohol consumption,
2. a diet rich in purines,
3. Kidney disease.

- NSAIDs, corticosteroids, or *colchicine* are effective alternatives for the management of acute gouty arthritis. *Indomethacin* is considered the classic NSAID of choice, although all NSAIDs are likely to be effective in decreasing pain and inflammation.
- Intraarticular administration of corticosteroids (when only one or two joints are affected)
- Patients are candidates for prophylactic urate-lowering therapy if they have more than two attacks per year or they have chronic kidney disease, kidney stones, or tophi (deposit of urate Crystals in the joints, bones, cartilage, or other body structures).

B. Treatment of chronic gout

- Treatment strategies include the use of xanthine oxidase inhibitors to reduce the synthesis of uric acid or use of uricosuric drugs to increase its excretion.
- Xanthine oxidase inhibitors (*allopurinol*, *febuxostat*) are firstline urate-lowering agents.
- Uricosuric agents (*probenecid*) may be used in patients who are intolerant to xanthine oxidase inhibitors or fail to achieve adequate response with those agents.
- Initiation of urate-lowering therapy can precipitate an acute gout attack due to rapid changes in serum urate concentrations.
- Medications for the **prevention** of an acute gout attack (low-dose *colchicine*, NSAIDs, or corticosteroids) should be initiated with urate-lowering therapy and continued for at least 6 months.]

C. Colchicine

- Used for the treatment of acute gouty attacks. It is neither a uricosuric or analgesic agent, although it relieves pain in acute attacks of gout.
- Colchicine decreasing the migration of granulocytes, into the affected area.

- The anti-inflammatory activity of colchicine is specific for gout, but NSAIDs have largely replaced colchicine in the treatment of acute gouty attacks for safety reasons (side effect included myopathy, neutropenia, aplastic anemia, and alopecia.
- The drug should not be used in pregnancy).
- Colchicine is also used as a prophylactic agent to prevent acute attacks of gout in patients initiating urate-lowering therapy.

D. Allopurinol

- Allopurinol a xanthine oxidase inhibitor is a purine analog. It reduces the production of uric acid by competitively inhibiting the last two steps in uric acid biosynthesis that are catalyzed by xanthine oxidase
- Allopurinol is an effective urate-lowering therapy in the treatment of gout and hyperuricemia secondary to other conditions, such as that associated with certain malignancies (those in which large amounts of purines are produced, particularly after chemotherapy) or in renal disease.

Probenecid

- Probenecid is a uricosuric drug. It is a weak organic acid that promotes renal clearance of uric acid by inhibiting the urate anion exchanger in the proximal tubule that mediates urate reabsorption.
- At therapeutic doses, it blocks proximal tubular reabsorption of uric acid. Probenecid blocks the tubular secretion of penicillin and is sometimes used to increase levels of β-lactam antibiotics.
- It also inhibits the excretion of methotrexate, naproxen, ketoprofen, and indomethacin. Probenecid should be avoided if the creatinine clearance is less than 50 mL/min.

Drugs Used To Treat Headache

- The most common types of headaches are migraine, tension-type, and cluster headaches. Migraine can usually be distinguished from cluster headaches and tension-type headaches by its characteristics as shown

	MIGRAINE	CLUSTER	TENSION TYPE
Family history	Yes	No	Yes
Sex	Females more often than males	Males more often than females	Females more often than males
Onset	Variable	During sleep	Under stress
Location	Usually unilateral	Behind or around one eye	Bilateral in band around head
Character and severity	Pulsating, throbbing	Excruciating, sharp, steady	Dull, persistent, tightening
Duration	2–72 hours per episode	15–90 minutes per episode	30 minutes to 7 days per episode
Associated symptoms	Visual auras, sensitivity to light and sound, pale facial appearance, nausea and vomiting	Unilateral or bilateral sweating, facial flushing, nasal congestion, lacrimation, pupillary changes	Mild intolerance to light and noise, anorexia

Types of migraine

* **There are two main types of migraine headaches.** * The first, **migraine without aura** these headaches are often aggravated by physical activity, the majority of patients with migraine do not have aura. * The second type, **migraine with aura**, the headache is preceded by neurologic symptoms called auras, which can be visual, sensory, and/or cause speech or motor disturbances, visual symptoms included (flashes, zigzag lines, and glare), occurring approximately 20 to 40 minutes before headache pain begins. In the 15% of migraine patients whose headache is preceded by an aura.

Biologic basis of migraine headaches

- The first manifestation of migraine with aura is a spreading depression of neuronal activity accompanied by reduced blood flow in the most posterior part of the cerebral hemisphere.
- This hypoperfusion gradually spreads forward over the surface of the cortex to other areas of the brain. The vascular alteration is accompanied by functional changes.
- Patients who have migraine without aura do not show hypoperfusion.
- The pain of both types of migraine may be due to extracranial and intracranial arterial vasodilation.

C. Symptomatic treatment of acute migraine

- Acute treatments can be classified as nonspecific (symptomatic) or migraine specific.
- **Nonspecific treatment** includes analgesics such as NSAIDs or Opioids and antiemetics (for example, *prochlorperazine*) to control vomiting.
- **Specific migraine therapy includes** triptans and ergot alkaloids, which are 5HT1B/1D receptor and 5-HT1D receptor agonists, respectively. It has been proposed that activation of 5-HT1 receptors by these agents leads either to vasoconstriction or to inhibition of the release of proinflammatory neuropeptides on the trigeminal nerve innervating cranial blood vessels.

Triptans: (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, Sumatriptan)

- These agents rapidly and effectively abort or markedly reduce the severity of migraine headaches
- The triptans are serotonin agonists, acting at serotonin receptors on small peripheral nerves that innervate the intracranial vasculature
- Sumatriptan is given subcutaneously, intranasally, or orally (Sumatriptan is also available in a combination product with naproxen).
- Triptans should not be administered to patients with risk factors for coronary artery disease without performing a cardiac evaluation prior to administration.
- Triptans less induce of vomiting as compare with ergot derivatives

Ergot alkaloids: (Ergotamine and dihydroergotamine)

- A semisynthetic derivative of ergotamine, are ergot alkaloids approved for the treatment of migraine headaches.
- The action of the ergot alkaloids is complex, with ability to bind to 5-HT1 receptors, α receptors, and dopamine receptors. 5-HT1 receptors located on intracranial blood vessels are targets that cause vasoconstriction with the use of these agents.
- Ergotamine available as an oral tablet or suppository containing both ergotamine and caffeine.

- Ergotamine is used with strict daily and weekly dosage limits due to its ability to cause dependence and rebound headaches.
- Nausea is a common adverse effect.
- Ergotamine and dihydroergotamine are contraindicated in patients with angina and peripheral vascular disease because they are significant vasoconstrictors.

D. Prophylaxis for migraine headache

- Therapy to prevent migraine is indicated if the attacks occur two or more times a month and if the headaches are severe or complicated by serious neurologic signs.
- B-Blockers are the drugs of choice for migraine prophylaxis Propranolol and other βblockers, such as metoprolol, atenolol, and nadolol, have been shown to be effective.
- The calcium channel blocker verapamil is an alternative.
- Anticonvulsants (divalproex) and antidepressants (tricyclics) have also shown effectiveness in preventing migraine especially in patients with comorbid depression.

E. Drugs for tension and cluster headache

- Analgesics such as NSAIDs (for example, *naproxen* and *ibuprofen*), *acetaminophen*, and *aspirin* are used for symptomatic relief of tension headaches.
- *Acetaminophen* and/or *aspirin* may also be combined with caffeine.
- Combination with *acetaminophen* or *aspirin* with or without caffeine is also used in tension headaches.
- Inhalation of 100% oxygen and triptans (especially *sumatriptan*) are used as first-line abortive strategies for cluster headache.

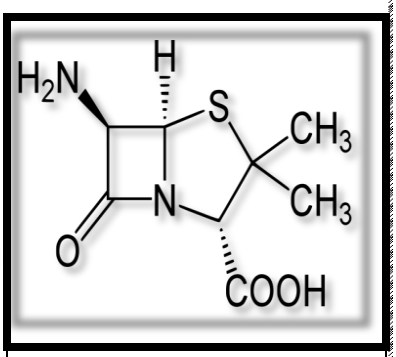
Cell Wall Inhibitors antibacterial

ž Some antimicrobial drugs selectively interfere with synthesis of the bacterial cell wall—a structure that mammalian cells do not possess. The cell wall is composed of a polymer called peptidoglycan that consists of glycan units joined to each other by peptide cross-links. To be maximally effective, inhibitors of cell wall synthesis require actively proliferating microorganisms; they have little or no effect on bacteria that are not growing and dividing

I- PENICILLINS

* The penicillins are among the most widely effective antibiotics and also the least toxic drugs known, but increased resistance has limited their use,

* Members of this family differ from one another in the R substituent attached to the 6-aminopenicillanic acid residue; the nature of this side chain affects the antimicrobial spectrum, stability to stomach acid, and susceptibility to bacterial degradative enzymes (β-lactamases).



6-aminopenicillanic structure

Mechanism of action:

- The penicillins interfere with the last step of bacterial cell wall synthesis (transpeptidation or cross-linkage1), resulting in exposure of the osmotically less stable membrane. Cell lysis can then occur, These drugs are thus bactericidal
- 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:

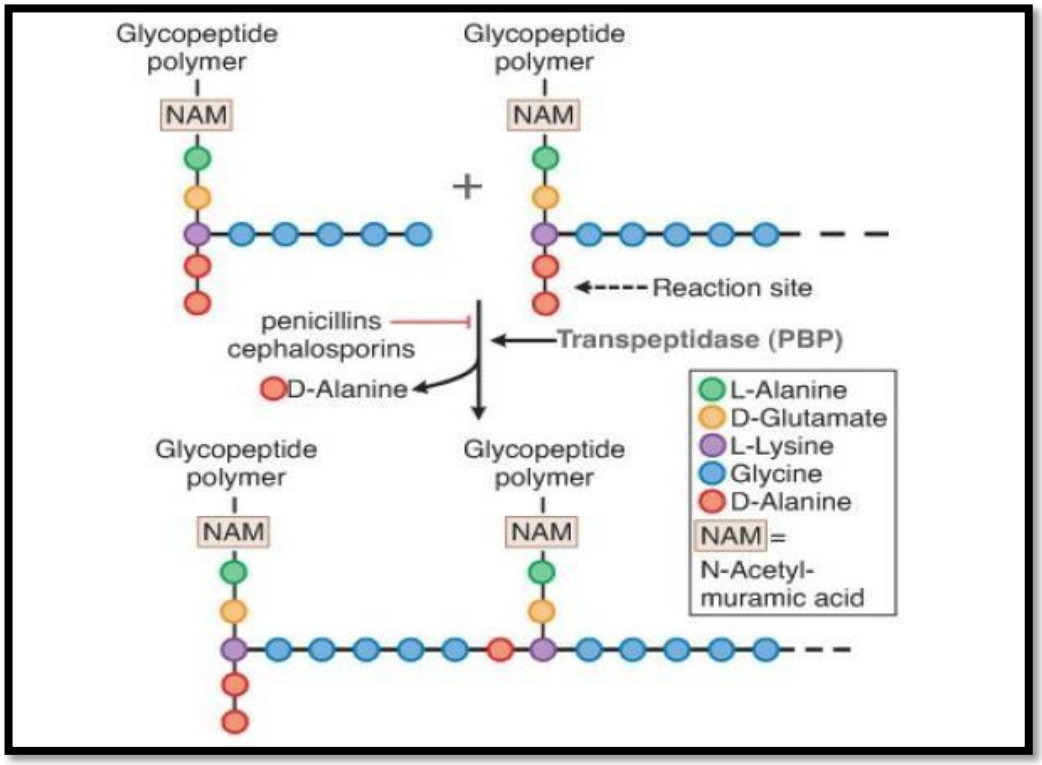
- ✓ Penicillins inactivate numerous proteins on the bacterial cell membrane. These penicillinbinding proteins (PBPs) are bacterial enzymes involved in the synthesis of the cell wall and in the maintenance of the morphologic features of the bacterium. Exposure to these antibiotics can therefore not only prevent cell wall synthesis but also lead to morphologic changes or lysis of susceptible bacteria.
- ✓ Alterations in some of these target molecules provide the organism with resistance to the penicillins, **Note: Methicillin-resistant Staphylococcusaureus (MRSA) apparently occurs because of such an alteration.**

2. Inhibition of transpeptidase

- Some PBPs catalyze formation of the cross-linkages between peptidoglycan chains
- Penicillins inhibit this transpeptidase-catalyzed reaction, thus hindering the formation of cross-links essential for cell wall integrity.

3. Production of autolysins:

- Many bacteria, particularly the 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.
- The antibacterial effect of penicillin is the result of both inhibition of cell wall synthesis and destruction of existing cell wall by autolysins.



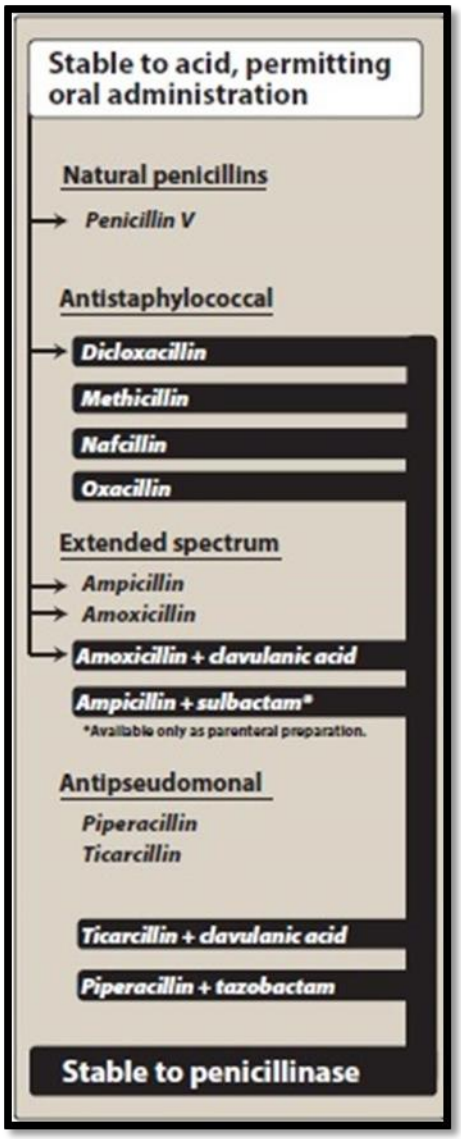
Antibacterial spectrum:

- The antibacterial spectrum of the various penicillins is determined; Factors that determine the susceptibility of PBPs to these antibiotics include the size, charge, and hydrophobicity of the particular β-lactam antibiotic, In general, gram-positive microorganisms have cell walls that are easily traversed by penicillins and, therefore, in the absence of resistance are susceptible to these drugs.
- Gram-negative microorganisms have an outer lipopolysaccharide membrane (envelope) surrounding the cell wall that presents a barrier to the water-soluble penicillins. However, gram-negative bacteria have proteins inserted in the lipopolysaccharide layer that act as water-filled channels (called porins)

to permit transmembrane entry. [Note: Pseudomonas aeruginosa lacks porins, making these organisms intrinsically resistant to many antimicrobial agents.

1. Natural penicillins:

- These penicillins, which include those classified as antistaphylococcal, are obtained from fermentations of the mold Penicillium chrysogenum. Other penicillins, such as ampicillin, are called semisynthetic, because the different R groups are attached chemically to the 6aminopenicillanic acid nucleus obtained from fermentation broths of the mold



Penicillin G (benzyl-penicillin) :

ž Is the cornerstone of therapy for infections caused by a number of gram-positive and gramnegative cocci, gram-positive bacilli, and spirochete, Penicillin G is susceptible to inactivation by β-lactamases (penicillinases).

Penicillin V :

ž Penicillin V Has a spectrum similar to that of penicillin G, but it is not used for treatment of bacteremia because of its higher minimum bactericidal concentration (the minimum amount of the drug needed to eliminate the infection, Penicillin V is more acid-stable than penicillin G. It is often employed orally in the treatment of infections, where it is effective against some anaerobic organisms.

2. Antistaphylococcal penicillins:

- Methicillin, nafcillin, oxacillin, and dicloxacillin are penicillinase-resistant penicillins. Their use is restricted to the treatment of infections caused by penicillinase-producing staphylococci; methicillin is not used clinically except to identify resistant strains of S. aureus.
- MRSA is usually susceptible to vancomycin and, rarely, to ciprofloxacin or rifampin.

Extended-spectrum penicillins:

- Ampicillin and amoxicillin have an antibacterial spectrum similar to that of penicillin G but are more effective against gram-negative bacilli.
- Ampicillin is the drug of choice for the gram-positive bacillus Listeria monocytogenes. These agents are also widely used in the treatment of respiratory infections, and amoxicillin is employed

prophylactically by dentists for patients with abnormal heart valves who are to undergo extensive oral surgery. Resistance to these antibiotics by inactivation by plasmid-mediated penicillinase

- Formulation with a β-lactamase inhibitor, such as clavulanic acid or sulbactam, protects amoxicillin or ampicillin, respectively, from enzymatic hydrolysis and extends their antimicrobial spectrum

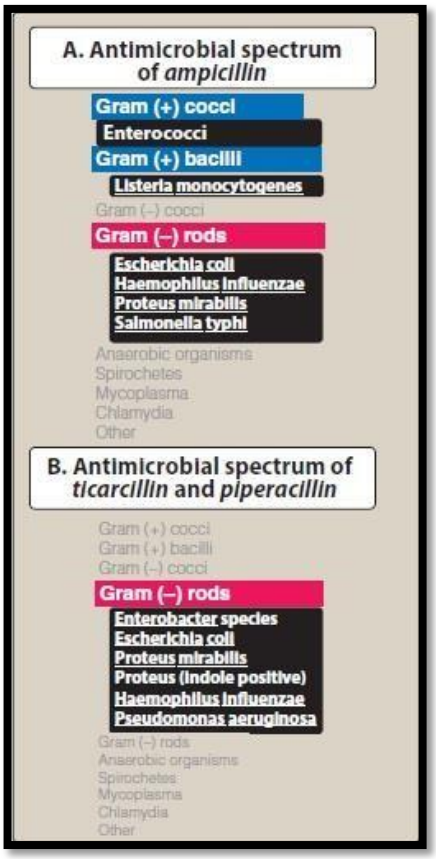
Antipseudomonal penicillins:

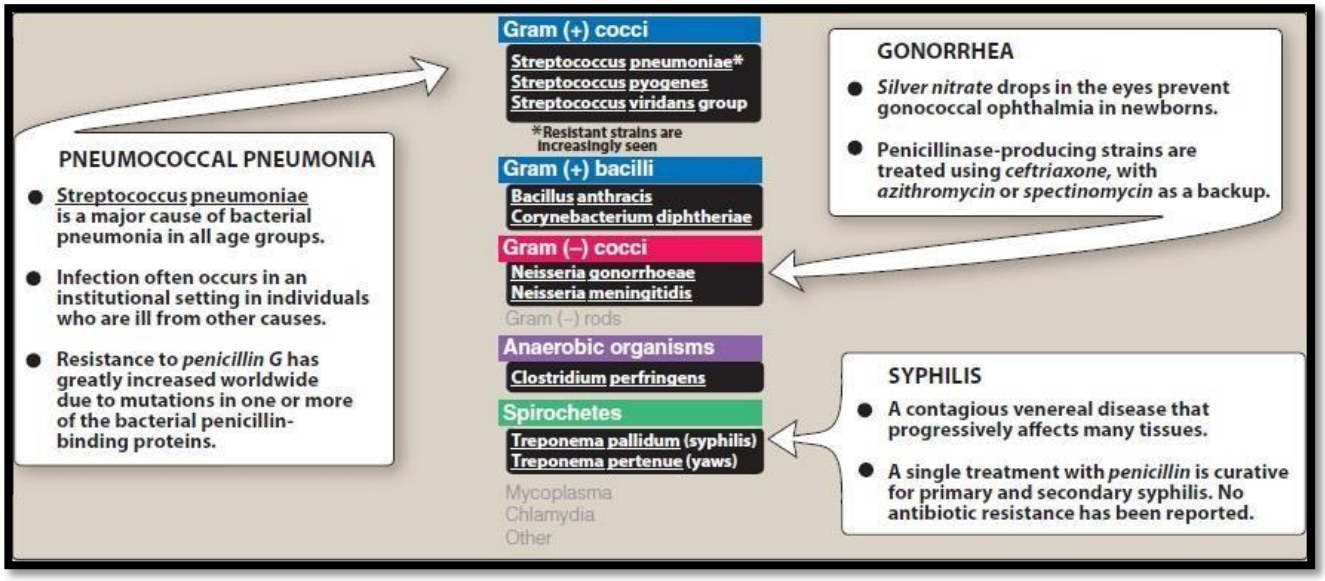
Carbenicillin, ticarcillin, and piperacillin are called Antipseudomonal penicillins because of their activity against P. aeruginosa; Piperacillin is the most potent of these antibiotics. They are effective against many gram-negative bacilli, but not against klebsiella, extends the antimicrobial spectrum of these antibiotics to include penicillinase-producing organisms

Penicillins and aminoglycosides:

The antibacterial effects of all the β-lactam antibiotics are synergistic with the aminoglycosides. Because cell wall synthesis inhibitors alter the permeability of bacterial cells, these drugs can facilitate the entry of other antibiotics (such as aminoglycosides) that might not ordinarily gain access to intracellular target sites. This can result in enhanced antimicrobial activity. [Although the combination of penicillin plus an aminoglycoside is used clinically, these drug types should never be placed in the same infusion fluid, because on prolonged contact, the positively charged aminoglycosides form an inactive complex with the negatively charged penicillins.]

Penicillin class	Drug	Antimicrobial spectrum
Natural Penicillins	**Penicillin G** **Penicillin V**	gram+ cocci and bacilli,some gram– cocci (*Neisseria*)
Penicillinase resistant penicillin	Nafcillin,methacillin Cloxacillin Dicloxacillin Oxacillin	*Staphylococcus aureus*
extended-spectrum (Aminopenicillins)	Ampicillins Amoxicillin Bacampicillin	Extended spectrumSame as Pen G plus some gram(–) organisms
antipseudomonas	Ticarcillin Piperacillin Carbenicillin Mezlocillin	gram(–)coverage, including *Pseudomonas*
Penicillin/β - Lactamase inhibitor combination	amoxicillin clavulanate (Augmentin) ampicillin/sulbactam (Unasyn) piperacillin/tazobactam (Zosyn) ticarcillin/clavulanate (Timentin)	Extended spectrumSame as Pen G plus some gram(–) organisms *and* *Staphylococcus aureus*





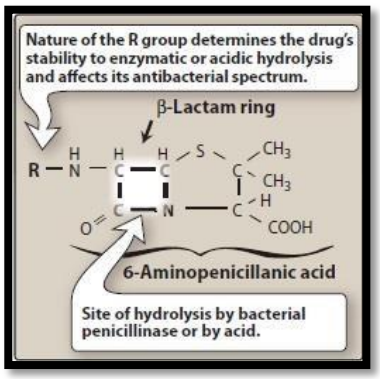
Resistance:

- Natural resistance to the penicillins occurs in organisms that either lack a peptidoglycan cell wall (for example, mycoplasma) or have cell walls that are impermeable to the drugs.

- Acquired resistance to the penicillins by plasmid transfer has become a significant clinical problem, because an organism may become resistant to several antibiotics at the same time due to (a plasmid that encodes resistance to multiple agents).

By obtaining a resistance plasmid, bacteria may acquire one or more of the following properties, thus allowing it to withstand β-lactam antibiotics

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
- B-Lactamases are acquired by the transfer of plasmids. Some of the βlactam antibiotics are poor substrates for β-lactamases and resist cleavage, thus retaining their activity against β-lactamase producing organisms. ○ Gram-positive organisms secrete β-lactamases extracellularly, whereas in gram-negative bacteria the enzymes found in the periplasmic space between the inner and outer membranes.

- ***2.*** **Decreased permeability to the drug:** Decreased penetration of the antibiotic through the outer cell membrane prevents the drug from reaching the target PBPs. The presence of an efflux pump can also reduce the amount of intracellular drug.

- ***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. This mechanism may explain MRSA.

D. Pharmacokinetics

- **1. Administration**: The route of administration of a β-lactam antibiotic is determined by the stability of the drug to gastric acid and by the severity of the infection.

- **a. Routes of administration**: Ticarcillin, Carbenicillin, piperacillin, and the combinations of ampicillin with sulbactam, ticarcillin with clavulanic acid, and piperacillin with tazobactam, must be administered intravenously (IV) or intramuscularly (IM).

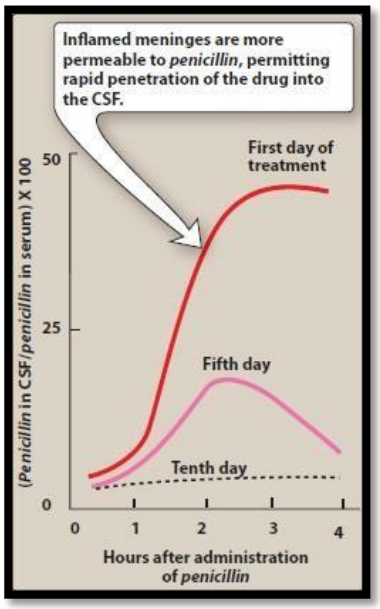
- Penicillin V, amoxicillin, amoxicillin combined with clavulanic acid and the Carbenicillin (for treatment of urinary tract infections) are available only as oral preparations.

- **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: Most of the penicillins are incompletely absorbed after oral administration, and they reach the intestine in sufficient amounts to affect the composition of the intestinal flora, Amoxicillin is almost completely absorbed.

- It is not appropriate therapy for the treatment of shigella- or salmonella-derived enteritis, because therapeutically effective levels do not reach the organisms in the intestinal crypts.

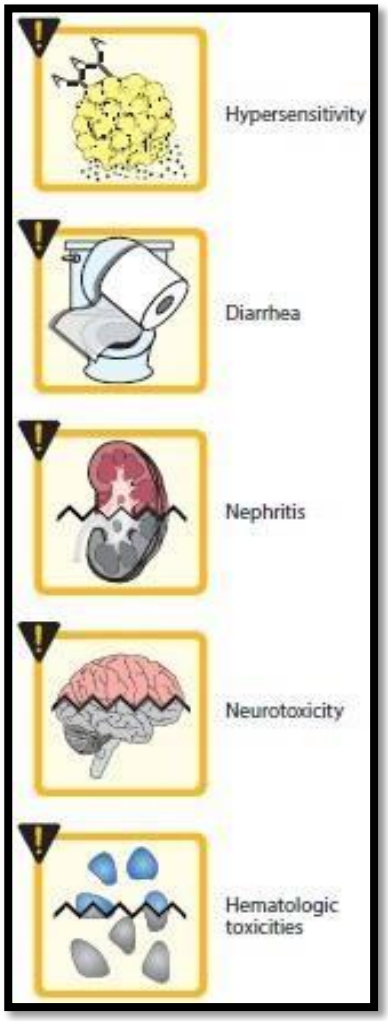
- Absorption of all the penicillinase-resistant penicillins is decreased by food in the stomach, because gastric emptying time is lengthened, and the drugs are destroyed in the acidic environment. Therefore, they must be administered 30 to 60 minutes before meals



- **3. Distribution**: The β-lactam antibiotics distribute well throughout the body. All the penicillins cross the placental barrier, but none has been shown to be teratogenic, however, penetration into certain sites, such as bone or cerebrospinal fluid (CSF), is insufficient for therapy unless these sites are inflamed, Penicillin levels in the prostate are insufficient to be effective against infections.

- **4. Metabolism**: Host metabolism of the β-lactam antibiotics is usually insignificant, but some metabolism of penicillin G has been shown to occur in patients with impaired renal function. (carbapenem cilastatin)

- **5. Excretion:** The primary route of excretion is through the organic acid (tubular) secretory system of the kidney as well as by glomerular filtration. Patients with impaired renal function must have dosage regimens adjusted. Thus, the half-life of penicillin G can increase from a normal of between 30 minutes and 1 hour, to 10 hours in individuals with renal failure. Probenecid inhibits the secretion of penicillins by competing for active tubular secretion via the organic acid transporter and, thus, can increase blood levels. Nafcillin is eliminated primarily through the biliary route



E. Adverse reactions:

- Penicillins are among the safest drugs, and blood levels are not monitored. However, the following adverse reactions may occur

- **Hypersensitivity:** This is the most important adverse effect of the penicillins. The major antigenic determinant of penicillin hypersensitivity is its metabolite, penicilloic acid, which reacts with proteins and serves as a hapten to cause an immune reaction. Approximately five percent of patients have some kind of reaction, ranging from maculopapular rash to angioedema and anaphylaxis Cross-allergic reactions occur among the Blactam antibiotics.

Diarrhea: This effect, which is caused by a disruption of the normal balance of intestinal microorganisms, is a common problem. It occurs to a greater extent with those agents that are incompletely absorbed and have an extended antibacterial spectrum. As with some other antibiotics, pseudomembranous colitis may occur.

- **Nephritis**: All penicillins, but particularly methicillin, have the potential to cause acute interstitial nephritis.
- **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.
- **Hematologic toxicities**: Decreased coagulation may be observed with the antipseudomonal penicillins (Carbenicillin and ticarcillin) and, to some extent, with penicillin G.
- It is generally a concern when treating patients who are predisposed to hemorrhage, or those receiving anticoagulants.

Cation toxicity: Penicillins are generally administered as the sodium or potassium salt. Toxicities may be caused by the large quantities of sodium or potassium that accompany the penicillin

II. Cephalosporins

- The cephalosporins are B-lactam antibiotics related structurally and functionally to the penicillins. Most of it are produced semisynthetically by the chemical attachment of side chains to 7-aminocephalosporanic acid
- Cephalosporins have the same penicillins mode of action and resistance but they tend to be more resistant than the penicillins to certain B-lactamases.

A. Antibacterial spectrum

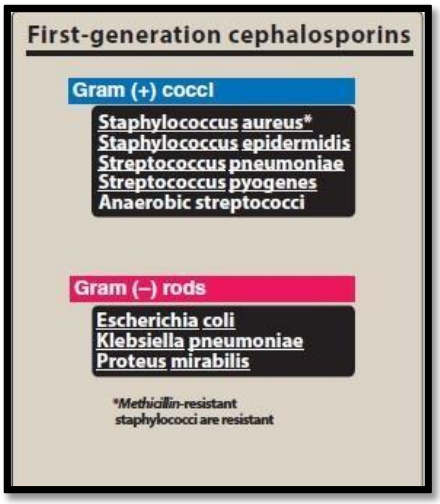
- Cephalosporins have been classified as first, second, third, or fourth generation, based largely on their bacterial susceptibility patterns and resistance to B-lactamases.
- ***First generation*:** The first-generation cephalosporins act as penicillin G substitutes. They are resistant to the staphylococcal penicillinase and also have activity against Proteus mirabilis, E. coli, and Klebsiella pneumoniae

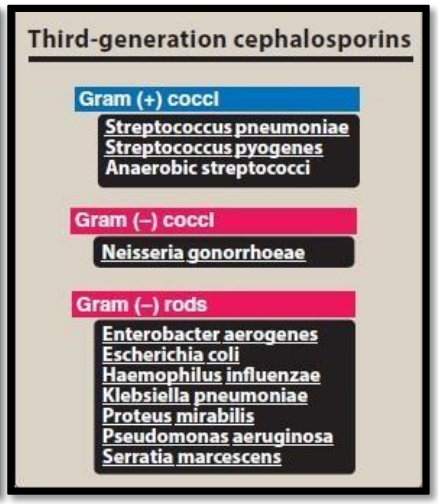
- **Second generation:** The second-generation cephalosporins display greater activity against three additional gram-negative organisms: H. influenzae, Enterobacter aerogenes, and some Neisseria species, whereas activity against gram-positive organisms is weaker

- **Third generation:** These cephalosporins have assumed an important role in the treatment of infectious disease; third-generation cephalosporins have enhanced activity against gramnegative bacilli, as well as most other enteric organisms plus Serratia marcescens.

  Ceftriaxone or cefotaxime have become agents of choice in the treatment of meningitis. Ceftazidime has activity against P. aeruginosa.

- **Fourth generation**: Cefepime is classified as a fourth-generation cephalosporin and must be administered parenterally. Cefepime has a wide antibacterial spectrum, being active against streptococci and staphylococci; Cefepime is also effective against aerobic gram-negative organisms, such as enterobacter, E. coli, K. pneumoniae, P. mirabilis, and P. aeruginosa.





Generation	Parenteral Agents	Oral Agents
1st generation	*Cefazolin, Cephalothin*	*Cefadroxil, cephalexin, cephradine*
2nd generation	*Cefotetan, cefoxitin, cefuroxime*	*Cefaclor, cefprozil, cefuroxime axetil*
3rd generation	*Cefotaxime, ceftazidime, ceftizoxime, ceftriaxone, Cefoperazone*	*Cefdinir, cefditoren, cefpodoxime proxetil, ceftibuten, cefixime*
4th generation	*Cefepime, cefpirome*	
5th generation	*Ceftaroline, Ceftobiprole*	

B. Resistance:

- Mechanisms of bacterial resistance to the cephalosporins are essentially the same as those described for the penicillins

C. Pharmacokinetics

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

Distribution:

- All cephalosporin distribute very well into body fluids. Included CSF regardless of inflammation, third-generation cephalosporin. For example, ceftriaxone or cefotaxime are effective for neonatal and childhood meningitis caused by H. influenza. Cefazolin finds application as a single prophylaxis use as prophylaxis prior to surgery; including orthopedic surgery because of its ability to penetrate bone. All cephalosporin cross the placenta.

- Elimination occurs through tubular secretion and/or glomerular filtration

Ceftriaxone is excreted through the bile into the feces and, therefore, is frequently employed in patients with renal insufficiency.

D. Adverse effects:

 Allergic manifestations: Patients who have had an anaphylactic response to penicillin should not receive cephalosporin. The cephalosporin should be avoided or used with caution in individuals who are allergic to penicillin's.

II. Other B-Lactam Antibiotics

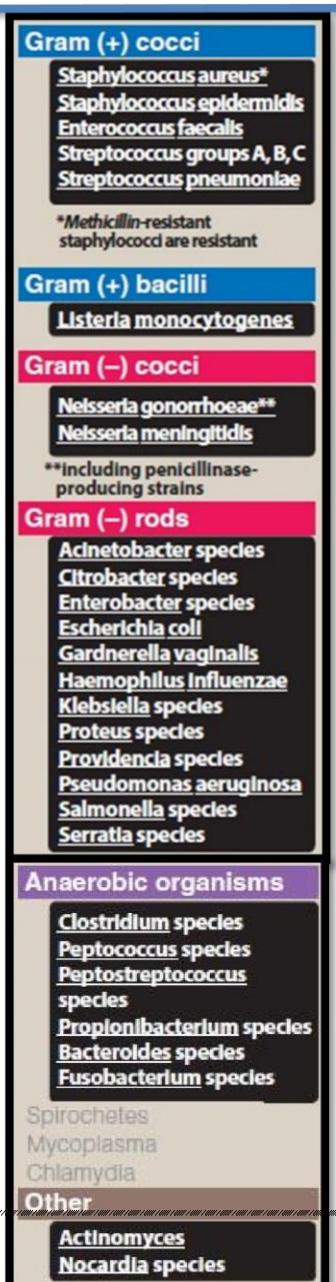
A. Carbapenems (Imipenem meropenem and ertapenem): Carbapenems are synthetic B-lactam antibiotics that differ in structure from the penicillins; Imipenem is compounded with cilastatin to protect it from metabolism by renal dehydropeptidase.

Antibacterial spectrum:

- Imipenem/cilastatin and meropenem are the broadest-spectrum B-lactam antibiotic preparations currently available Imipenem resists hydrolysis by most B-lactamases,
- The drug plays a role in empiric therapy because it is active against penicillinase-producing gram-positive and gram-negative organisms, anaerobes, and P. aeruginosa
- Meropenem has antibacterial activity similar to that of imipenem. Ertapenem is not an alternative for P. aeruginosa coverage, because most strains exhibit resistance

Pharmacokinetics:

- Imipenem and meropenem are administered IV and penetrate well into body tissues and fluids, including the CSF when the meninges are inflamed
- They are excreted by glomerular filtration. Imipenem undergoes cleavage by a dehydropeptidase found in proximal renal tubule
- This enzyme forms an inactive metabolite that is potentially nephrotoxic. Compounding the imipenem with cilastatin protects the parent drug and, thus, prevents the formation of the toxic metabolite. This allows the drug to



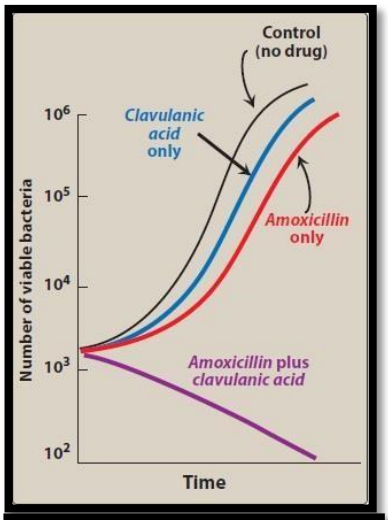
- This enzyme forms an inactive metabolite that is potentially nephrotoxic. Compounding the imipenem with cilastatin protects the parent drug and, thus, prevents the formation of the toxic metabolite. This allows the drug to be used in the treatment of urinary tract infections. Meropenem does not undergo metabolism. Ertapenem can be administered via IV or IM injection.

Adverse effects: Imipenem/cilastatin can cause nausea, vomiting, and diarrhea. High levels of imipenem may provoke seizures, but meropenem is less likely to do so.

B. Monobactams (Aztreonam):

- The monobactams, which also disrupt bacterial cell wall synthesis, are unique, because the B-lactam ring is not fused to another ring ,(in contrast to most other β-lactams, which have at least two rings)
- Aztreonam which is the only commercially available monobactam has antimicrobial activity directed primarily against the *enterobacteriaceae,* but it also acts against aerobic gramnegative rods, including *P. aeruginosa.*
- It lacks activity against gram-positive organisms and anaerobes. This narrow antimicrobial spectrum precludes its use alone in empiric therapy
- Aztreonam is resistant to the action of B-lactamases. It is administered either IV or IM and is excreted in the urine. It can accumulate in patients with renal failure

- It shows little cross-reactivity with antibodies induced by other B-lactams. Thus, this drug may offer a safe alternative for treating patients who are allergic to penicillins and/or cephalosporins.



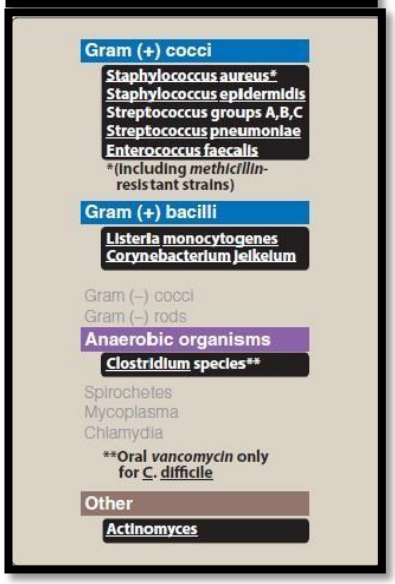
C. β-Lactamases Inhibitors:

Hydrolysis of the B-lactam ring, either by enzymatic cleavage with a Blactamase or by acid, destroys the antimicrobial activity of a B-lactam antibiotic. B-Lactamase inhibitors, such as clavulanic acid, sulbactam, and tazobactam contain a B-lactam ring but, by them, do not have significant antibacterial activity. Instead, they bind to and inactivate B-lactamases enzyme

- Therefore it mixed with B-lactamase sensitive antibiotics as (clavulanic acid and amoxicillin) on the growth of B-lactamase producing E. coli.

D. Vancomycin:

- is a tricyclic glycopeptide
- use for the treatment of life-threatening MRSA and *methicillin*-resistant Staphylococcus epidermidis (MRSE) infections, as well as enterococcal infections



- Using of vancomycin is restrict for 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) , to avoid the development of resistance toward vancomycin as (Enterococcus faecium and Enterococcus faecalis)

- Intravenous *vancomycin* is used in individuals with prosthetic heart valves and in patients undergoing implantation with prosthetic devices, especially in those hospitals where there are high rates of MRSA or MRSE.

- *Vancomycin* is not absorbed after oral administration, so the use of the oral formulation is limited to the treatment of severe antibiotic associated C. difficile colitis.

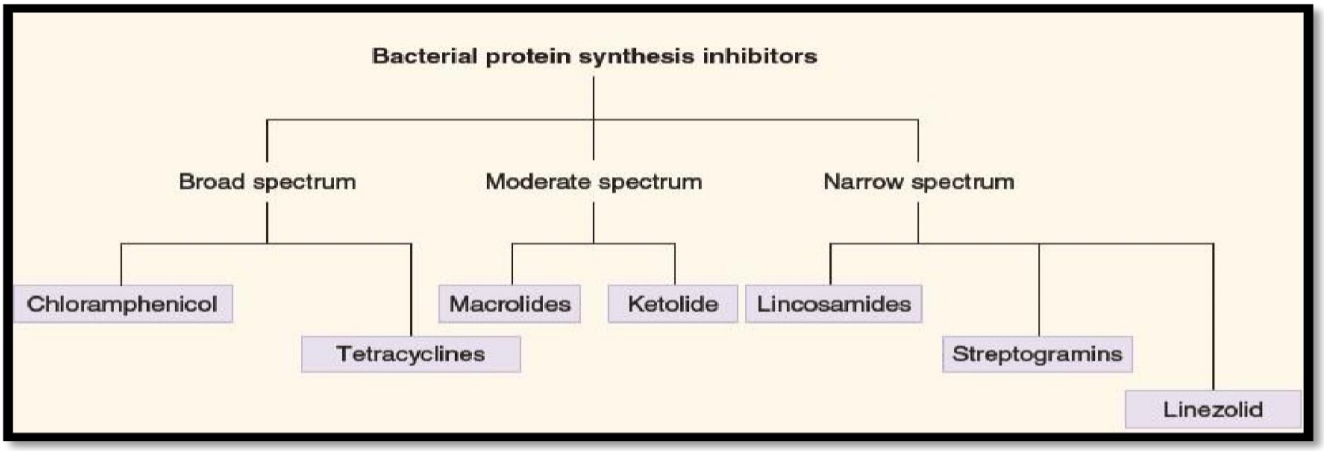
E. Daptomycin:

- Daptomycin ,is a bactericidal concentration-dependent
- itis used as alternative to (linezolid and quinupristin/dalfopristin), for treating infections caused by resistant gram-positive organisms, including MRSA and vancomycin resistant enterococci (VRE)
- Daptomycin is indicated for the treatment of complicated skin and skin structure infections and bacteremia caused by S. aureus.

- Daptomycin is inactivated by pulmonary surfactants; thus, it should never be used in the treatment of pneumonia.

Protein Synthesis Inhibitors 18

- A number of antibiotics exert their antimicrobial effects by targeting the bacterial ribosome, which has components that differ structurally from those of the mammalian cytoplasmic ribosome , In general, the bacterial ribosome is smaller (70S) than the mammalian ribosome (80S) and is composed of 50S and 30S subunits (as compared to 60S and 40S subunits .) The mammalian mitochondrial ribosome, however, more closely resembles the bacterial ribosome) , high levels of drugs such as chloramphenicol or the tetracycline's may cause toxic effects as a result of interaction with the host mitochondrial ribosomes



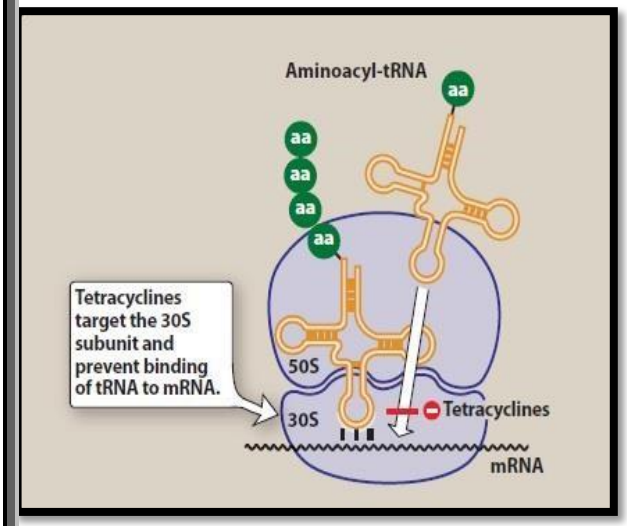
I-Tetracyclines (tetracycline, doxycycline, minocycline, demeclocycline)

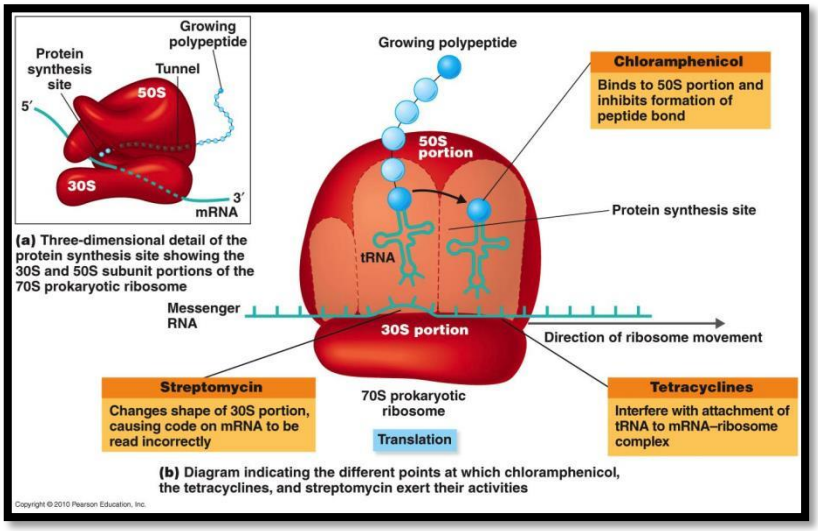
- The Tetracyclines are a group of closely related compounds
- Modification in Tetracyclines rings structure are responsible for variation in the drugs' individual pharmacokinetics, which cause small differences in their clinical efficacy

A- Mechanism of action:

- Entry of these agents into susceptible organisms is mediated both by passive diffusion and by an energy-dependent transport protein mechanism
- The drug binds reversibly to the 30S subunit of the bacterial ribosome, thereby blocking access of the amino acyl-tRNA to the mRNA-ribosome complex at the acceptor site

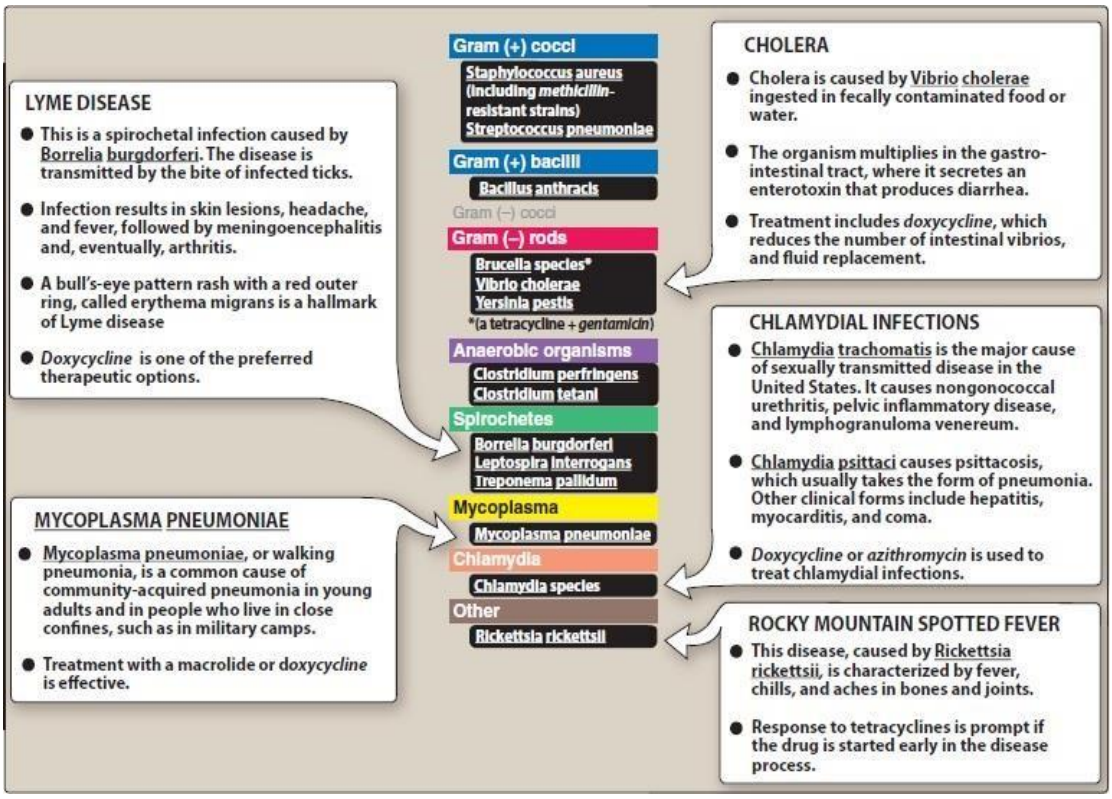
By this mechanism, bacterial protein synthesis is inhibited.





B. Antibacterial spectrum:

- As broad-spectrum, bacteriostatic antibiotics, the Tetracyclines are effective against gram-positive and gram-negative bacteria as well as against organisms other than bacteria; they are commonly used for the treatment of acne.



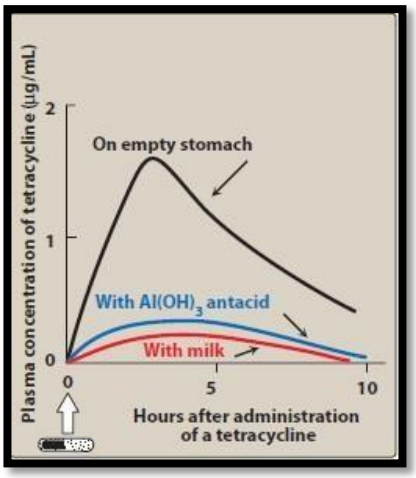
C-Resistance:

A- efflux of the drug, mediated by the plasmid-encoded resistance protein

B- enzymatic inactivation of the drug (less important mechanisms) , Any organism resistant to one tetracycline is resistant to all ,

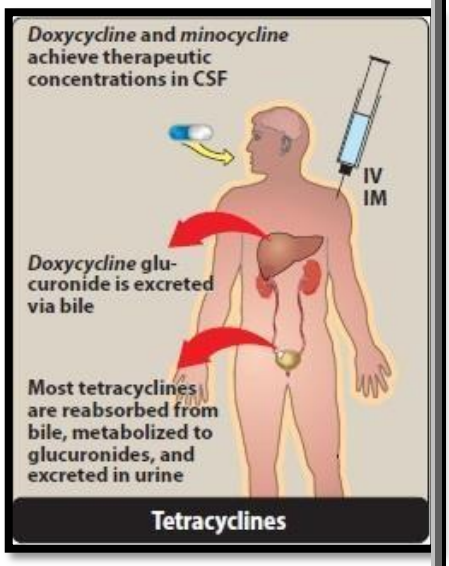
C- Ribosomes protection by production of proteins that interfere with the Tetracyclines binding with ribosomes.

D- Absorption :



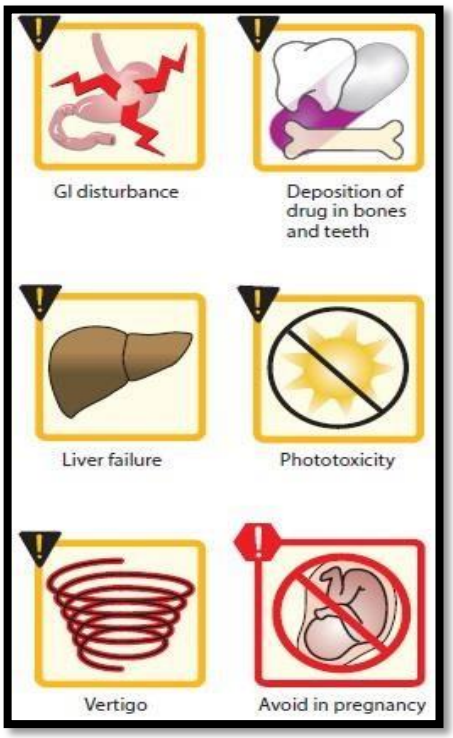
- All Tetracyclines are adequately but incompletely absorbed after oral ingestion
- taking these drugs concomitantly with dairy foods in the diet decreases absorption due to the formation of nonabsorbable chelates of the Tetracyclines with calcium ions
- Nonabsorbable chelates are also formed with other divalent and trivalent cations (for example, those found in magnesium and aluminum antacids and in iron preparations.
- Doxycycline and minocycline are almost totally absorbed on oral administration. Currently, doxycycline is the preferred tetracycline for parenteral administration.

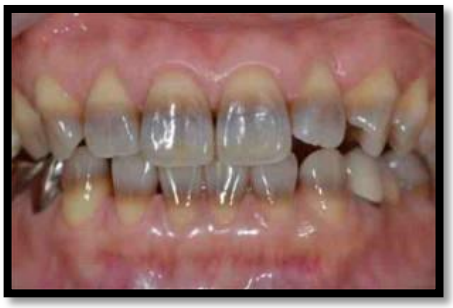
E- Distribution :



- The Tetracyclines concentrate in the liver, kidney, spleen, and skin, and they bind to tissues undergoing calcification (for example, teeth and bones) or to tumors that have a high calcium content (for example, gastric carcinoma.
- Although all Tetracycline enter the cerebrospinal fluid (CSF), levels are insufficient for therapeutic efficacy, except for minocycline
- All tetracycline cross the placental barrier and concentrate in fetal bones and dentition
- The parent drug and/or its metabolites are secreted into the bile , Most tetracycline are reabsorbed in the intestine via the enterohepatic circulation and enter the urine by glomerular filtration
- Obstruction of the bile duct and hepatic or renal dysfunction can increase their half-life.
- Doxycycline can be employed for treating infections in renally compromised patients, because it is preferentially excreted via the bile into the feces tetracycline are also excreted in breast milk.

F- Adverse effects:





A- **Gastric discomfort:** Epigastric distress commonly results from irritation of the gastric mucosa , The discomfort can be controlled if the drug is taken with foods other than dairy products

B- **Effects on calcified tissues**: Deposition in the bone and primary dentition occurs during calcification in growing children. This causes discoloration and hypoplasia of the teeth

C- **Fatal hepatotoxicity:** This side effect has been known to occur in pregnant women who received high doses of tetracyclines, especially if they were experiencing pyelonephritis

D- **Phototoxicity:** Phototoxicity, such as severe sunburn, occurs when a patient receiving a tetracycline is exposed to sun or ultraviolet rays , This toxicity is most frequently occur with tetracycline ,doxycycline, and demeclocycline.

E- **Vestibular problems**: These side effects (for example, dizziness, nausea, and vomiting) occur particularly with minocycline Doxycycline may also cause vestibular effects.

F- **Pseudotumor cerebri**: Benign, intracranial hypertension characterized by headache and blurred vision may occur rarely in adults , discontinuation of the drug reverses this condition

G- **Superinfections:** Overgrowths of Candida (for example, in the vagina) or of resistant staphylococci (in the intestine) may occur. Pseudomembranous colitis due to an overgrowth of Clostridium difficile has also been reported.

G- Contraindications: Renally impaired patients should not be treated with any of the tetracyclines except doxycycline; Accumulation of tetracyclines may aggravate preexisting azotemia (a higher-than-normal level of urea

By interfering with protein synthesis, thus promoting amino acid degradation. The tetracyclines should not be employed in pregnant or breast-feeding women or in children less than 8 years of age

2- Glycylcyclin (Tigecycline)

- Tigecycline is the first available member of a new class of antimicrobial agents called glycylcyclines
- Tigecycline is structurally similar to the tetracyclines and has a broad-spectrum activity.
- Tigecycline is indicated for treatment of complicated skin and soft tissue infections

A- Mechanism of action:

Tigecycline exhibits bacteriostatic action by reversibly binding to the 30S ribosomal subunit and inhibiting protein translation

B- Antibacterial spectrum:

Tigecycline exhibits expanded broad-spectrum activity that includes methicillin-resistant staphylococci, multidrug-resistant Streptococcus pneumoniae, and other susceptible strains of streptococcal species,

C- Resistance :

Tigecycline was developed to overcome the recent emergence of tetracycline class-resistant organisms

D. Adverse effects:

Adverse effects being similar to those of the tetracycline class

E. Drug interactions :

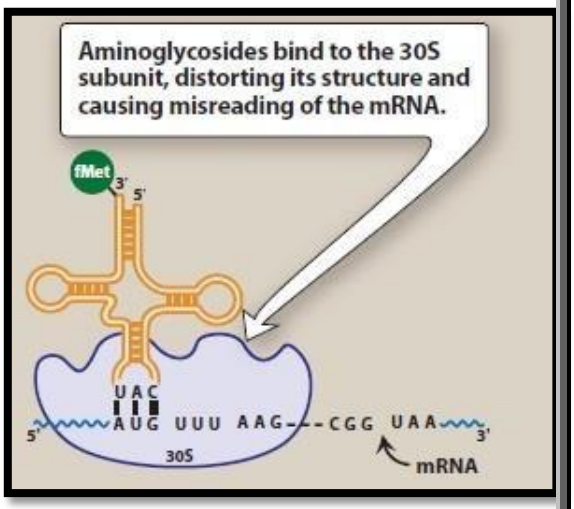
- It not affected by medications that induce or inhibit these enzymes.
- It inhibits the clearance of warfarin. Therefore, it is recommended that anticoagulation be monitored closely when tigecycline is coadministered with warfarin.
- another method of contraception is suggested when Tigecycline and oral contraceptives are Coad ministered, because the oral contraceptives may become less effective

3- Aminoglycosides.

- Aminoglycoside antibiotics had been the mainstays for treatment of serious infections due to aerobic gram-negative bacilli
- However, because their use is associated with serious toxicities, they have been replaced to some extent by safer antibiotics, such as the third- and fourth-generation Cephalosporins, the fluoroquinolones, and the carbapenems
- All members of this family are believed to inhibit bacterial protein synthesis

A- Mechanism of action:

- Susceptible gram-negative organisms allow aminoglycosides to diffuse through porin channels in their outer membranes
- The antibiotic then binds to the 30S ribosomal subunit prior to ribosome formation
- There, it interferes with assembly of the functional ribosomal apparatus and/or can cause the 30S subunit of the completed ribosome to misread the genetic code
- *The aminoglycosides synergize with B-lactam antibiotics because of the latter's action on cell wall synthesis, which enhances diffusion of the aminoglycosides into the bacterium*.



B. Antibacterial spectrum:

- The aminoglycosides are effective in the empirical treatment of infections suspected of being due to aerobic gram-negative bacilli, including Pseudomonas aeruginosa
- To achieve an additive or synergistic effect, aminoglycosides are often combined with a B-lactam antibiotic, or vancomycin, or a drug active against anaerobic bacteria
- All aminoglycosides are bactericidal
- *The aminoglycosides are effective only against aerobic organisms because strict anaerobes lack the oxygen-requiring drug transport system*.

C. Resistance:

1. decreased uptake of drug when the oxygen-dependent transport system for aminoglycosides or porin channels are absent
2. enzymes (for example, acetyl transferases, nucleotidyltransferases, and phosphotransferases) that modify and inactivate aminoglycoside antibiotics
3. Cross-resistance is not an invariable rule.

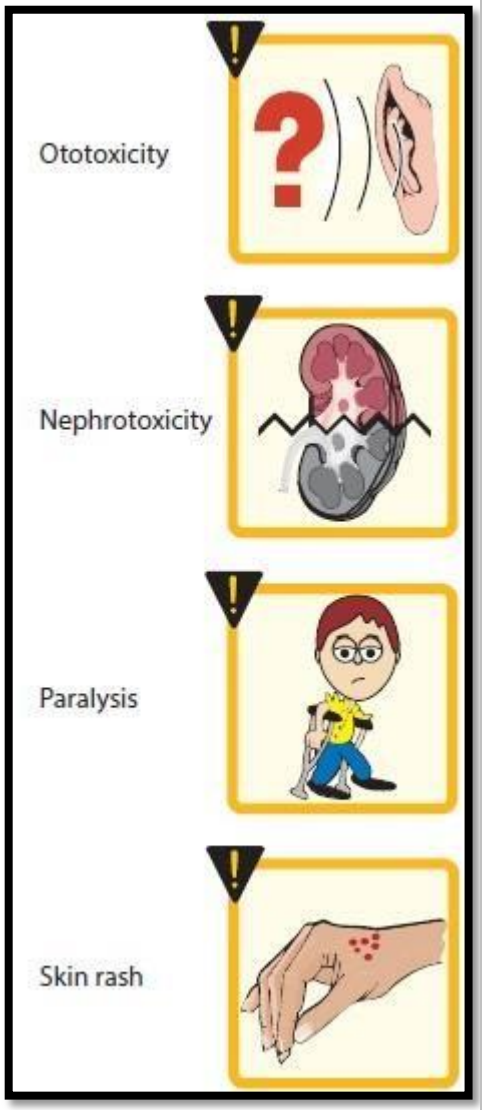
D. Pharmacokinetics:

Administration: The highly polar, polycationic structure of the aminoglycosides prevents adequate absorption after oral administration Therefore, all aminoglycosides (except neomycin) must be given parenterally to achieve adequate serum levels .

- The severe nephrotoxicity associated with neomycin precludes Parenteral administration its current use is limited to topical application for skin infections
- The bactericidal effect of aminoglycosides is concentration and time dependent, They also have a Postantibiotic effect
- Once-daily dosing with the aminoglycosides can be employed. This results in less toxicity and is less expensive to administer

High concentrations accumulate in the renal cortex and in the endolymph and perilymph of the inner ear, which may account for their nephrotoxic and ototoxic potential.

E. Adverse effects: (The elderly are particularly susceptible to nephrotoxicity and ototoxicity.(



Ototoxicity : Ototoxicity (vestibular and cochlear) is directly related to high peak plasma levels and the duration of treatment

- The antibiotic accumulates in the endolymph and perilymph of the inner ear, and toxicity correlates with the number of destroyed hair cells in the organ of Corti
- Deafness may be irreversible
- Patients simultaneously receiving another ototoxic drug, such as cisplatin or the loop diuretics, furosemide, are particularly at risk. Vertigo and loss of balance (especially in patients receiving streptomycin

Nephrotoxicity: Retention of the aminoglycosides by the proximal tubular cells disrupts calcium-mediated transport processes

- This results in kidney damage ranging from mild, reversible renal impairment to severe, acute tubular necrosis, which can be irreversible.

Neuromuscular paralysis: This due to a decrease in both the release of acetylcholine from prejunctional nerve endings and the sensitivity of the postsynaptic site Patients with myasthenia gravis are particularly at risk, administration of neostigmine can reverse the block.

Allergic reactions：(Contact dermatitis is a common reaction to topically applied neomycin).

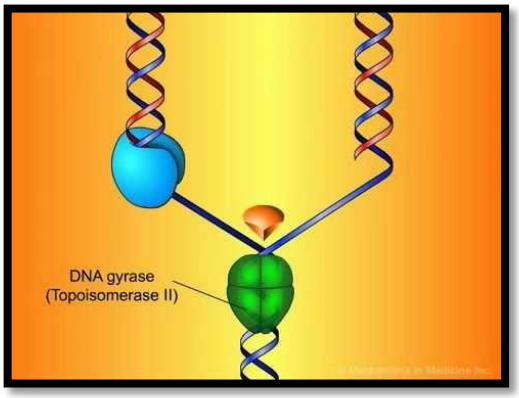
Quinolones, Folic Acid Antagonists, and Urinary Tract Antiseptics

I. FLUOROQUINOLONES:

- Nalidixic acid is the predecessor to all fluoroquinolones,
- Fluoroquinolones offer greater efficacy, a broader spectrum and a better safety profile than their predecessors.
- Unfortunately, fluoroquinolone use has been closely tied to Clostridium difficile infection and the spread of antimicrobial resistance in many organisms (for example, methicillin resistance in staphylococci).

The unfavorable effects of fluoroquinolones on the induction and spread of antimicrobial resistance are sometimes referred to as **"collateral damage,"** a term which is also associated with third-generation cephalosporin (for example, **ceftazidime).**

Mechanism of action:



- **Fluoroquinolones** enter bacteria through **porin channels**.
- Its exhibit antimicrobial effects on **DNA gyrase** (bacterial **topoisomerase II**) and bacterial **topoisomerase IV**.
- Inhibition of DNA gyrase results in **relaxation of supercoiled DNA**, promoting **DNA strand breakage**.
- Inhibition of **topoisomerase IV impacts chromosomal stabilization during cell division**, thus interfering with the **separation of newly replicated DNA**.
- In gram-negative organisms (as Pseudomonas aeruginosa), the inhibition of DNA gyrase is more

significant than that of topoisomerase IV, whereas in gram-positive organisms (as Streptococcus pneumoniae), the opposite is true. Agents with higher affinity for topoisomerase IV (for example, **ciprofloxacin**) should not be used for **S. pneumoniae** infections, while those with more **topoisomerase II** activity (for example, **moxifloxacin**) should not be used for P. aeruginosa infections.

B. Antimicrobial spectrum

- Fluoroquinolones are bactericidal concentration -dependent killing.
- Fluoroquinolones are effective against gram-negative organisms (Escherichia coli, P. aeruginosa, and Haemophilus influenzae), atypical organisms (Legionellaceae, Chlamydiaceae), gram-positive organisms (streptococci), and some mycobacteria (Mycobacterium tuberculosis).
- Fluoroquinolones not used for the treatment of Staphylococcus aureus or enterococcal infections.
- They are not effective against syphilis.

- *Levofloxacin* and *moxifloxacin* are sometimes referred to as "respiratory fluoroquinolones," because they have excellent activity against S. pneumoniae, which is a common cause of community-acquired pneumonia (CAP).

  Fluoroquinolones are commonly considered alternatives for patients with a documented severe β-lactam allergy.

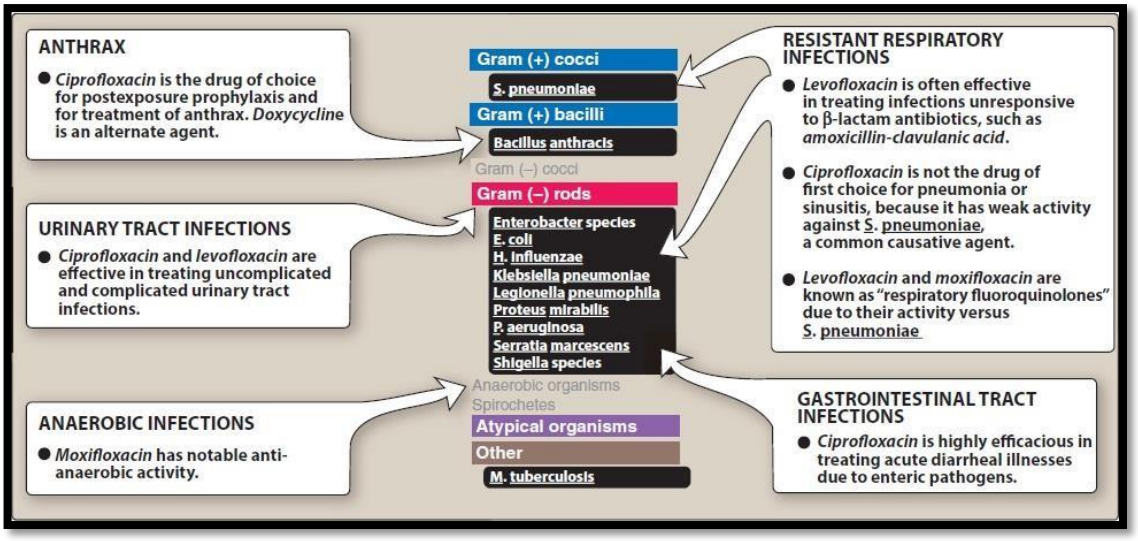
Fluoroquinolones may be classified into "generations" based on their antimicrobial targets.

1st generation (nalidixic acid): a narrow spectrum

2nd generation: (Ciprofloxacin and norfloxacin): it's active against aerobic gram negative and Intracellular microorganism (for example, chlamydia, mycoplasma, and mycobacteria).

3rd generation: (Levofloxacin): it's active against gram-positive bacteria.

4th generation (moxifloxacin): its activity against anaerobic and gram- positive organisms.



Examples of clinically useful fluoroquinolones

1. **Norfloxacin:** is infrequently prescribed due to poor oral bioavailability and a short half-life. It is effective in treating nonsystemic infections, as urinary tract infections, prostatitis, and infectious diarrhea.
2. **Ciprofloxacin:**

- is effective in the treatment of many systemic infections caused by gram- Negative bacilli , it has the best activity against P. aeruginosa
- Used in **cystic fibrosis** patients, **Traveler's diarrhea** caused by E. coli as well as **typhoid fever** caused by Salmonella typhi can be effectively treated with *ciprofloxacin*.
- *Ciprofloxacin* is also used as a second-line agent in the treatment of **tuberculosis**.

3. Levofloxacin:

- Use for treatment of wide range of infections, including **prostatitis**, **skin infections**, and **nosocomial pneumonia**.

- Unlike *ciprofloxacin*, *levofloxacin* has excellent activity against **S. pneumoniae** respiratory infections.(dosed once daily).

4. Moxifloxacin:

- has enhanced activity against **gram-positive organisms** (for example, S. pneumoniae) and many **anaerobes**, Although resistance to Bacteroides fragilis has been reported, It has poor activity against P. aeruginosa.
- Moxifloxacin does not concentrate in urine and is not indicated for the treatment of UTIs

D. Resistance:

✓ No plasmid-mediated resistance, but emerged due to chromosomal mutations. mechanisms responsible for this resistance include the following ;

✓ Altered target: Mutations in the bacterial DNA gyrase have been associated with a decreased affinity for fluoroquinolones

Decreased accumulation : decreased number of porin proteins in the outer membrane of the resistant cell , impairing access of the drugs.

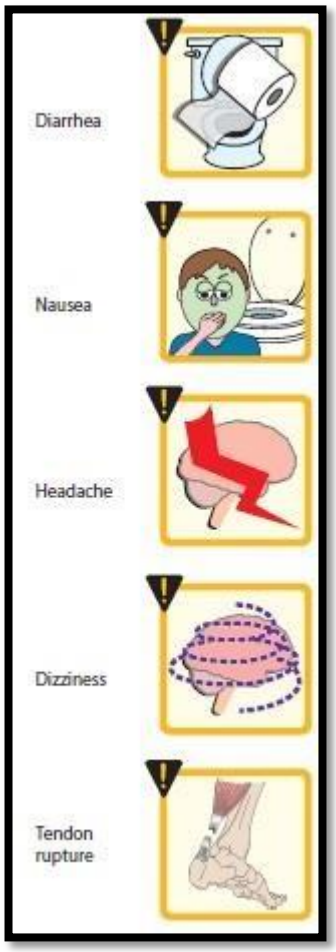
✓ **E. Pharmacokinetics:**

- Intravenous preparations of ciprofloxacin, levofloxacin, and norfloxacin are available.
- Ingestion of the fluoroquinolones with sucralfate, antacids containing aluminum or magnesium, or dietary supplements containing iron or zinc can interfere with the absorption of these antibacterial drugs. Calcium and other divalent cations have also been shown to interfere with the absorption of these agents

- All the fluoroquinolones distribute well into all tissues and body fluids.

Levels are high in bone, urine, kidney, and prostatic tissue (but not prostatic fluid),

Penetration into cerebrospinal fluid is low except for norfloxacin; they are excreted by the renal route.



F. Adverse reactions:

- Gastrointestinal: nausea, vomiting, and diarrhea
- Phototoxicity: Patients taking fluoroquinolones are advised to avoid excessive sunlight and to apply sunscreens it is advisable that the drug should be discontinued at the first sign of Photo toxicity
- Connective tissue problems: Fluoroquinolones should be avoided in pregnancy, in nursing mothers, and in children under 18 years of age,

  because articular cartilage erosion (arthropathy)

  Contraindications: Moxifloxacin may prolong the QTc interval and, thus, should not be used in patients who are predisposed to arrhythmias or are taking antiarrhythmic medications.

Drug interactions:

- Ciprofloxacin and norfloxacin can increase the serum levels of theophylline by inhibiting its metabolism

  May raise the serum levels of warfarin, caffeine, and cyclosporine.

II. Overview of the Folate Antagonists:

- Enzymes requiring Folate-derived cofactors are essential for the synthesis of purines and pyrimidines[2] (precursors of RNA and DNA)
- absence of folate, cells cannot grow or divide
- many bacteria are impermeable to folic acid and other folates and, therefore, must rely on their ability to synthesize Folate de novo
- sulfonamides (sulfa drugs) are a family of antibiotics that inhibit this de novo synthesis of folate
- A second type of folate antagonist-trimethoprim-prevents microorganisms from converting dihydrofolic acid to tetrahydrofolic acid
- with minimal effect on a human cell's ability to make this conversion
- Sulfamethoxazole with trimethoprim (the generic name for the combination is cotrimoxazole) provides a synergistic combination that is used as effective treatment of a variety of bacterial infections.

1- Sulfonamides

The sulfa drugs are seldom prescribed alone except in developing countries, where they are still employed because of their low cost and efficacy.

A. Mechanism of action:

1) dihydrofolic acid is synthesized from p-amino benzoic acid (PABA), pteridine, and glutamate
2) Sulfonamides are synthetic analogs of PABA.
3) Because of their structural similarity to PABA; the sulfonamides compete with this substrate for the bacterial enzyme, dihydropteroate syntheses.
4) They thus inhibit the synthesis of bacterial dihydrofolic acid.

B. Antibacterial spectrum:

- Sulfa drugs are active against select Enterobacteriaceae in the urinary tract and Nocardia infections. In addition,
- ***(Sulfadiazine* with pyrimethamine** (dihydrofolate reductase)) combination use for treatment toxoplasmosis. ***(Sulfadoxine* with *pyrimethamine)*** used as an antimalarial drug.

Administration:

- 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**).
- Intestinal flora split sulfasalazine into **(sulfapyridine)** and (**5-aminosalicylate**, has anti-inflammatory effect).
- Because of the **risk of sensitization**, sulfa drugs are not usually applied topically
- Burn units, creams of silver sulfadiazine have been effective in reducing burnassociated sepsis because they prevent colonization of bacteria.

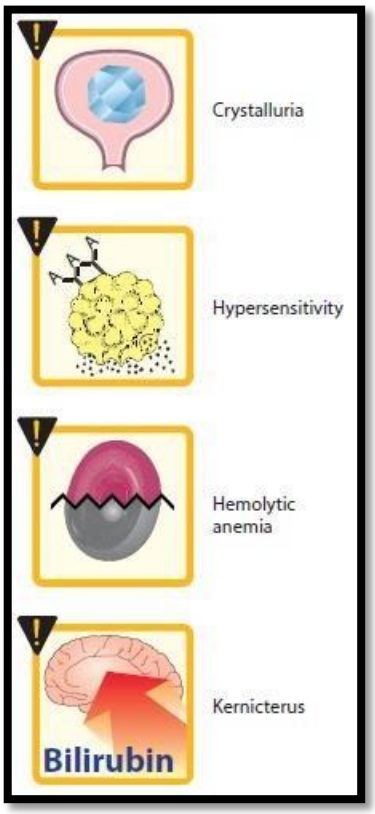
Distribution: Sulfa drugs distribute throughout the body's water and penetrate well into cerebrospinal fluid-even in the absence of inflammation.

Metabolism: primarily acetylated in the liver, precipitate at neutral or acidic pH. This causes crystalluria –stone and, therefore, potential damage to the kidney.

Excretion: Sulfa drugs are eliminated by glomerular filtration depressed kidney function causes accumulation of both the parent compounds and their metabolites.

Adverse effects:

- **Crystalluria**: Nephrotoxicity develops as a result of crystalluria , Adequate hydration and alkalinization of urine prevent the problem by reducing the concentration of drug
- **Hypersensitivity**: Hypersensitivity reactions, such as rashes, angioedema, and Stevens-Johnson syndrome, occur more frequently with the longer-acting agents.
- **Hemopoietic disturbances**; Hemolytic anemia is encountered in patients with glucose 6-phosphate dehydrogenase deficiency.
- **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 baby's blood-brain barrier is not fully developed.
- **Drug potentiation**: Transient potentiation of the hypoglycemic effect of tolbutamide or the anticoagulant effect of warfarin results from their displacement from binding sites on serum albumin



Contraindications: sulfa drugs should be avoided in newborns and infants less than 2 months of age as well as in pregnant women at term , Because sulfonamides condense with formaldehyde, they should not be given to patients receiving methenamine for UTIs

2- Trimethoprim

A potent inhibitor of bacterial dihydrofolate reductase, antibacterial spectrum similar to that of the sulfonamides, often compounded with sulfamethoxazole, producing cotrimoxazole

A. 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**. o The bacterial reductase has a much stronger affinity for trimethoprim than does the mammalian enzyme, which accounts for the selective toxicity of the drug.

B. Antibacterial spectrum:

- Similar to that of sulfamethoxazole, with 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**.

C. Resistance:

- Altered dihydrofolate reductase causing a lower affinity for *trimethoprim*.
- Efflux pumps and decreased permeability to the drug.

D. Pharmacokinetics:

- 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 **excreted renally**.

E. Adverse effects:

- **Trimethoprim** can produce the effects of folic acid deficiency; 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 (**leucovorin**), which ***does not enter bacteria.***

3- Cotrimoxazole

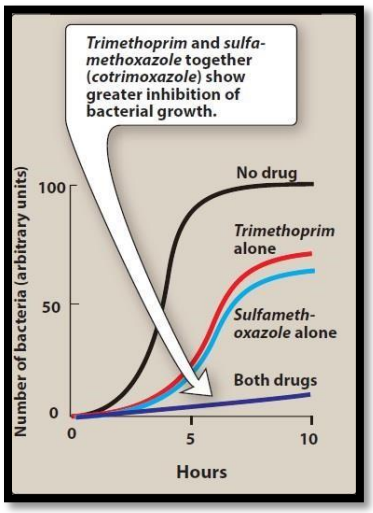
- Cotrimoxazole Is the combination of trimethoprim with sulfamethoxazole, **greater antimicrobial activity** greater than equivalent quantities of either drug used alone (1+1= 3).
- The combination was selected because of the (synergistic activity) and (similarity of half-lives).

A. Mechanism of action:

✓ Results from 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**

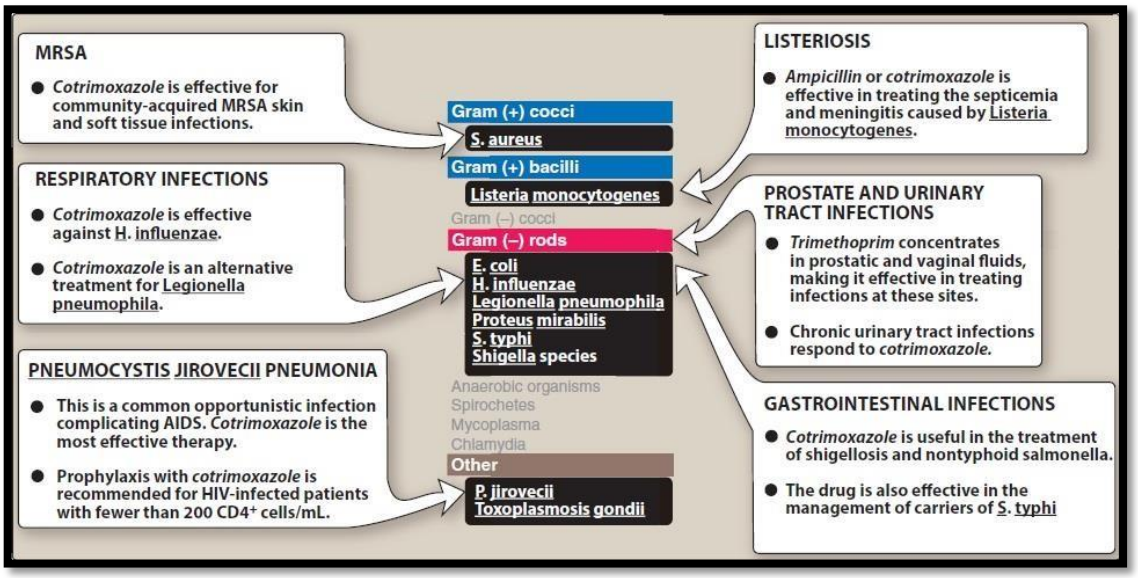
B. Antibacterial spectrum:



- Cotrimoxazole has a broader spectrum of antibacterial action than the sulfa drugs alone
- It is effective in treating **UTIs and respiratory tract infections**, as well as Pneumocystis pneumonia (PCP), **toxoplasmosis**, and **ampicillin- or chloramphenicol-resistant salmonella infections**.
- It has **activity against MRSA** and can be particularly useful for community-acquired **skin and soft tissue infections** caused by this organism.
- It is the drug of choice for infections caused by susceptible Nocardia species.

C. Resistance:

- Resistance to the *trimethoprim–sulfamethoxazole* combination is less than resistance to either of the drugs alone, because it requires that the bacteria have simultaneous resistance to both drugs.
- Significant resistance has been documented in a number of clinically relevant organisms, including E. coli and MRSA.



D- Pharmacokinetics:

- Cotrimoxazole is generally administered **orally**; **Intravenous administration** use for patients with **severe pneumonia** caused by PCP.
- Both agents distribute throughout the body.

- **Trimethoprim** concentrates in the relatively acidic milieu of prostatic fluids, and this accounts for the use of *trimethoprim–sulfamethoxazole* in the treatment of prostatitis.
- *Cotrimoxazole* readily crosses the blood– brain barrier. Both parent drugs and their metabolites are excreted in the urine.

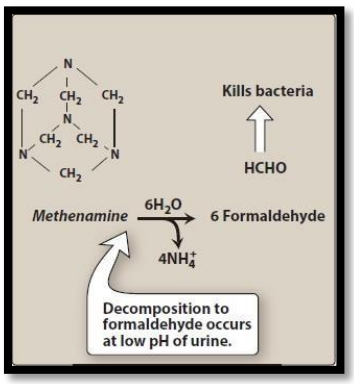
Adverse effects:

- (**Gastrointestinal**): Nausea and vomiting, Glossitis and stomatitis.
- **Megaloblastic anemia**, leukopenia, and thrombocytopenia may occur and have been fatal. Which can be reversed by administration of *folinic acid*,
- **Hemolytic anemia** may occur in patients with G6PD deficiency due to the *sulfamethoxazole* component.
- **Immunocompromised patients with PCP**, show drug-induced fever, rashes, diarrhea, and/or pancytopenia.
- **Prolonged prothrombin times** (increased INR) in patients receiving both *sulfamethoxazole* and *warfarin* have been reported, and increased monitoring is recommended when the drugs are used concurrently. o The plasma half-life of *phenytoin* may be increased due to inhibition of its metabolism. *Methotrexate* levels may rise due to displacement from albuminbinding sites by *sulfamethoxazole*.

III- 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. o 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**.

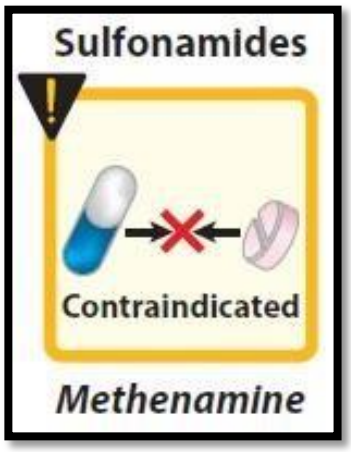
— A. Methenamine:



- ***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, to keep the urine acidic. The urinary pH should be maintained below 6. Antacids, such as *sodium bicarbonate*, should be avoided.]

Antibacterial spectrum:

- Used for **chronic suppressive therapy** to reduce the **frequency of UTIs**.
- Routine use in patients with **chronic urinary catheterization** to reduce catheter associated **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.



— Adverse effects:

- Gastrointestinal distress o At higher doses, albuminuria, hematuria, and rashes may develop.
- Methenamine mandelate is contraindicated in patients with renal insufficiency.
- [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.]

B- Nitrofurantoin :

- Nitrofurantoin sensitive bacteria reduce the drug to a highly active intermediate that inhibits various enzymes and damages bacterial DNA.
- It is useful against E. coli, but other common urinary tract gram-negative bacteria may be resistant. Gram-positive cocci (for example, S. saprophyticus) are typically susceptible.

Adverse effect:

- Hemolytic anemia may occur in patients with G6PD deficiency.
- 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.