Antibiotics

Antibiotic substance is substance produced by microorganism which has capacity of inhibiting the growth and even of destroying other microorganism.

Classification of antibiotics is based on chemical structure

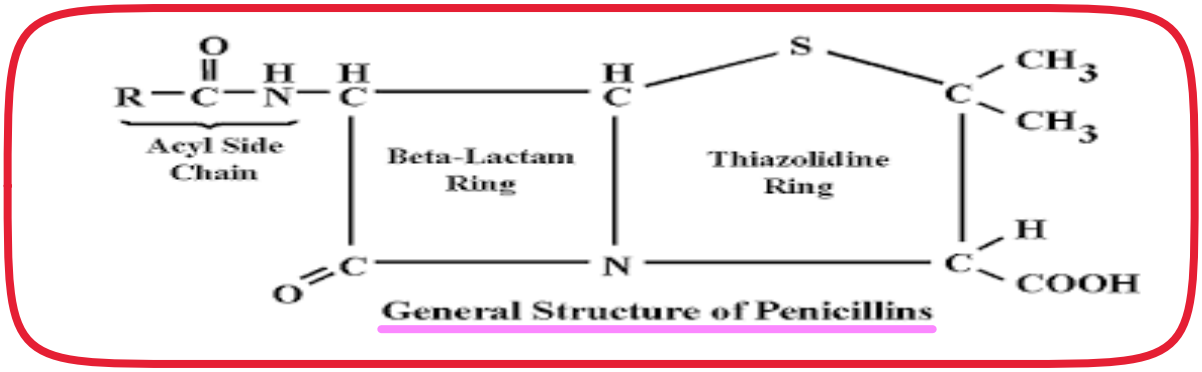
1. Beta lactam antibiotics:-
   Ex penicillin,cepholosporins, monobactum
2. Aminoglycosides
   Ex Streptomycin neomycin kanamycin
3. Tetracyclines :-
   Ex Tetracycline oxytetracycline chlortetracycline Minocycline Doxycycline
4. Macrolide :-
   Ex Erthromycine Azithromycine
5. LINCOMYCINS
   Ex lincomycine HCl , clindamycines HCl
6. Polypeptides :-
   Ex gramicidin , bacitracin, bacitracin zinc
7. Miscellaneous
   Ex chloramphenicol Clindamycine

Mechanism of action

1. By interfering with cell wall synthesis
   Ex penicillin's, cephalosporin, bacitracin
2. Promoting leakage from cell membranes
   Ex colistin nystatin polymyxins
3. Interfering with protein synthesis in ribosomes in the cells of the organism
   Ex chloramphenicol tetracycline erythromycin
4. Interfering with DNA and m-RNA synthesis
   Ex Actinomycin griseofulvin
5. Interfering with DNA function
   Ex rifampicin

Penicillin: - β lactam antibiotics

The basic structure of penicillin consists of thiazolidine ring fused with a β lactam ring. This is essential for antibacterial activity.



Mechanism of action of Action

The synthesis of cell wall of bacteria is completely depending upon an **enzyme named transpeptidase.**

Penicillin inhibits the cell wall of bacteria by blocking transpeptidase after binding to penicillin –binding protein (PBP) and prevents is synthesis and causes cell lysis for bacteria.

Diuretics

Diuretics (water pills) are drug which are increase the urine output of electrolytes and water from the kidney by interfering with one or more reabsorption process occurring at different segment of nephron.

Diuretics increase the formation & excretion of urine

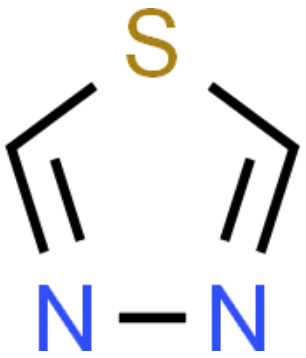
Uses

- Hypertension
- Edema.
- Glaucoma.
- Congestive heart failure

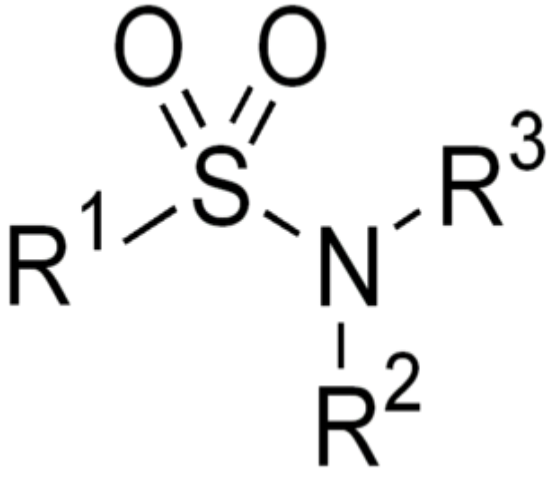
Classification

1- Carbonic anhydrase inhibitors:- acetazolamide methazolamide.
2- Thiazide & thiazide like diuretics :- chlorothiazides Benzthiazide .
3- High – ceiling are loop diuretics :- furosemide .
4- Potassium sparing diuretics :- spironolactone, amiloride
5- Miscellaneous :- mannitol

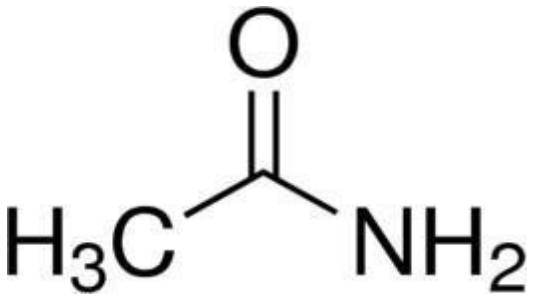
Basic structures of basic Moiety of diuretics



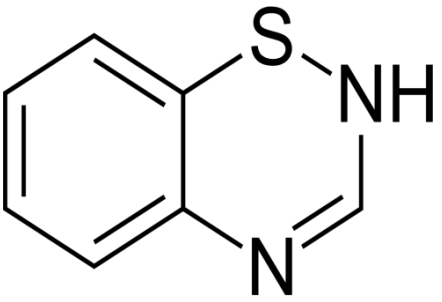
1 3 4 thiadiazole



sulfonamide



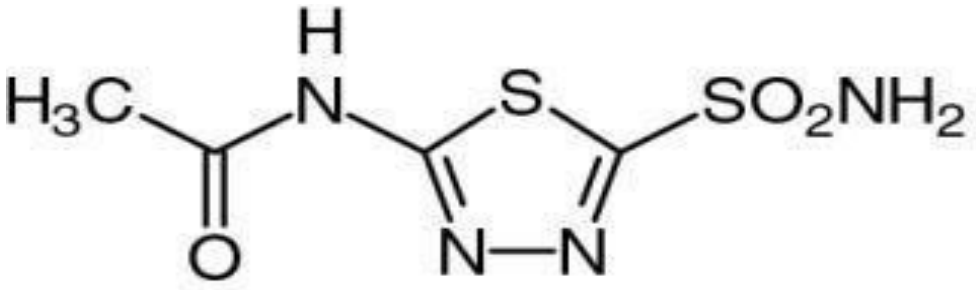
Acetamide



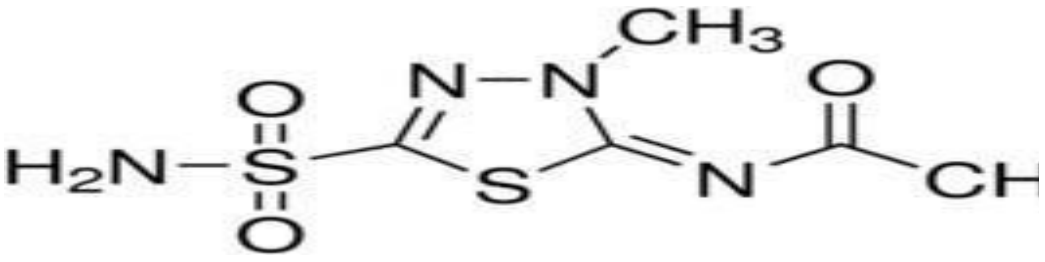
Thiazide

1- Acetazolamide

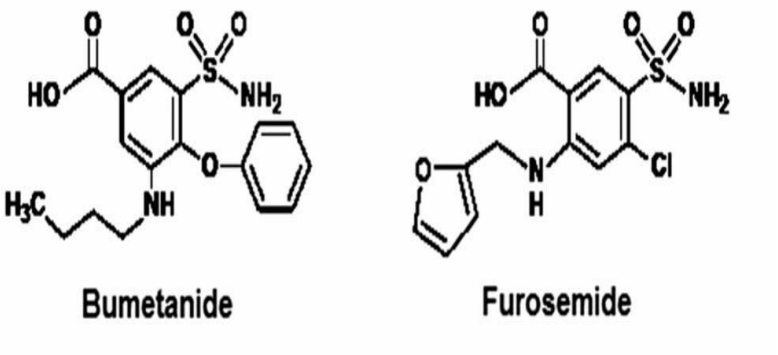
The structure of acetazolamide



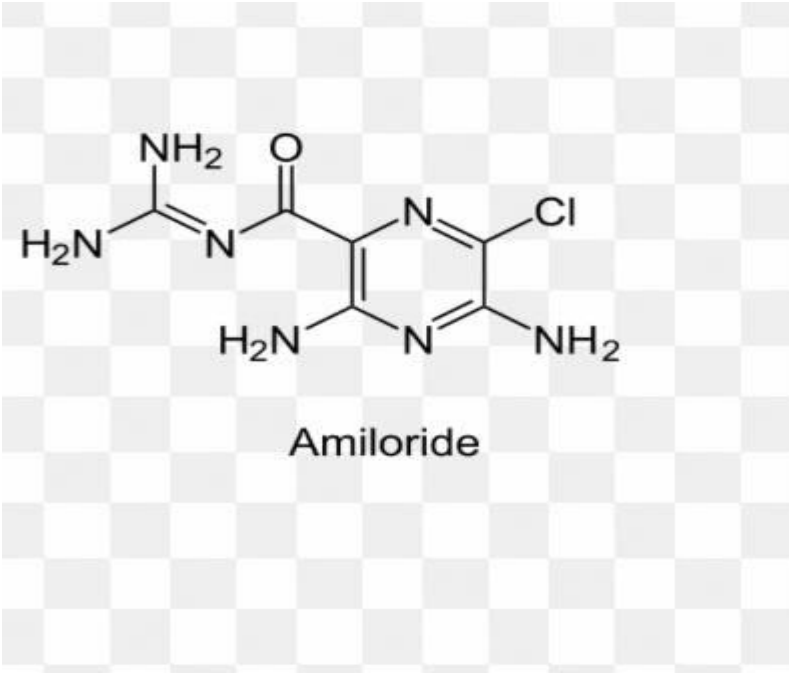
2- Methazolamide.

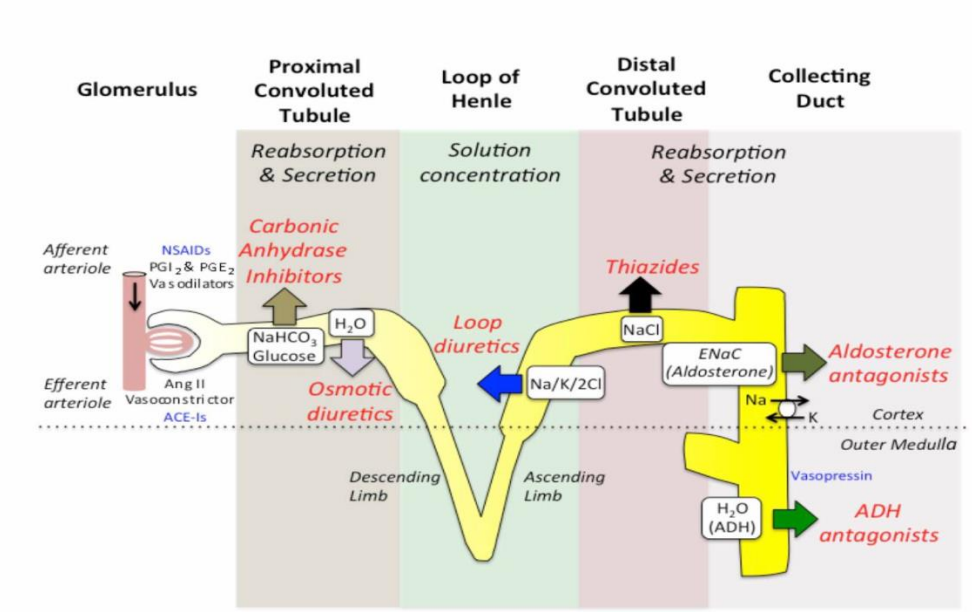


3- Furosemide .



4- Amiloride .




Glomerulus
Proximal Convoluted Tubule
Loop of Henle
Distal Convoluted Tubule
Collecting Duct
Reabsorption & Secretion
Solution concentration
Reabsorption & Secretion
Afferent arteriole
NSAIDs
PGI2 & PGE2
Vasodilators
Carbonic Anhydrase Inhibitors
Thiazides
NaHCO3
Glucose
H2O
Loop diuretics
NaCl
ENaC (Aldosterone)
Aldosterone antagonists
Efferent arteriole
Ang II
Vasoconstrictor
ACE-Is
Osmotic diuretics
Na/K/2Cl
Na
K
Cortex
Outer Medulla
Descending Limb
Ascending Limb
Vasopressin
H2O (ADH)
ADH antagonists

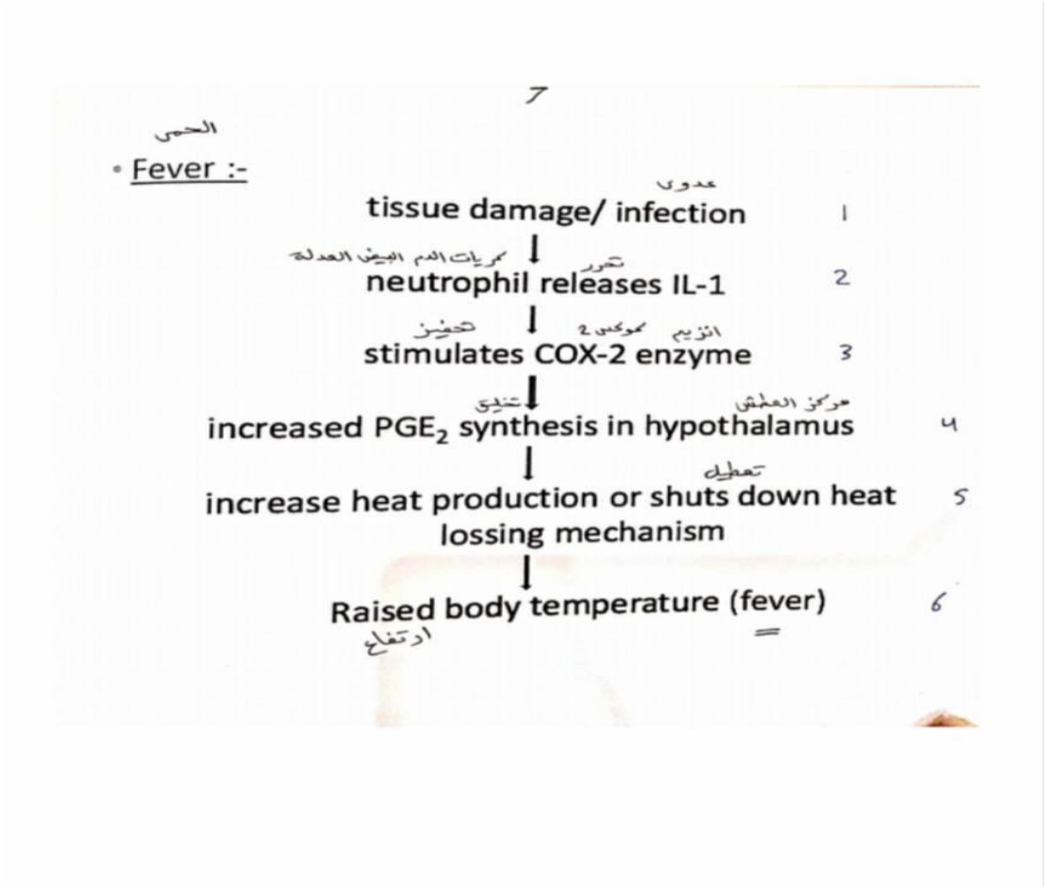
Fever:- Is an elevation of body temperature above normal circadian variation as a result of change in thermoregulatory centre, located in anterior hypothalamus

Pathogenesis of fever

Pyrogen-Any substance that cause fever Exogenous pyrogens - derived from outside the patient: microbial products, microbial toxins, or whole microorganisms

They induce host cells, i.e, blood leukocytes, tissue macrophages to produce endogenous pyrogens (e.g., interleukin-1(IL-1).

Endogenous pyrogens increase set point hypothalamic thermoregulatory center through prostaglandin E2.



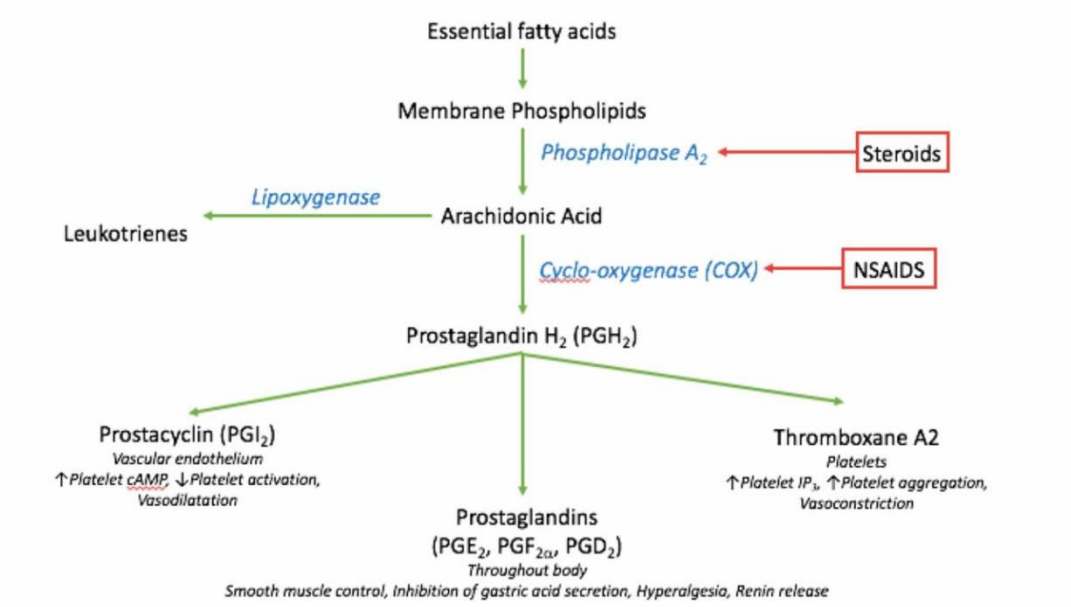


Figure 1. Prostaglandin synthesis.

Acetaminophen

Acetaminophen (also known as paracetamol) has similar analgesic and antipyretic efficacies to the conventional NSAIDS such as aspirin, ibuprofen, or diclofenac. However, it lacks the anti platelet effects of aspirin or the GI side effects associated with NSAIDS. Acetaminophen also has little or no anti-inflammatory properties. Although it has been in use for century, the mechanism of action of acetaminophen remains unknown

Drug classification include:
Analgesics
Sedative –hypnotic
Antacids
Antimicrobial
Stimulants
Depressants
Diuretic

Analgesics drugs

Analgesics are a class of drugs that relieve pain (painkiller) .

Classification :

1. The opioids (or narcotic analgesics), which play a major role in the relief of acute pain and in the management of moderate to severe chronic pain .

2. The NSAIDS and acetaminophen, which are the most widely used analgesic drugs for relieving mild to moderate pain and reducing fever.

3. The triptans (the antimigraine medications), which are specifically designed and targeted for acute and abortive treatment of migraine and cluster headaches

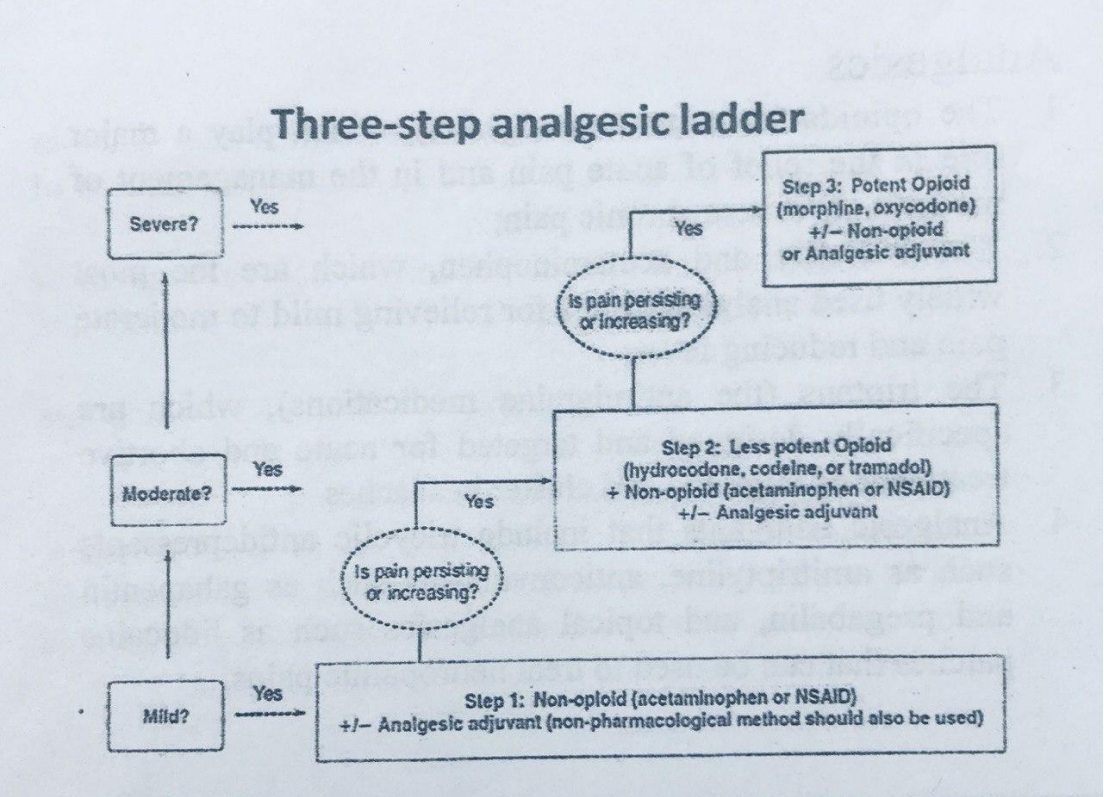
4. Analgesic adjuvant that include tricyclic antidepressants such as amitriptyline, anticonvulsants such as gabapentin and pregabalin, and topical analgesics such as lidocaine patches that can be used to treat .neuropathic pains

Origin of Pain

1- Physiological (nociceptive): is the most common and is often caused by an injury to body organs or tissues. It is further categorized, according to the source of the pain, into cutaneous pains (skin and surface tissues), somatic pains (ligaments, tendons, bones, blood vessels), and visceral pains (body organs and internal cavities).

2- Inflammatory: originates from an infection or inflammation as a result of the initial tissue or organ damage

3- Neuropathic: Neuropathic pain is a very complex, chronic pain, resulting from injury of the nervous systems



OPIOIDS

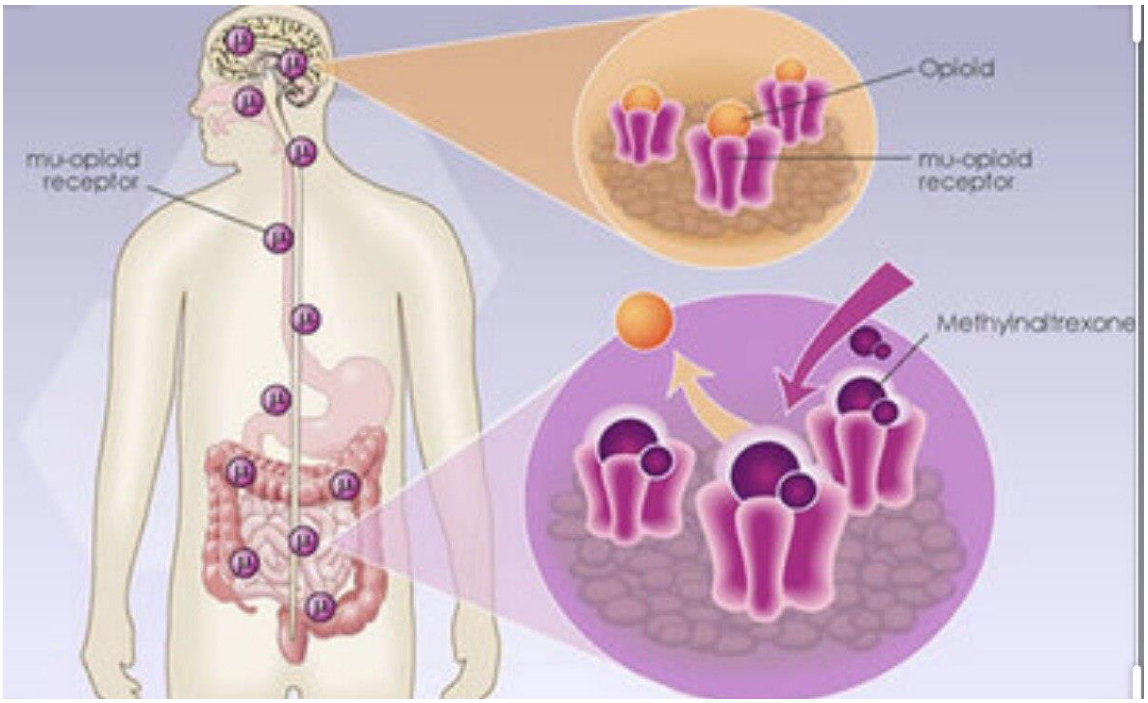
Endogenous opioid peptides , Opioid Receptor

There are three well-characterized families of opioid peptides produced by the body Opioid : enkephalins, B-endorphin and dynorphins

- The first endogenous peptide was termed enkephalin, which was found to be a mixture of the two pentapeptides that only differ in their terminal amino acid (**Met**-enkephalin) and (**Leu**-enkephalin).

Opioid Receptors

- Opioid receptors are distributed throughout the brain, spinal cord, and peripheral tissues (μ, δ, and k)



In general, agonists at the μ-receptor (agonist _ morphine) produce analgesia, respiratory depression, decreased gastrointestinal (GI) motility, euphoria and the release of hormones

Sedative- hypnotic drug

Anxiety is a normal emotion. It’s your brain’s way of reacting to stress.

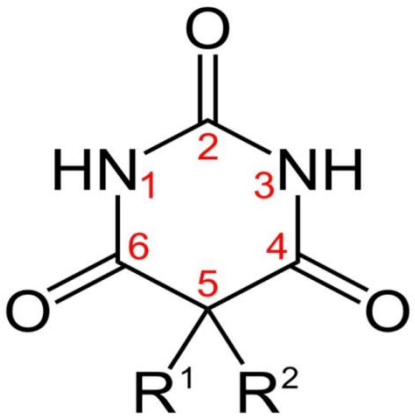
Insomnia is a sleep disorder in which you have trouble falling and/or staying asleep.

Sedative drugs: that calm the patient and reduce anxiety without inducing normal sleep.

Hypnotic drugs: that inițiate and maintain the normal sleep.

Chemical classification:-

1. Barbiturates : is the older sedative-hypnotics consist of acyclic amides and it derivatives of barbituric acid (which is not pharmacologically active). The hypnotic action is characteristic for derivative of barbituric acid which have in the position 5,5 alkyl and aryl.

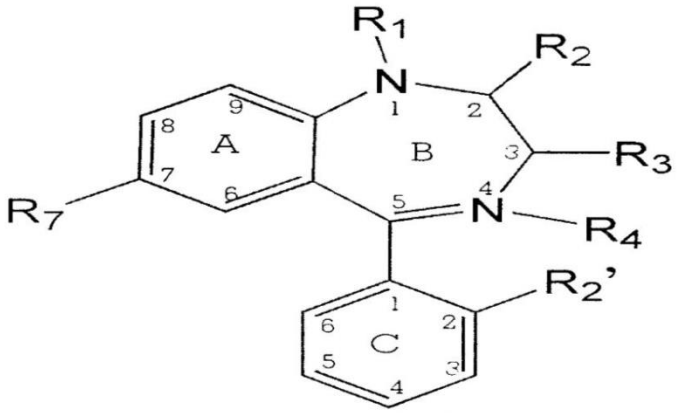


Barbiturates

2-Non-barbiturates: aldehydes and their derivative such as chloralhydrate.

3- Benzodiazepines : it most uses, contain of 7-membered heterocyclic ring structure with substituent in the 7- position is required for sedative- hypnotic activity

-phenyl group at 5-position is promotes the activity and -alkyl group at 3-position decrease the activity and methyl group at 1-position increase the activity.

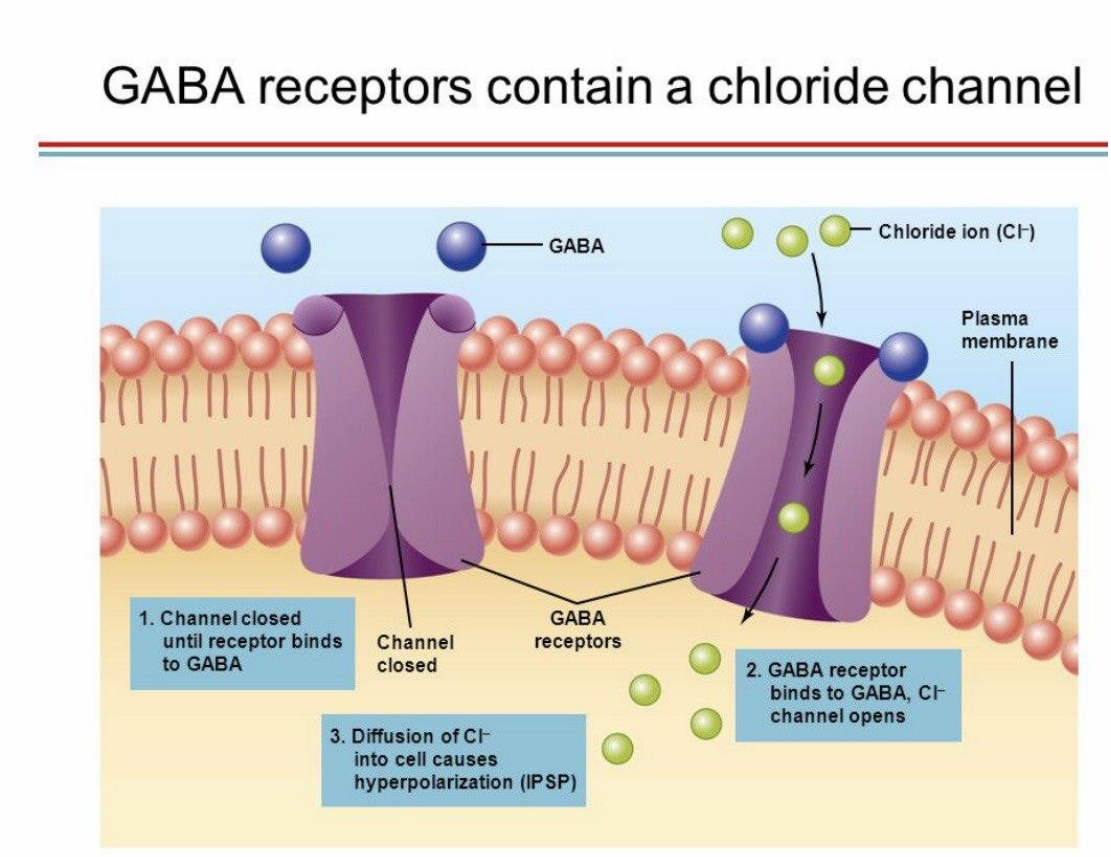


Benzodiazepines

GABA

is an amino acid inhibitory neurotransmitter which acts on the central nervous system. GABA's natural function is to reduce the activity of the neurons to which it binds. It inhibits nerve transmission in the brain, calming nervous activity.

Gamma-aminobutyric acid (GABA) has 2 types of receptors, A and B. When GABA binds to a GABA-A receptor, the passage of chloride, a negatively charged ion, into the cell is facilitated via chloride channels (see the image below). This influx of chloride increases the negativity of the cell . This causes the cell to have greater difficulty reaching the action potential.



Mechanism action of Barbiturates

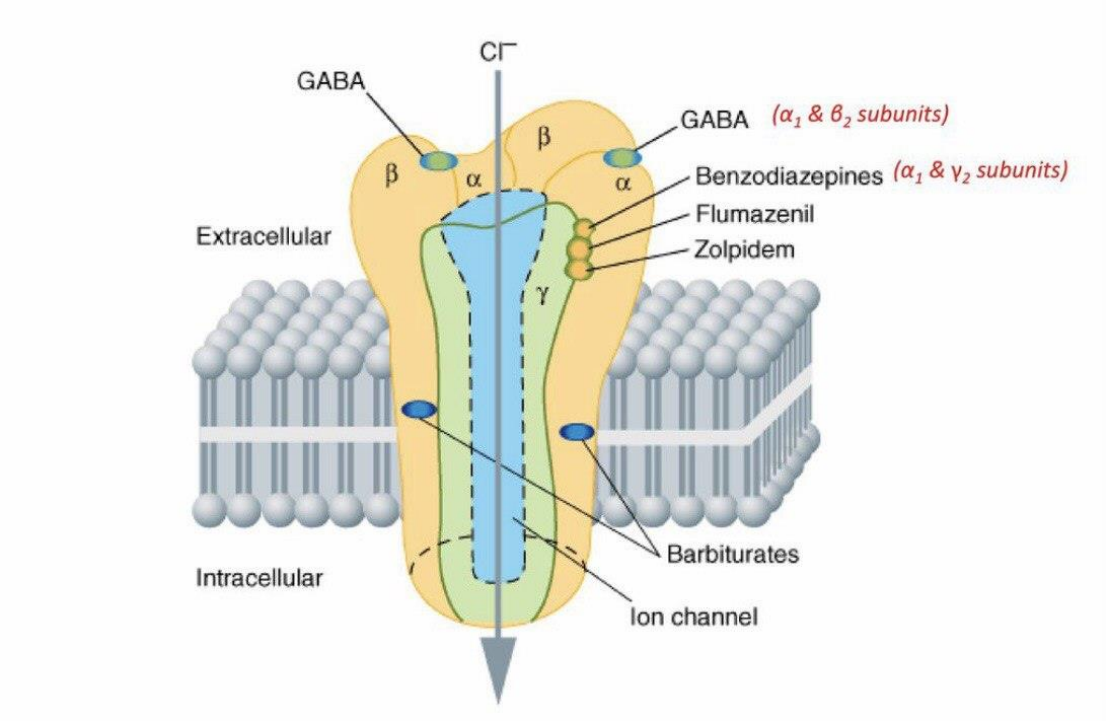
Barbiturates are drugs that act as central nervous. system (CNS) depressants, barbiturates are GABA (gamma amino butyric acid) agonists acting on the GABA a receptor . At lower doses barbiturates simply increase the effect of GABA at GABAA receptor . The GABA channel is a Chloride channel that has five cells at its gate. When barbiturates bind to the GABA channel they lead to prolonged opening of the channel letting in Chloride ions into the cells . This leads to increased negative charge and alters the voltage in the brain cells .

Mechanism action Benzodiazepines

It is widely used as sedative-hypnotics, Benzodiazepines are indirect GABAA agonists that bind to GABA-A receptors → ↑ affinity of GABA to bind to GABAA receptors → ↑ GABA action → ↑ opening frequency of chloride channels → hyper polarization of the neuronal membrane → decreased neuronal excitability

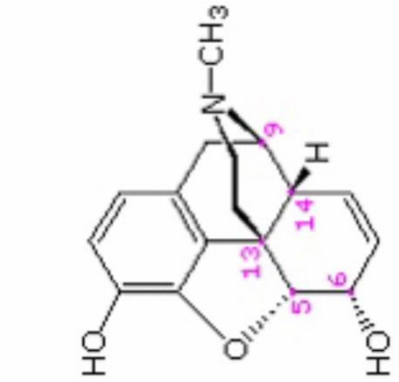
Chloral hydrate

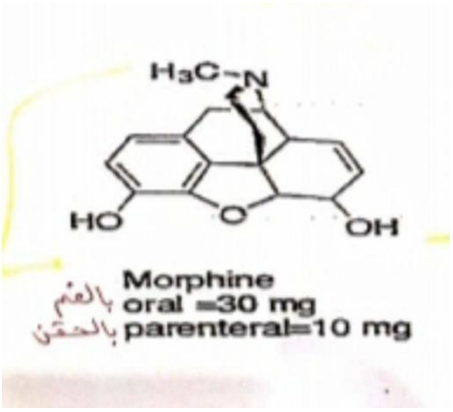
Treating sleep disorders it may be used to prevent symptoms of alcohol , it used to produce sedation or sleep or to relieve anxiety. Chloral hydrate is non-barbiturate sedative and hypnotic, and work by depressing the CNS (brain).


Cl⁻
GABA
GABA
(α1 & β2 subunits)
β
α
β
α
Benzodiazepines
(α1 & γ2 subunits)
Flumazenil
Zolpidem
Extracellular
γ
Barbiturates
Intracellular
Ion channel

Opioids drugs

MORPHINE

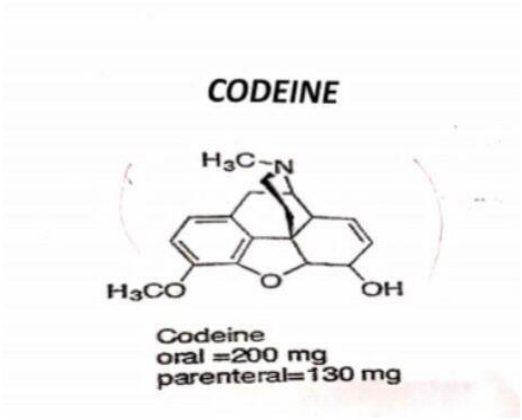




The prototype ligand for the mu -receptor is morphine . Morphine contains 5 chiral centers and has 16 optical isomers (not 32 because of the restriction of C-9 to C-13 ethanamino bridge).

- Morphine is the drug to which all other mu-agonists are compared, it is used as analgesic agent.
- Morphine was isolated from opium.
- Opium is isolated from the opium poppy
- Opium contains over 40 different alkaloids with most alkaloids represented in the following five structures: morphine , codeine , thebaine, papaverine, and noscapine.

CODEINE



- It 3-methyl morphine

- It is used to a limited extent in cough preparations.

- Approximately 5% of codeine is metabolized to morphine via O-demethylation.

HEROIN

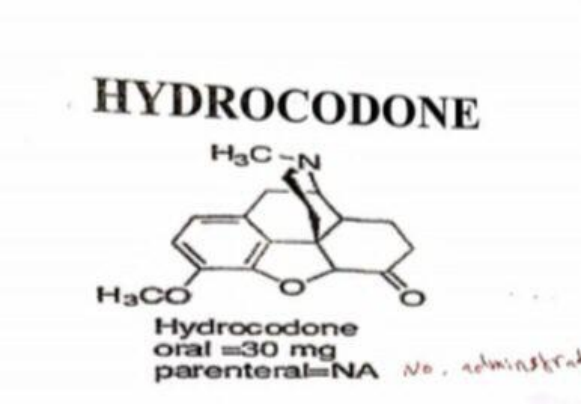
- Heroin is the 3,6 diacetylated form of morphine.

- Heroin can pass through the blood-brain barrier quicker than morphine "and lead to the euphoric "rush.

Hydromorphone

- Hydromorphone, is a synthetic derivative of morphine.
- Reducing the 7,8 double bond of morphine increased the flexibility of the molecule and resulted in a compound with slightly enhanced binding and increased potency (approximately 5 times as potent as morphine)

HYDROCODONE



- The protecte 3-position has better brain penetration, and the 7,8-dihydro-6-keto C ring contributes to the increased binding of the compound to the μ-receptor .
- It is marketed as an antitussive agent, also marketed in combination with acetaminophen or aspirin for the treatment of pain.

OXYCODONE

- Oxycodone is the 14 beta-hydroxyl version of hydrocodone.

- This additional functional group gives oxycodone greater potency (1.5 times orally) than hydrocodone by increasing receptor affinity.

- Oxycodone is marketed in combination with acetaminophen, aspirin, and ibuprofen.

OXYMORPHONE

- Oxymorphone is the 14 beta-hydroxyl version of hydromorphone.

- The addition of the OH group increase its binding affinity at the receptor

Macrolides

The macrolides are class of natural products that consist of a large Macrocyclic lactone ring

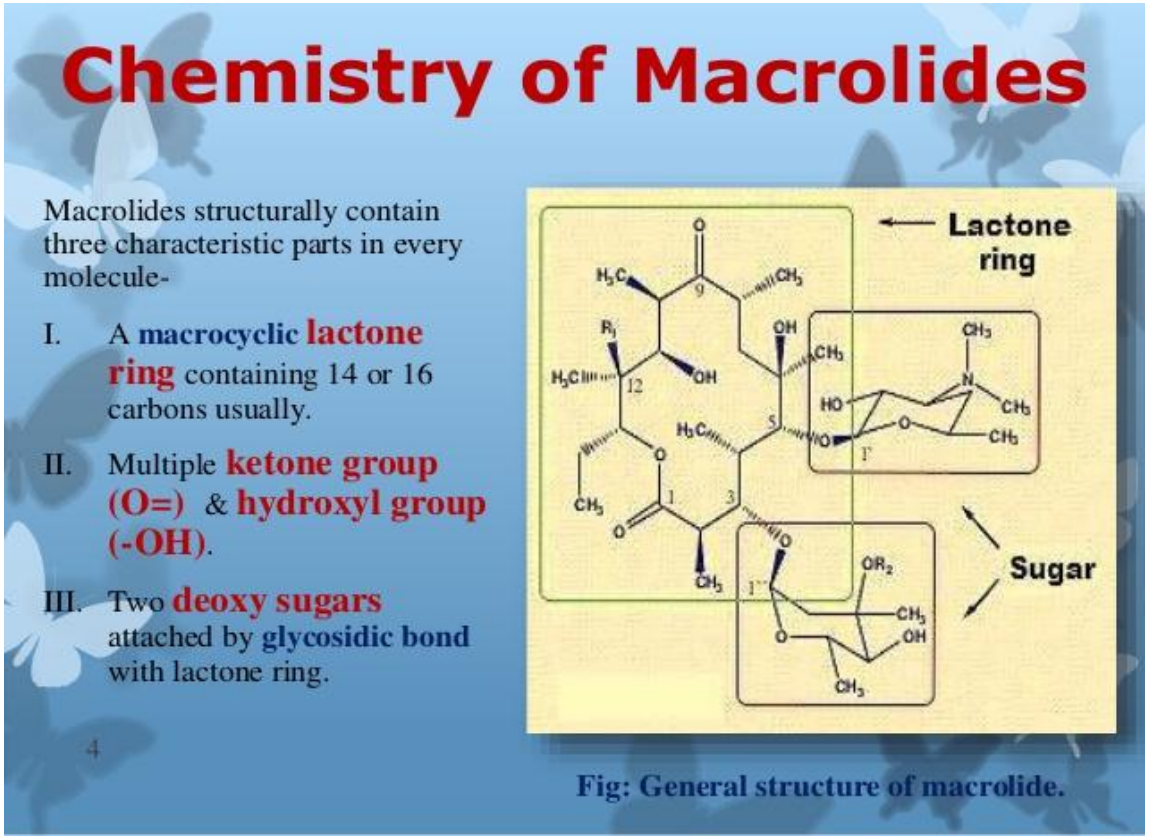


Fig: General structure of macrolide.

Macrolide antibiotic are classify as

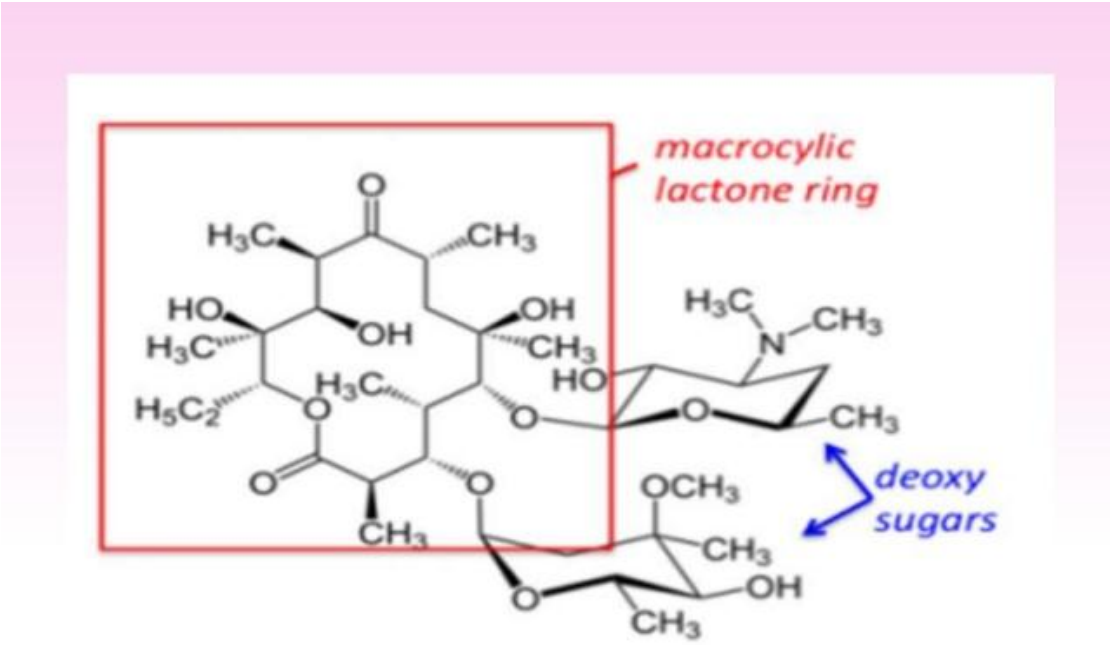
1. Natural Macrolide erythromycin
2. Semisynthetic macrolide Azithromycin ,clindamycin

Erythromycin

Is a broad spectrum macrolide antibiotic with antibacterial activity produced by Streptomyces erythreus

Mechanism of action

Erythromycin diffuse through the bacterial cell membrane and reversibly binds to 50s subunit of the bacterial ribosome. This prevents bacterial protein synthesis also inhibits the translocation of the aminoacyl peptide during protein synthesis



Erythromycin

Azithromycin

Azithromycin is derived from **erythromycin** however, is differs chemically from **erythromycin** in methyl substituted nitrogen atom is incorporated into lactone ring thus making the lactone ring 15 membered

Mechanism of action

It acts as protein inhibitor the translation of m RNA, a vital step in protein synthesis needed for bacterial growth.