Veterinary Pharmacology & Toxicology

- Pharmacology is the science of drugs (Greek: Pharmacon-drug; logos-discourse in).
- Pharmacology is the branch of science which deals with drugs i.e. history, source, properties of drugs and their effects on living systems.
- Properties of drugs –physical and chemical properties.
- Effects on living system – Biochemical, physiological effects, mechanism of action, absorption, distribution, biotransformation, metabolism and excretion.
- In a broad sense, it deals with interaction of exogenously administered chemical molecules with living systems, and any single chemical substance which can produce a biological response is a 'drug'
- Pharmacology deals with the history, source, physical and chemical properties, compounding, biochemical and physiological effects, mechanism of action, absorption, distribution, biotransformation and excretion in healthy living animals, organs or tissues

- **Drug:** The term ***drug*** is derived from the old French word – **drogue** which meant herb. It is broadly defined as any chemical agent other than food that affects processes of living and is used for the prevention, diagnosis and treatment of human and animal diseases.

- A drug has both beneficial as well as harmful effects. There is no completely safe compound unless the compound is pharmacologically inert.

NOMENCLATURE

- **Names of drugs:** Any drug generally has three types of names.

- **Chemical names:** It describes the name as per chemical formula of the compound. It is generally difficult to remember and not suitable for use in prescribing drugs.
  e.g. N-acetyl-p-aminophenol. (paracetamol)
- **Common Name or Generic Name:** This name is given by an official agency as WHO. When this name is included in a pharmacopoeia. It is called official name.
  e.g. Paracetamol
- **Trade Name or Proprietary Name:** It is name assigned by the manufacturer. These are the names given by the manufacturing/marketing agencies. The same drug may be marketed by different Trade names by different companies.
- CROCIN®, CALPOL®, METALGIN®

- **Orphan drugs:**These are the drugs for rare diseases. Development of such drugs may be a costly affair. These drugs are not usually available commercially. Govt. usually provides some help in the development of such drugs, e.g. acetyl cysteine for paracetamol poisoning, 4-methyl pyrazole for methanol poisoning.

- **Essential Drugs:** WHO defines as those drugs that satisfy the health care of majority of the population, they should, therefore, be available at all times in adequate amounts and in appropriate dosage form.

- WHO brought out first list of essential drugs and their dosage form in 1977.
- India gave its National Essential drugs list in 1996 and includes 279 drugs.

Scopes of Pharmacology

- **Pharmacognosy**: It is the science which deals with the identification and characterization of drugs of vegetable or animal origin. Therefore, it includes the study of sources of drugs.

- **Pharmacodynamics**: It refers to the study of response of an organism to action of drugs in absence of disease. This includes the biochemical and physiological effects of drugs and their mechanism of action. We study the site of action
  - Biochemical constituents involved
  - Biochemical reactions affected
  - Changes in physiology of an organ or system.
  - Receptor participating in the action of drugs.
- Therefore, as a whole, all aspects of a drug that it does to the body are studied in pharmacodynamics.

- **Pharmacokinetics**: deals with the absorption, distribution, biotransformation and excretion of drugs by living organisms. Various processes related to time and travel of drug in the body starting from administration of drug to its excretion from the body are studied in this.
- **Pharmacotherapeutics**: The study of the therapeutic uses and effects of drugs.
- **Therapeutics**: is a term describing treatment of diseases in general and includes use of drugs, surgery, radiation, behavioural modification and other modalities.
- Types of therapeutics:
- **Rational therapeutics:** logical use of drugs for the treatment of disease. Here both the nature of disease and the action of drug on the disease process are well understood.
- **Emperical therapeutics:** When the knowledge of disease process or the action of the drug on the disease process is incomplete. Here the treatment is based on experience only.
- **Symptomatic therapeutics:** When treatment is based on symptoms, e.g. use of analgesics in painful conditions.

- **Chemotherapy**: is a branch of pharmacology which deals with the drugs/chemicals that selectively inhibit or destroy specific agents of disease such as bacteria, viruses, fungi and other parasites. Chemotherapy is based on the principle of selective toxicity. This term has been extended to the use of drugs in the treatment of neoplastic diseases.
- **Toxicology**: Toxicon = poison, Logos = study
- It is concerned with the study of toxic or poisonous effects of chemicals/drugs in body system.

- **Posology**: It is concerned with the study of dose and dosage of drugs.
- **Dose**: A dose is the amount of drug to be administered at one time to produce the desired therapeutic response in the patient.
- **Dosage**: refers to the determination and regulation of doses.

- **Metrology**: Study of weights and measures as applied to preparation and administration of drugs.
- **Pharmacy**: It is a separate and complimentary health-care profession concerned with collection, preparation, standardization and dispensing of drugs generally for the immediate use of patients.
- **Materia medica:** It involved pharmacy, posology and pharmacognosy and now it has been replaced by pharmacology.
- **Pharmacometrics**: refers to the evaluation and quantitative assessment of desirable and undesirable effects of drugs. It is important branch of pharmacology related to drug development programme.
- **Pharmacoepidemiology**: The study of the use and effects of drugs in large no. of people or animal population. It helps in understanding the efficacy and safety of new drugs after they are released for the treatment of patients.

- **Pharmacoeconomics**: The analysis of the cost of drug therapy to the health care system and the society.
- **Pharmacovigilance**: the process of identifying and responding to the issues of drug safety through the action of drug effects, usually adverse effects. It is a short of post marketing surveillance and relies on voluntary reporting, prescription monitoring, medical records and statistical studies in the population.
- **Pharmacogenetics**: Pharmacogenetics is the study of how people's genetic makeup affects their responses to drugs.
- **Pharmacogenomics**: Pharmacogenomics uses information about a person's genetic makeup, or genome, to choose or develop effective, safe medications and doses. This new field combines the science of how drugs work, called pharmacology, with the science of the human genome, called genomics.

Sources of Drug Information

- **Pharmacopoeia**: is an official code containing a selected list of the established drugs and medicinal preparations with description of their physical and chemical properties and tests for their identity, purity and potency.
- Indian Pharmacopoeia (I.P.) – published by Ministry of Health and Family Welfare, GOI.
- **Drug Reference Books – Formularies**
- Compiled by various pharmaceutical associations and revised periodically like pharmacopoeias. E.g. British National Formularies (B.N.F.)
- Extra Pharmacopoeia (Martindale): generally deals with drugs and medicaments in current use through out the world. First edition was compiled by William Martindale in 1883.
- Merk Index: first published in 1889

History

- The oldest writings of medicinal agents belonged to:
  - Ancient INDIA (3000 BC)
  - Chinese (2700 BC)
  - Egyptian literatures (2000 BC)

- AYURVEDA The oldest system of medicine, recommends herbal remedies and animal origin products for treatment of disease in man and animals.
- Bhagvan Dhanvantari: Lord of Ayurveda
- Charaka , Sushruta and Vaghbata pioneered in Ayurveda. Nakula , one of the Pandavas followed sound principles of animal husbandry and veterinary science
- Chinese Herbal Formulary (Materia Medica) - “ Pen Tsao ” written by Emperor Shen Nung (2700 BC).

- **Kahun papyrus**, which was written about 2000 B.C., deals with Vety. Medicine and uterine disease of women and contain no. of prescriptions.

- **Ebers Papyrus**, is the papyrus discovered by Ebers in 1872, was prepared in 1500 B.C. It is a collection of drugs prevalent at that time in Egypt with classification and uses. It contains 829 prescriptions including castor oil, pomegranate bark and opium.

- Hippocrates (460– 375 B.C.): Ancient Greek Physician - Father of Medicine
- **Theophrastus (380-287 B.C.)**, systematically classified medicinal plants on the basis of individual characteristics. He is known as **Father of Pharmacognosy.**
- Dioscorides, a surgeon, compiled **the first Materia Medica**. This consisted of six volumes and describe about 600 plants.
- Valerius Cordus (1514-44): A German compiled the **first pharmacopoeia**.
- **Oswald Schmiedeberg (1838-1921)**: **Father of Pharmacology**.
- **John J. Abel (1858-1938)** – Father of Pharmacology in U.S.A.
- **Father of Modern Pharmacology** is **Sir James Black**. He discovered beta blockers and H_2-histamine blockers (antagonists).
- **Sir Col. Ram Nath Chopra (1882-1973)** – **Father of Indian Pharmacology.**

Sources of Drugs

- Natural: Plants, Animals, Microorganisms, Minerals
- Synthetic: Synthetic, Semisynthetic, Gene therapy, Biopharmaceuticals

Plant Sources

- **The ancient or original sources of drugs are the plants collectively known as medicinal plants. All parts of the medicinal plants have therapeutic values.**

Root	**:**	**Sarpgandha**
Rhizome	**:**	**Ginger, Haldi**
Bark	**:**	**Cinchona, Catechu, Acacia**
Leaves	**:**	**Atropine, Cocaine, Physostigmine**
Flowers	**:**	**Digitalis, Chrysenthemum**
Fruits	**:**	**Papaya, Anise**
Seeds	**:**	**Nux vomica, Kali mirchi, Methi**

- Animal Sources
- Hormones : Oxytocin, Gonadotrophins Insulin, Thyroxine
- Vitamins : Cod or shark liver oil (Rich sources of Vitamin A & D)
- Antisera : Antisnake venom, Canine distemper antiserum etc.
- Others : Heparin, Liver extract, Immunoglobulins, Blood/Plasma.

- Microbial Sources
- Fungi/ Actinomycetes: Sources of antibiotics (penicillin, streptomycin, and Bacteria gentamicin, neomycin etc.)
- Yeasts : Dried yeast as source of Vitamin B-complex
- Viruses/ Bacteria : Preparation of vaccines :

- Mineral Sources
- Antacid : Magnesium oxide, Sodium bicarbonate
- Purgative : Magnesium sulphate
- Expectorant : Potassium iodide
- Diuretic : Potassium nitrate
- Haematinic : Ferrous sulphate
- Hypothyroidism : Iodine
- Mineral oils : Liquid paraffin

- Synthetic Sources
- Majority of the current day dugs are from synthetic source.
- Antipyretics, Barbiturates, Tranquillizers, Anti-inflammatory drugs, Anaesthetics, Antiseptics Antiprotozoals, Antihistamines etc

- Semi-Synthetic Sources
  - Agonists and antagonists of morphine
  - Dihydrostreptomycin – from streptomycin
  - Semi-synthetic penicillins– from penicillin.

- Gene Therapy: It means prevention or treatment of disease through manipulation of gene function.
- It is insertion of specific genes (therapeutic genes) exogenously into the animal cells
- Recombinant DNA technology forms the basis of synthesis of therapeutic genes
- Biopharmaceuticals
- Functional human peptides: ADH, Oxytocin, GnRH, ACTH, TSH/TRH, Calcitonin, Insulin, Somatostatin, Growth hormone etc.
- Enzymes/ Peptides : Streptokinase, Asparaginase, DNAase, Erythropoietin, Clotting factors, Interferons, Monoclonal antibodies, Vaccines etc

Active Principles

- Alkaloids: Basic, nitrogenous substances.
- Insoluble in water, less soluble in alcohol, soluble in ether, chloroform and oils.
- Form water soluble crystalline salts with acids.
- Mostly derived from plants. Exception Epinephrine (obtained from adrenal medulla).
- Atropine: Atropa belladona
- Reserpine: Rauwolfia serpentina
- Morphine: Papaver somniferum

- Glycosides : Compounds containing a sugar (glycone) and a non-sugar (aglycone or genin) part joined together through an ester linkage. So, these are sugar esters.
- The pharmacological action resides in the aglycone/ genin.
- Glycone part determines solubility, tissue permeability and duration of action of aglycone.
- Glycosides do not form salt with acids. On acid, alkali or enzyme hydrolysis, the glycosides break into two parts i.e. glycone and aglycone.

Category	Glycoside	Source
Cardiac glycosides	Digitoxin, Gitoxin, Digoxin & Gitalin	*Digitalis lanata/ purpurea* (leaves)
	Strophanthin	*Strophanthus gratus* (seeds)
	Ouabain	*Urginea maritima* (bulb)
Cyanogenic glycosides	Amygdalin	*Prunus amygdalus*
	Dhurrin	*Sorghum vulgare*
	Linamarin	*Linum usitatissimum*
Miscellaneous glycosides	Mangeferin (Hepatoprotective/ Antioxidant)	*Manfifera indica* (Leaves, fruit)
	Swertiamarin (Cardiotonic/ Hepatoprotective)	*Swertia chirata* (Stem, leaves)

- Oils These are of two types: Fixed oils and Volatile oils.

- Fixed oils: These are glycerides of oleic, palmitic and stearic acids.
- Many fixed oils have food value (i.e. cooking oils). e.g. corn, ground nut, sunflower, mustard, soybean, coconut, palm oils etc.
- Cooking oils are pharmacologically inert and serve as vehicle for fat soluble vitamins
- Castor oil: Ricinus communis - purgative
- Linseed oil: Linum usitatissimum - Demulcent, vehicle, purgative
- Croton oil: Croton tiglium - Drastic purgative

- Volatile oils: Also known as Aromatic, Essential, Ethereal or Flavouring oils.
- These have no food value.
- These are volatile and emit characteristic odour while evaporation.
- Most of these have medicinal values.

Volatile oils	Source	Pharmacological action
Eucalyptus oil	*Eucalyptus globulus*	Expectorant, Rubefacient
Ginger oil	*Zingiber officinale*	Stomachic, Carminative
Turpentine oil	*Cedrus deodara*	Counterirritant, Astringent
Clove oil	*Eugenia caryophyllus*	Analgesic, Antiseptic
Pippermint oil	*Mentha piperata*	Antiseptic, Antiemetic
Asafoetida oil	*Ferula foetida*	Carminative, Anthelmintic

- Resins: These are brittle,amorphous compounds formed from oxidation or polymerization of terpene components of volatileoils.
- These are insoluble inwater, soluble in alcohol and other organic solvents.
- Form soap with alkali.
- Colophonium, Podophylline

- Oleoresins:These are mixtures of volatile oils, gums and resins. E.g. Asafoetida
- Balsams: These are also considered as oleoresins. These contain an aromatic acid, resin and volatile oil.
- Balsam of Tolu, Balsam of Peru

- Gums: These are polysaccharide secretory products of plants capable of forming thick mucilaginous colloids when mixed with water.
- Gums are pharmacologically inert with no systemic effects, but exert demulcent action on surfaces and are mainly used as suspending or emulsifying agents in pharmacy
- Agar, Gum acaia

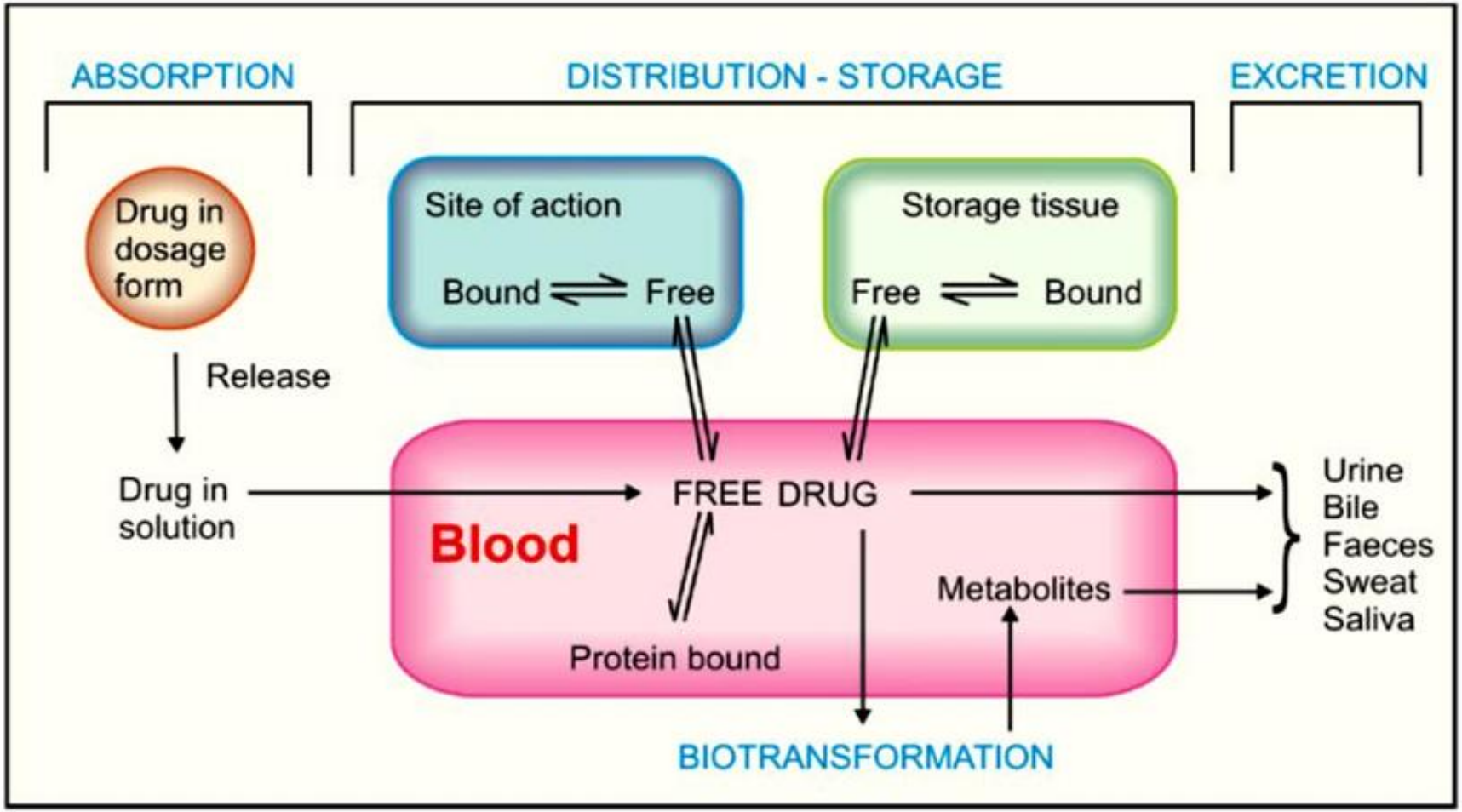
- Saponin: These are non-nitrogenous substances soluble in water which form foam or froth when shaken with water.
- Saponins upon hydrolysis, split into a sugar and a non-sugar (sapogenin), hence considered as a sub class of glycosides
- Examples– Quillaris, Senega etc.

- Tannins: These are water soluble, non-nitrogenous plant constituents having characteristic astringent action (precipitation of protein) upon mucous membrane.
- These exert a protective action on the mucosa (GI) against irritants
- E.g. catechu

Pharmacokinetics

- Pharmacokinetics is the quantitative study of drug movement in, through and out of the body .
- Study of absorption, distribution, metabolism and excretion of drug
- How the body affects the drug

- Pharmacokinetic (PK)processes
- Four pharmacokinetic properties determine the onset, intensity, and the duration of drug action.
- Absorption: First, absorption from the site of administration permits entry of the drug (either directly or indirectly)intoplasma.
- Distribution: Second, the drug may then reversibly leave the bloodstream and distribute into the interstitial and intracellular fluids.
- Metabolism: Third, the drug may be biotransformed by metabolism by the liver or othertissues.
- Elimination: Finally, the drug and its metabolites are eliminated from the body in urine, bile, or faeces


ABSORPTION
DISTRIBUTION - STORAGE
EXCRETION
Drug in dosage form
Release
Drug in solution
Site of action
Bound ⇌ Free
Storage tissue
Free ⇌ Bound
Blood
FREE DRUG
Protein bound
Metabolites
BIOTRANSFORMATION
Urine
Bile
Faeces
Sweat
Saliva

- pharmacological action/effects depend upon concentration of drugs at the target tissue.
- The time-course of a drug's action generally reflects time course of the rise and fall of its concentration at the target tissue.
- The concentration of any drug at any point of time after its administration in the body depends upon two processes.
  - **Translocation of drug molecules**: movement of molecules to different parts of the body from its site of drug administration. It comprises of absorption, distribution & excretion.
  - **Chemical transformation of drug molecules/Biotransformation of drug molecules**: results in formation or disappearance of active drug molecules.

Translocation of drug molecules

- By bulk flow transfer (i.e. in the blood stream) – it provides very fast long distance distribution system for all solutes irrespective of their chemical nature.
- By diffusional transfer (i.e. molecule by molecule transfer or short distance transfer)
- The transfer of drug molecules occurs across cell membrane barriers that separates the various aqueous compartments of the body
  - The drug is present in bound and free form in these compartments except fats (where the drug is in free form).
  - The free form of drug is able to move between compartments and its movement and availability at the site of action depends upon
    - Molecular size and shape
    - Degree of ionization
    - Relative lipid solubility of its ionized and nonionized forms.
    - Binding to serum/tissue proteins.

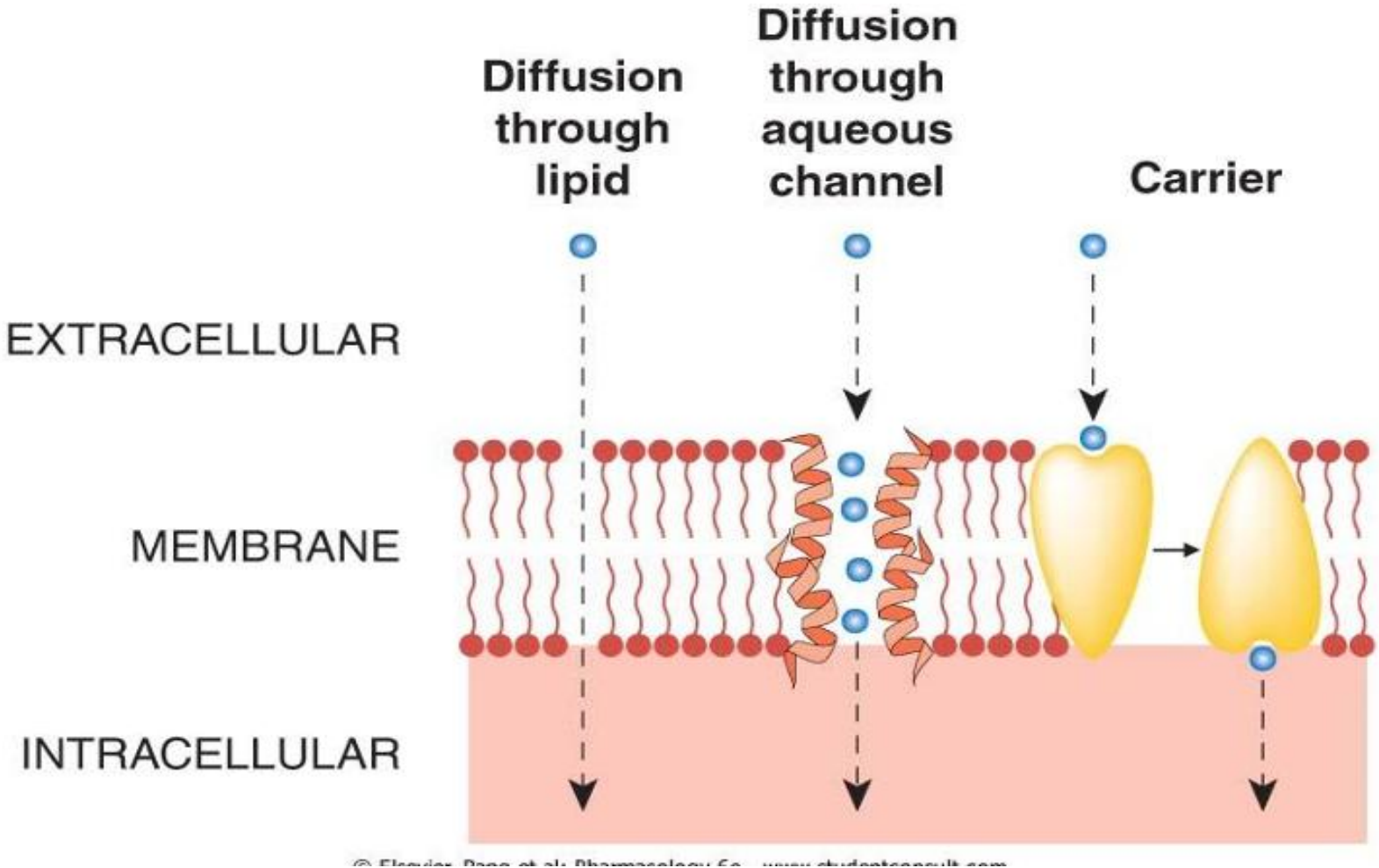
- Structure of Cell membrane:
  - **Bilayer of amphipathic lipids** i.e. contains both hydrophilic and hydrophobic portions. The hydrophilic heads are oriented outwards and hydrophobic hydrocarbon chains oriented inwards to the centre of the bilayer to form a continuous hydrophobic phase.
  - **Individual lipid molecule** in the bilayer moves laterally and can organize with cholesterol molecule and provide fluidity, flexibility, organization, high electrical resistance and relative impermeability to highly polar molecules.
  - **Membrane protein embedded in the lipid bilayer** serve as receptor, ion channels or transporters to transduce electrical or chemical signaling pathways and provides selective targets for drug action.

Mechanism of drug transport

- Simple transfer: Drug moves from higher concentration to lower concentration. Further of two types:
  - Passive membrane transport or simple diffusion or passive diffusion
  - Filtration
- Facilitated transport: Drug transport is facilitated by net expenditure of energy or with a carrier molecule or both. Further of three types.
- Active transport
- Facilitated diffusion
- Pinocytosis

- Passive Diffusion: The drug diffuses across the membrane in the direction of its concentration gradient, the membrane playing no active role in the process.
- Most important mechanism for majority of the drugs.
- Lipid soluble drugs: Diffuse by dissolving in the lipoidal matrix of the membrane, the rate of transport being proportional to lipid : water partition coefficient of the drug.
- A more lipid soluble drug attains higher concentration in the membrane and diffuses quickly.
- Also, greater the difference in the concentration of the drug on two sides of the membrane, faster is its diffusion.

- Filtration (Diffusion through aqueous channel)
- Passage of drugs through aqueous pores/channels is called as filtration.
- Majority of cells have very small pores (4 Å)
- Very small particles (Mol. Size <100) or polar and nonpolar substance are filtered alongwith bulk flow of water occurring due to hydrostatic pressure or osmotic differences.
- Capillary endothelial cells (except those in brain) which are separated by slits that serves as pores and are nearly 40Å size. Many large molecules can filter through them.



Active transport

- Active transport is energy dependent and carrier mediated i.e. transport across the membrane barrier takes place with the help of a carrier molecule and a net energy is utilized in this process as the movement of molecule occurs across the concentration or electrochemical gradient i.e. from lower concentration to higher concentration or up-hill movement.
- This process is structure specific i.e. carriers possess special affinity for and transport drugs of specific chemical structures only.
- Drugs of similar structure compete for a particular carrier molecule.

- Types of active transport:

a) Primary active transport: Only one substance is carried by the carrier molecule against its concentration gradient.

b) Secondary active transport: Two substrates are carried by a carrier molecule. One is driving solute (Na^+, K^+ or Ca^{+2}) which is transported along its concentration gradient and the other is actual substrate which is transported against its concentration gradient.

i) When the direction of transport of driving solute and actual substrate is same the process is called cotransport or symport. eg. Na^+ cotransport of glucose or a.a. in GIT mucosa.

ii) When the direction of transport of the two is opposite then the process is called counter transport or antiport. e.g. Na^+ counter transport of H^+ions.

- **Facilitated diffusion:**
- It is a carrier mediated passive transport that operates along the concentration gradient (down hill movement)
- Since the driving force is concentration gradient so it does not require energy.
- proceeds more rapidly then simple diffusion and can translocate non diffusible substances.
- Structure specific and saturable process like active transport and is subject to competition between agents having similar structures.
- It is not a major mode of drug transport e.g. Glucose transport in R.B.C.s, Intestinal absorption of Vit B_1

- **Pinocytosis:** operates for agents having molecular mass more than 1000 Da.
- involves engulfing extracellular materials within a segment of the cell membrane to form saccules or vesicles.
- Vesicles are pinched off intracellularly and release the engulfed particles.
- Like active transport, it also requires energy, shows low order structure selectivity and is a competitive and saturable process.
- It operates for uptake of macromolecular nutrients like fats, starch, proteins, fat soluble vitamins (A,D,E & K) and drugs as insulin and poliovaccine
- It contributes little to transport of most drugs.

ABSORPTION

- process of movement of unchanged drug from its site of administration to the blood stream i.e. central compartment.
- The rate and extent (fraction) to which a total administered drug reaches the central compartment is called bioavailability.
- It is expressed in fraction or in per cent values i.e. 0.2 or 20%.
- The bioavailability of intravenously administered drug is 100%.

Factors affecting absorption of drug

- The rate of drug absorption is determining factor for duration and intensity of drug action.
  - A drug absorbed completely may fail to show therapeutic response if minimum effective conc. is not reached at the site of action due to slow rate of absorption.
  - A rapidly and completely absorbed drug attains the therapeutic level easily to attain its pharmacological effect.
- Physico-chemical properties of drug – Oil: water partition coeff. (lipid solubility), pKa and mole size are important. Lipid soluble unionized drugs are rapidly absorbed.
- Nature and type of dosage form: This affects the rate of dissolution i.e. the release of drug from pharmaceutical dosage form to the aqueous phase at the absorptive site.
- The absorption of drug from various dosage form decreases in the following order – solutions > emulsions > suspensions > capsules > tablets > sustained release products.
- Concentration and volume: High dose/conc. and large volume develop conc. gradients, therefore, absorbed at a faster rate.

- Blood flow to the site of administration: More the perfusion of absorptive tissue more will be absorption as the drug is removed from other side of memb. readily and a conc. gradient is maintained.
- Area of absorbing surface: Larger the surface area more will be the absorption.
- Route of administration: Absorption of drug is in decreasing order for the following routes of administration i.p. > i.m.> s.c. > oral.
- Disease states: Diseases affecting acid-base balance of body fluids and tissue perfusion of absorptive site affects absorption of drugs.

Site of drug administration

- For a drug to be absorbed, it should be placed at a proper site, called the site of drug administration.
- The different sites may be: Skin/dermal site/m.m., Subcutaneous tissue, Sublingual, GIT, Muscular tissues, Veins, heart, directly at the site of action.
- The process occurring between the administration of a drug and the production of its effects may be divided into following three phases.
- Pharmaceutical phase: Disintegration of dosage form & Dissolution of drug
- Pharmacokinetic phase
- Pharmacodynamic phase

Routes of Drug Administration

Local (Topical) Routes

1. Skin
2. Mucous Membranes

Systemic

1. Oral
2. Sublingual
3. Rectal
4. Cutaneous
5. Inhalational
6. Nasal
7. Parenteral
   - (i) S.C.
   - (ii) I.M.
   - (iii) I.V.
   - (iv) I.D.
   - (v) I.P.

Factors determining route of drug administration

- Physico-chemical properties of the drug:
- High lipid solubility – increased absorption from all routes including GIT.
- Polar/ ionized drug –not absorbed from GIT and administered by parenteral routes.
- Formulation of drug –Suspension and emulsion are not suitable for i.v. route.
- Nature of drug – Peptides & acid labile drug not suitable through oral route.
- Onset of action required -

  Oral/S.C. – slow absorption – slow onset of action

  i/v – immediate action so route of emergency
- Type of response required:- Type of pharmacological action depends upon route of administration

  Magnesium sulphate – when administered through i.v. → m. relaxation

  – when administered through oral route → purgation

- Site of desired action –
- Topical /Local route → Localized conditions
- Parenteral routes → Systemic/generalized conditions.
- Biotransformations:- Drugs with short half lives (e.g. dopamine) should be administered by i/v infusion.
- Condition of patients – Oral route not suitable for unconscious, uncooperative or vomiting patients.
- Parenteral routes are less preferred against GI Parasites.

Administration for Local Effects i.e. Topical application

- **Skin:**

1. Bath / dip: The drug is applied in the form of bath or dip. Baths are generally given for their local effects upon the skin in cutaneous disorders. Dips are generally used in small animals where the whole animal is immersed for a brief time in medicated fluid particularly insecticidal fluid.

2. Inunctions: Inunction is the application of a semisolid or liquid drug preparation on the surface of body with smearing or rubbing. Drugs in the form of ointments, liniments, lotions, tinctures are applied on the affected part.

3. Dusting powders: Powders of solid drugs are applied for superficial skin conditions or in body cavities for surgical conditions.

4. Topical – on skin or m.m. as powders, ointment, lotions, liniments.

Liniments (embrocations): Semi-liquid preparations prepared in oily or alcoholic solution, with rubefacient or analgesic intentions, are rubbed into unbroken skin.

- **Mucous membrane**:

i) Mouth m.m. as mouth wash or throat paint
ii) Eye as ointment or lotion
iii) Ear as Lotion
iv) Nostrils as nasal drops
v) Intramammary as i/mam preparation for mastitis.
vi) Intrarectal as enema or suppositories.

  - Intra uterine/Intravaginal – Pessaries, solutions for Irrigations, infusions.
  - Microinjections/Microiontophoretic administration – directly in individual neurons.

- **Systemic Administration**: Broadly divided into two categories

1. Enteral / Oral and related route of administration - oral, rectal, sublingual, inhalation,
2. Parenteral route of administration – Injections (Par-beyond, enteral – intestinal)

* Enteral / ORAL and Related Routes

i) Oral administration

ii) Rectal administration

iii) Sublingual administration

iv) Inhalation

Oral administration

- Absorption occurs through gastro-intestinal mucosa.
- Before entering systemic circulation – drug undergoes three events – i) release from dosage form, ii) transport across the GI mucosal barrier and iii) Passage across the liver.

i) Release from dosage form – rate of drug dissolution directly affects the rate of drug absorption. It can be enhanced by administering drug in salt form and by decreasing particle size i.e. micronization.

ii) Transport across the GI mucosal barrier is effective when

  - the drug is dissolved in GIT lumen
  - the drug is stable chemically or enzymatically
  - the drug is lipid soluble and not completely ionized.

- Cephalexin (Cephalosporin) – acid resistant → used orally
- Cefazolin/cephalothin – acid labile – not used orally
- Aminoglycosides (Gentamicin, Streptomycin) low solubility in lipid – poorly absorbed from GIT
- Small intestine is the principle site of drug absorption: extensive area and rich blood supply.

The pH Partition Hypothesis

- Most drugs are weak organic acids or bases and **exist in solution as both non-ionized and ionized forms**.

✓ **Non-ionized form:** Lipid-soluble & diffusible.

✓ **Ionized form:** Relatively lipid insoluble and poorly diffusible.

- For an effective diffusion, the drug should be soluble in lipid phase and aqueous phase i.e. a perfect lipophilic – hydrophilic balance (LHB) should be there.
- Highly hydrophilic drugs are poorly diffusible because of their inability to cross lipid membrane
- Extremely lipid soluble drugs are poorly diffusible because they are totally insoluble in aqueous body fluids and so cannot gain access to surface of cell.

- For ionic compounds, the concentration depends upon the electrochemical gradient of unionized fraction and on differences in pH across the membrane which may influence the degree of ionization of molecule. This can be explained by the pH - partition hypothesis
- Most of the drugs are weak acids or bases that are present in solution as ionized and non ionized species.
- Drugs in non ionized form can diffuse across the cell membrane as they are more lipid soluble.
- The degree of ionization depends upon the pKa of the drug and pH gradient across the membrane.
- The pKa of a drug is the pH at which half the drug is in ionized form.

- The relative amount of ionized and unionized drug in the body fluid at a particular pH and the per cent of drug ionized at this pH can be determined by Handerson-Hasselbalch equation.
- pKa – pH = log [concentration of unionized drug / concentration of ionized drug]
- For acidic drugs, when the pH of environment is lesser than pKa then unionized fraction is more than ionized fraction and more absorption occurs.
- For weak basic drugs, when pH of environment is more than its pKa value then unionized fraction is more and hence absorption of such drugs is more in intestines than stomach.

- Lipid soluble parentrally administered organic bases diffuse from circulation into rumen and ionized in acidic pH of ruminal fluid and are trapped in rumen, called as ion trapping.
- **Ion Trapping:** At steady state, an acidic drug will accumulate on the more basic side of the membrane and a basic drug on the more acidic side.
- Blood from intestinal tract passes to liver where some drugs are metabolized and some stored and released slowly. This is called as First Pass Effect.

Distribution of drugs

- Distribution of drug may be defined as a process by which drugs following absorption or systemic administration into blood stream, reversibly leave the blood stream and enter the extra vascular fluid and tissues.
- By this process the drug is transported to their site of action, to organ of metabolism and excretion and to other sites.

- Various factors which determine drug distribution are:
- Physico-chemical properties of the drug
- Cardiac output and regional blood flow
- Capillary permeability and membrane permeability
- Plasma protein binding and tissue protein binding
- pH partition
- Fat: water partition
- Specialized transport system in particular tissues
- Diseased states
- Distribution in specialized compartments

- **Physico-chemical properties of the drugs:**
  - Mol. Wt. of the drugs: Drugs of 500-600 Da size can easily cross capillary membrane to penetrate into ECF.
  - Lipid solubility: Lipid soluble unionized drugs can easily cross plasma membrane barrier.
  - A drug having high lipid: water partition coefficient is partitioned more in body fat e.g. Thiopentone with coeff. of 10 is accumulated in body fat to the 75% of the drug administered. This leads to no pharmacological action rather body fat acts as a reservoir for such drugs and drugs remain lodged there for longer duration.
  - pH partition: more ionized lesser will be lipid solubility.

- **Cardiac output and regional blood flow:** It affects tissue perfusion. More the tissue perfusion more will be drug distribution. Therefore, initially the drug is distributed into well perfused organs – Liver, kidney, brain, lungs and heart.
- **Capillary permeability and membrane permeability**

Plasma protein binding and tissue protein binding

- Free form of drug is usually dissolved in plasma water and is pharmacologically active, diffusible & available for metabolism and excretion.
- Protein bound drug remain in blood.
- Plasma protein binding affects distribution and access of drugs to the site of action.
- The extent of binding, ie. Ratio of bound form: free form, is fixed for a particular drug and an equilibrium is maintained between free form and bound form.
- Acidic drugs and anionic compounds bind to plasma albumin. Albumin constitutes more than 50% of total protein.

  - Basic drugs and cationic compounds bind to 1- acid glycoprotein.

  - Binding to other plasma proteins –lipoproteins and globulins is minor

  - Binding may also be with blood components e.g. phenytoin and pentobarbitone bind to Hb.
- Drug-protein complex serves as a circulating reservoir of potentially active drug.

- **Mechanism of protein binding**: Usually drugs bind with proteins by 3 broad mechanisms.
  - Covalent binding: Such complexes are stable and cannot dissociate. Further distribution of drug is not there as the complex cannot dissociate.
  - Noncovalent binding: Drug-protein complex is dissociable, therefore, important in distribution of drugs. Further of three types.
  - Ionic interactions or electrostatic attraction, occurs between two oppositely charged ions on a drug and a protein.
  - Hydrogen bonds.
  - Van der Waals forces.
  - Hydrophobic interactions: This occurs between two nonpolar groups with exclusion of water molecule between them.

- Binding to tissue proteins:
- Binding of drug to one or more of several tissue components can be there which results in accumulation of drug in tissues.
- The binding of drugs to tissue proteins may be reversible or irreversible.
- The irreversible binding generally results due to covalent bonding of drug molecules with tissue proteins and often results in adverse effects and toxicity.
- e.g. metabolites of paracetamol and chloroform bind covalently with liver tissue → hepatotoxicity.

- Blood-Brain Barrier: The **blood-brain barrier** (BBB) is a separation of circulating blood and cerebrospinal fluid (CSF) in the central nervous system (CNS). It occurs along all capillaries and consists of tight junctions around the capillaries that don't exist in normal circulation.

1. The capillary endothelium in brain has tight junctions and lack pores or gaps.
2. Surrounding this is a continuous basement membrane.
3. This in turn is surrounded by a perivascular foot processes formed by astrocytes.

- All those three structures form a non polar barrier called the blood brain barrier (BBB). It does not allow entry of polar drugs in the brain and only some water soluble drugs *viz*. l-dopa and methyl dopa, and endogenous substances e.g. sugars and a.a.
- BBB allows only the drugs having high to moderate to high oil:water partition coeff.
- Some areas of the brain *viz*. CTZ and posterior lobe of HPT do not have BBB and these sites may be exposed to some polar drugs.

- Placental barrier: A layer of trophoblastic cells separates maternal and foetal blood vessels.
- It is not as effective as BBB as restricted amount of lipid insoluble drugs, especially when present in high conc. or for long period may gain access to the foetus by non-carrier mediated processes.

- Redistribution is the distribution of drug from its site of action to other tissues or sites. It is seen with highly lipid soluble drugs which are administered rapidly to act on brain or cardiovascular centres.
- e.g. Thiopental, a highly lipid soluble drug reaches brain within a min. of its i.v. injection. As the drug then diffuses into other tissues, plasma conc. falls and conc. and drug in blood also goes down and effect is terminated.
- Therefore, redistribution is also a mode of termination of drug effect in addition to metabolism and excretion.

DRUG ELIMINATION

- Two ways:

I. Biotransformation or metabolism

II. Excretion

DRUG METABOLISM /BIOTRANSFORMATION

- conversion of one chemical form of a substance into another in the body of the animals
- During metabolism the physicochemical properties are altered so as to increase their excretion.
- Enzymes that metabolize xenobiotics (substances foreign to the body) have historically been called drug-metabolizing enzymes
- The xenobiotic-metabolizing enzymes convert drugs and xenobiotics into compounds that are hydrophilic derivatives that are more easily eliminated through excretion into the aqueous compartments of the tissues.

Outcomes of metabolism

- Pharmacological inactivation:
  - Phenobarbitone ——> p- hydroxyphenobrbitone
  - Phenytoin ——> p- hydroxyphenytoin
- Bioactivation:
  - Codeine ——> morphine
  - Malathion ——> malaoxon
- Pharmacological activation:
  - Levodopa ——> dopamine
  - Phenacetin ——> paracetamol
  - Enalapril ——> enalaprilat
- *Inactive drugs that undergo metabolism to an active drug are called prodrugs.*

- No change in pharmacological action:
  - Digitoxin ——> digoxin
  - Diazepam ——> nordiazepam
  - Phenylbutazone ——> oxyphenbutazone
- Change in type of pharmacological action
  - Iproniazid (antidepressant) ——> isoniazid (antitubercular).

SITES OF BIOTRANSFORMATION

- Apart from liver, metabolism of drugs takes place in blood plasma and lumen of the gut as well as in other tissues (intestinal mucosa, kidney & lung).
- Therefore, metabolism can be Hepatic (liver) or Extrahepatic (tissues other than liver).
- liver is considered the major "metabolic clearing house" for both endogenous chemicals (e.g., cholesterol, steroid hormones, fatty acids, and proteins), and xenobiotics.
- Within a cell, metabolizing activity is found in:
  - Smooth endoplasmic reticulum and cytosol – major sites
  - Mitochondria, nuclear envelope and plasma membrane – minor sites

- DRUG METABOLIZING ENZYMES (DME):
- The DME broadly are of two types: **microsomal** enzymes and **non microsomal** enzymes.
- Microsomes are minute spherical vesicles derived from endoplasmic reticulum (EPR) after disruption of hepatic cells by centrifugation. Enzymes present in these microsomes are primarily involved in phase-1 reactions.
- The enzymes occurring at sites other than EPR/ microsomes are called non microsomal enzymes. They are usually present in cytoplasm, mitochondria, plasma etc.

- THE PHASES or PATHWAYS OF DRUG METABOLISM
- There are two major pathways; Phase-1 and Phase-2 reactions.
- The general pattern of drug metabolism is usually biphasic i.e. pass through phase-1 reactions and then phase-2 reactions. Other substances may pass through one phase only (either).
- Drugs ——> phase-1 ————> phase-2 ————> metabolites
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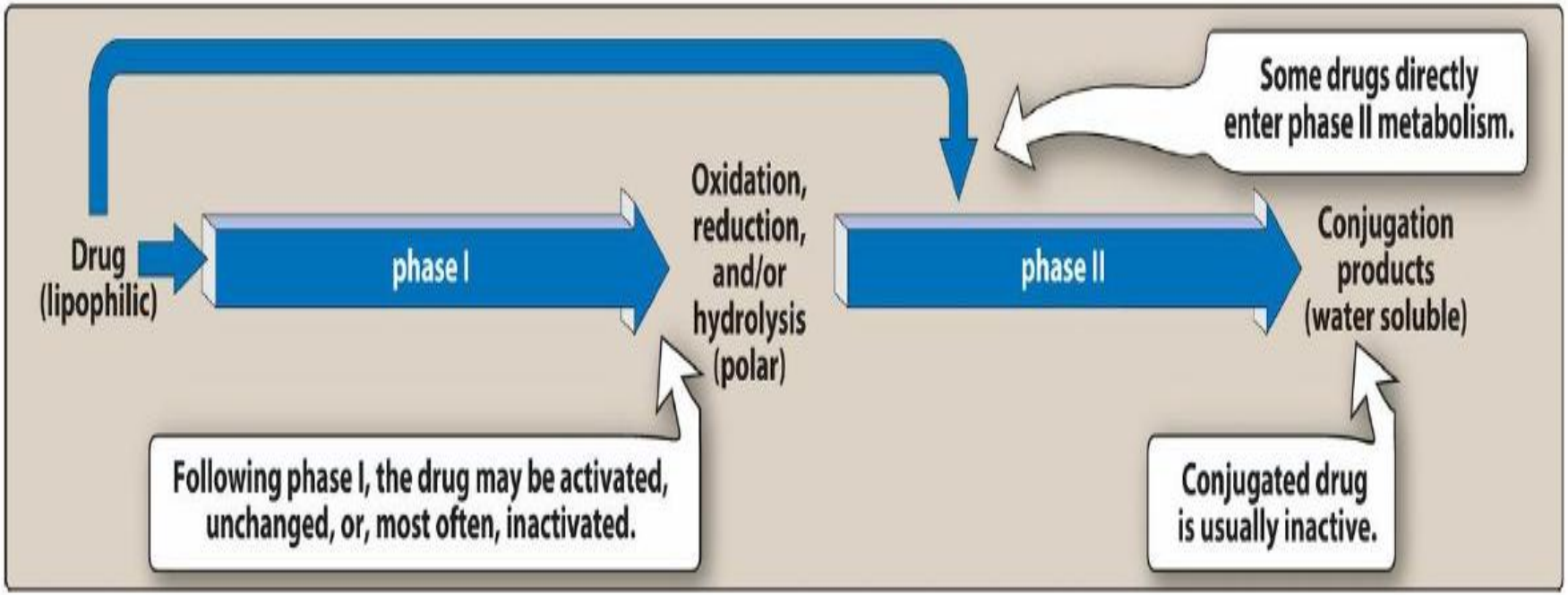
Some drugs directly enter phase II metabolism.
Drug (lipophilic)
phase I
Oxidation, reduction, and/or hydrolysis (polar)
phase II
Conjugation products (water soluble)
Following phase I, the drug may be activated, unchanged, or, most often, inactivated.
Conjugated drug is usually inactive.

- The initial phase (Phase I): Non-synthetic reactions like Oxidation, Reduction & Hydrolysis.
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- Reactions are oxidative, reduc-tive, and hydrolytic reactions.
- Phase-1 transformations usually unmask or introduce into the drug molecule polar groups such as -OH, -COOH, -SH, -O- or NH_2.
- These functional groups enable the compound to undergo conjugation with endogenous substances such as glucuronic acid, acetate (acetylation), sulfate (sulfuric acid ester formation), and various amino acids.
- Reactions carried out by phase-1 enzymes usually lead to the inactivation of an active drug

Oxidative reactions

- These reactions increase hydrophilicity of drugs by introducing polar functional groups. Reactions may be catalysed by i) microsomal oxidative enzymes and ii) non microsomal oxidative enzymes.
- microsomal oxidative enzymes:
  - Microsomal monooxygenases or Microsomal mixed function oxidases
  - Flavin containing monooxygenases
  - Epoxide hydrolases
  - Carboxylesterases
- non microsomal oxidative enzymes:
  - Aldehyde dehydrogenase
  - Xanthine oxidase
  - Monoamine oxidase

Microsomal monooxygenases or Microsomal mixed function oxidases

- The most commonly occurring enzyme of this system is cytochrome P_{450}.
- carried out by a group of monoxygenases in the liver, which in the final step haemoprotein, involve a Cytochrome P-450 NADPH, cytochrome P-450 reductase and O2.
- Nomenclature: The family name is indicated by the Arabic number that follows CYP, and the capital letter designates the subfamily, for example, CYP3A. A second indicates the specific isozyme, as in CYP3A4.
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Aliphatic oxidation	Pentobarbital *	Pentobarbital alcohol
O-dealkylation	Phenacetin *	Acetaminophen *
N-dealkylation	Diazepam *	N-desmethyldiazepam *
Oxidative deamination	Amphetamine *	Phenylacetone
Desulfuration	Parathion	Paraxon *

* Pharmacologically active compound.

Reduction

- Microsomal reductions occur less frequently than oxidations, but can take place in drugs which contain– disulphide (S=S), azo (N=N), or nitro (–NO2) groups.
- These reactions are converse of oxidations and involve cytochrome P-450 enzymes working in opposite direction. The enzymes involved are reductases.
- Reductive biotransformation reactions are as follow:
- Drug
- Prontosil --→ Sulfanilamide *
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- Hydrolysis is an important metabolic pathway for compounds with an ester linkage (–COO–) or an amide (–CONH–) bond.
- Hydrolytic cleavage reactions can take place in liver, intestines, plasma and other tissues.
- Examples :
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- Suxamethonium (plasma) by plasma pseudocholinesterase
- Atropine (plasma) by atropinase
- Procaine (plasma) by plasma cholinesterase
- Lignocaine (liver) by non-microsomal hepatic amidase.

- **Intraarticular Route**: Drug administered into joint space in inflamed joint condition.
- **Intrathecal Route:** The drug is deposited in subarachnoid space in lumber area by inserting needle through vertebral interspinous spaces into spinal fluid.
- **Epidural injection:** used in cattle and buffalo to produce local anesthesia.
- Injection is given between I & II coccygeal vertebral or between lumbosacral space and the drug is deposited through a vertebral interspace into epidural space.

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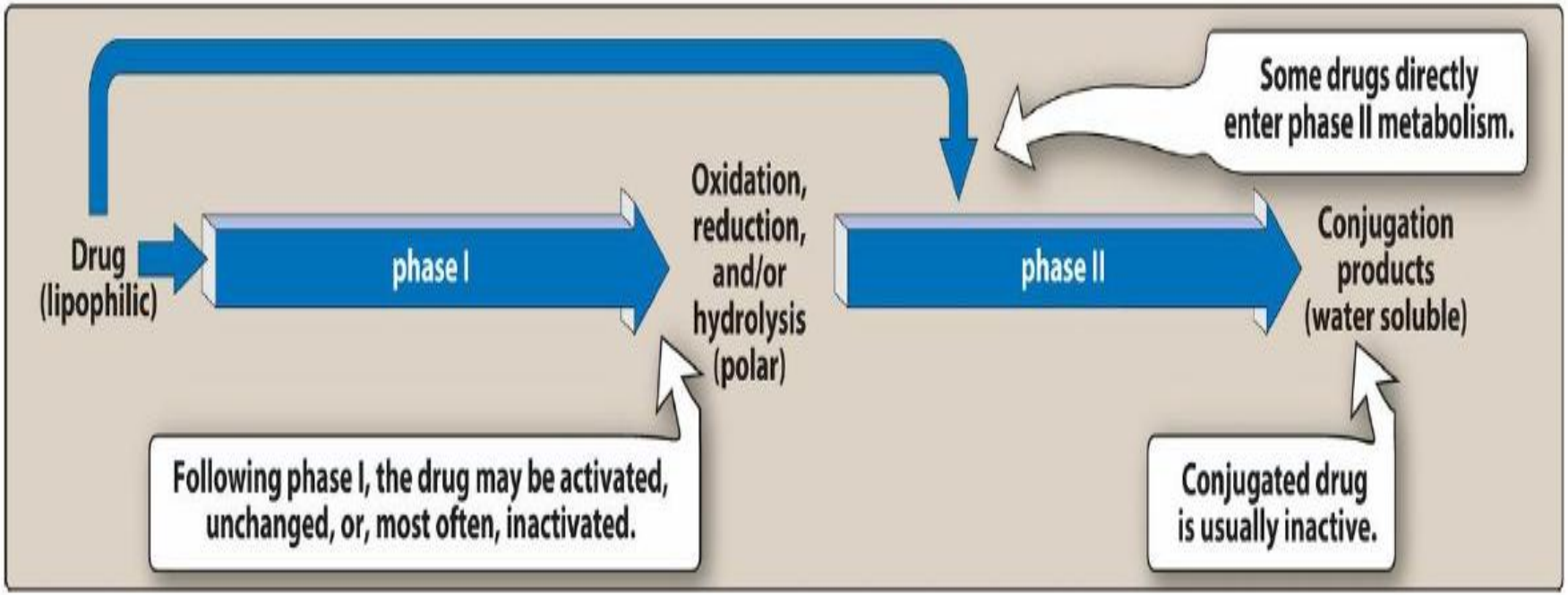
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- Lignocaine (liver) by non-microsomal hepatic amidase.

Phase II (Synthetic/ Conjugation)

- Synthetic reactions may take place when a drug or phase I metabolite contains a chemical group such as hydroxyl (–OH), carboxyl (–COOH), amino (–NH2) or sulfhydryl (–SH) and is suitable for combining with a natural compound provided by the body to form readily excreted water soluble polar metabolites.
- Conjugating agents include Glucuronic acid, Glutathione, Glycine, Methionine Cysteine, Sulphate & Acetate

GLUCURONIDE CONJUGATION

- most common in vertebrates except in cats and fish.
- The biochemical donor of glucuronic acid is uridine diphosphate glucuronic acid (UDPGA) and the reaction is catalysed by UDP-glucuronyl transferase or glucuronyl transferase. This enzyme is a microsomal enzyme present in Liver
- The cat synthesizes glucuronide conjugates at a slow rate, as this species is deficient in the transferring enzyme, glucuronyl transferase .
- Fish: certain breeds are deficient of activated form of glucuronic acid i.e. uridine diphosphate glucuronic acid (UDPGA).
- Examples– Morphine, salicylates, acetaminophen, chloramphenicol, sulphadimethine and phase-1 metabolites of diazepam (oxazepam), phenylbutazone (oxyphenbutazone).
- The glucuronyl conjugates are extensively excreted in the bile.

SULPHATE CONJUGATION

- The endogenous donor of sulphate group is 3-phosphoadenosine-5-phosphosulfate (PAPS).
- The enzyme sulfotransferases (SULTs) are located in the cytosol, and are nonmicrosomal enzymes.
- The conjugates are called as sulphates ester conjugates or Ethereal conjugates.
- In Pigs –> sulphation is lesser than other animals.
- In Cats –> it is an important conjugation reaction as glucuronidation is deficient.
- Examples Phenol, aliphatic alcohols, isoproterenol, ascorbic acid etc. and endogenous compounds like chondroitin, heparin etc.

Methylation

- conjugation with $–CH_3$ group.
- Enzyme is methyltransferases and methyl donor is S-adenosylmethionine.
- This pathway is of lesser importance for drug metabolism as addition of $–CH_3$ group does not improve polarity or water solubility of the conjugates.
- This reaction is more involved in the biosynthesis or inactivation of endogenous amines.

  Noradrenaline ——> adrenaline (synthesis)

  Histamine ——> methyl histamine (inactive)

Conjugation with glutathione or Mercapturic acid formation:

- Glutathione is a tripeptide synthesized from glutamic acid, cysteine and glycine. The reaction is catalysed by glutathione-S-transferase (GSTs).
- strong nucleophilic character due to the presence of a –SH (thiol) group in its structure.
- In absence of GSH, electrophiles may react with nucleophilic groups present in tissues and may lead to oxidative damages of a no. of cellular molecules.
- GSH protects the cellular environment from damage. Glutathione exists in the cells as oxidized (GSSG) or reduced form (GSH).

ACETATE CONJUGATION

- Reticuloendothelial cells rather than parenchymal cells of liver, spleen, lungs and intestinal mucosa.
- Cytosolic N-acetyltransferases (NATs) are responsible for the metabolism of drugs
- Dogs and foxes do not acetylate.
- Acetylation reaction takes place in two stages

  (i) formation of Acetyl CoA

  (ii) nucleophilic attack by the amino– containing compound on the acetylated enzyme.
- Examples– Sulphonamide compounds etc.
- Acetylation decreases water solubility as well as lipid solubility of metabolites. e.g. Acetylation of sulphonamides lead to chances of crystalluria

- Conjugation with aminoacids: Aminoacids like glycine, glutamine (man) and ornithine (birds) are important in making conjugation. Glycine or glutamine is conjugated with salicylic acid, nicotinic acid and cholic acid.
- Conjugation with thiosulphate: Transfer of sulphur atom takes place from thiosulphate in the presence of enzyme rhodanase.
- e.g. metabolism of CN^- ions, $CN^- + S_2O_3^{-2} \longrightarrow SCN + SO_3^{-2}$

EXCRETION

- Excretion may be defined as a process by which drugs and / or their metabolites are irreversibly transferred from body to outside / external environment. Two broad routes of excretion are:
- Renal route of excretion i.e. excretion through urine
- Extrarenal route of excretion
- Renal excretion of drugs: Most important route of excretion. Water soluble, non volatile and small molecular size agents are excreted in the urine. Excretion of drugs in the urine is a sum of three processes:
    - Glomerular filtration
    - Tubular secretion
    - Tubular reabsorption

- **Glomerular filtration:** substances lower than the mol. wt. of 6500 are filtered through glomerular membranes.
- All types of non protein bound drugs or metabolites i.e. lipid soluble, water soluble or ionized are filtered in glomerular filtrate.
- Two factors are important for filtration of drug molecules protein unbound (free) drug and renal blood flow.
- The drug which is passed in glomerular filtrate may be reabsorbed or excreted in urine.

- **Tubular secretion**: By this process the drug or metabolites are secreted from blood to tubular lumen by an active process. This process occurs in PCT. It is:
  - Energy dependent and involve a carrier molecule. It occurs against conc. gradient or electrochemical gradient.
  - Carrier molecules are non specific i.e. either transport organic acids or organic bases.
  - Concurrent administration of two drugs (either acids or bases that are substrate for the same carrier-mediated secretion process) will cause delayed excretion of the less readily transported substance, e.g. probenecid decreases the rate of elimination of penicillin-G by reducing tubular secretion.

Tubular reabsorption

- transportation of drug or their metabolites from tubular fluid to blood circulation. This process takes place all along the renal tubules. It is further of two types: i) passive tubular reabsorption and ii) active tubular reabsorption.
- **Passive tubular reabsorption**:
- Lipid soluble unionized drugs are reabsorbed. It takes place down the conc. gradient and conc. gradient is established on reabsorption of water from renal tubules.
- The pka of drug and pH of tubular fluid is imp in determining unionized fraction and hence the passive tubular reabsorption.
- Weak bases ionize more and reabsorbed less in acidic urine. Weak acids ionize more and reabsorbed less in alkaline urine.
- The excretion of drug can be manipulated by changing pH of tubular fluid using urinary acidifiers or alkalizers, i.e. urine is acidified in poisoning with basic drugs e.g. amphetamine, morphine etc. and urine is alkalinized in poisoning with acidic drugs, e.g. barbiturates, salicylates

- **Active tubular reabsorption**: It is less imp for reabsorption of drugs and very few drugs are reabsorbed through this mechanism, e.g. oxopurinol. Mostly nutrient are reabsorbed through this mechanism, e.g. glucose, a.a.

Extra renal excretion of drugs

1. Biliary excretion: Drugs are excreted by hepatocytes into bile canaliculi alongwith bile and then in duodenum.

- Large molecular size polar compounds are preferentially excreted through biliary route.
- Metabolic reactions which increases the polarity and molecular size, e.g. glucuronide conjugation and glutathione conjugates, are excreted via bile. Biliary excretion of drugs may occur actively or passively, e.g. cardiac glycosides.

2. Pulmonary excretion: Gaseous and volatile substances like general anaesthetics and alcohols are excreted through lungs. Rates of excretion depends upon solubility, less soluble is excreted rapidly (nitrous oxide) than more soluble (ethyl alcohol).

3. Salivary secretion: route of lesser importance. Excretion occur by passive diffusion. Excretion of drug in saliva result in absorption from intestine. Therefore, if antibiotic is excreted via saliva then it may disturb the ruminal microflora and results in idigestion.

4. GIT excretion: It may occur when passive diffusion of drugs occur from blood to GIT lumen due to high conc. gradient in blood. Weakly basic drugs are partitioned in rumen of ruminants.

5. Mammary excretion: Drugs are excreted in milk through passive diffusion. Excetion in milk may affect the suckling young ones.

6. Other routes of excretion: Skin, sweat, lachrymal fluid, genital and tracheobronchial secretion.

Concepts and principles of pharmacokinetics

- Various processes of drug kinetics have been studied theoretically so far.
- These processes can be described mathematically in terms of drug concentration changes in the body with respect to time called as kinetics of ADE.
- Levels of drug concentration can be related to pharmacological and toxicological effects of a drug.
- Orders of Kinetic Processes
- The manner in which the conc of a drug affects the rate of various kinetic processes (ADME) is called order of kinetic processes. There are two types of orders of kinetics:
- First order kinetics or Linear kinetics
- Zero order kinetics or Nonlinear kinetics or Saturation kinetics.

First order Kinetics

- The rate of drug metabolism and elimination is directly proportional to the concentration of free drug.
- This means that a constant fraction of drug is metabolized per unit of time (that is, with each half life, the concentration decreases by 50%).
- Rate of elimination is directly proportional to drug concentration.
- Clearance remains constant.
- First-order kinetics is also referred to as linear kinetics.
- Majority of drugs follow first order kinetics.

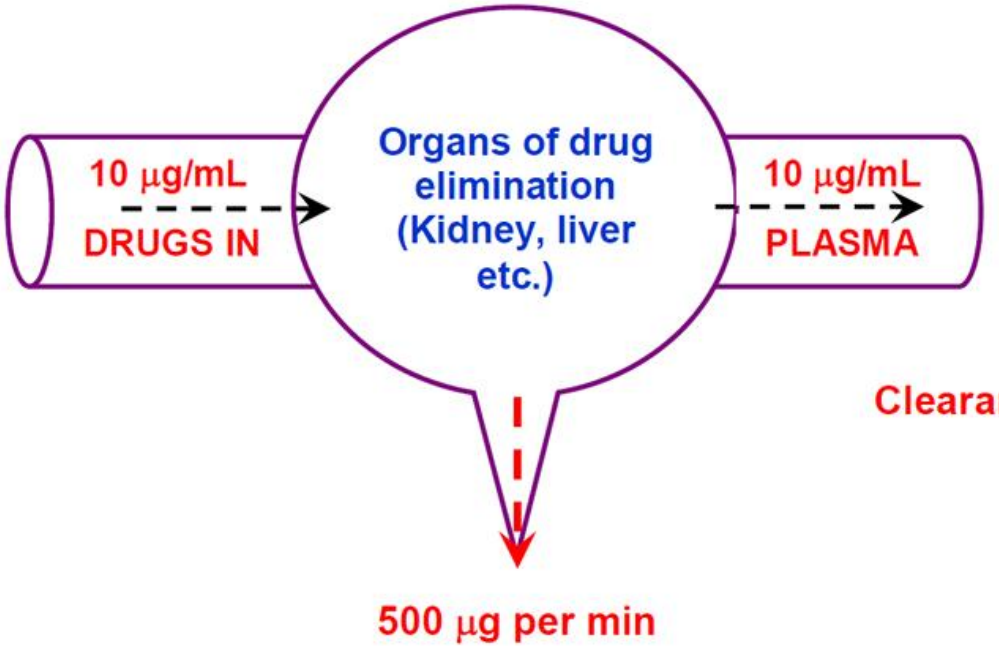
Zero order Kinetics

- Rate of elimination remains constant irrespective of drug concentration.
- CL decreases with increase in concentration.
- A constant amount of drug is eliminated in unit time.
- Few drugs follow zero order kinetics. e.g. Ethyl alcohol

- Plasma Half Life (t½): The plasma half life of a drug is the time taken for its plasma concentration to be reduced to half of its original value.
- First order kinetics: t1/2 remains constant.
- Zero order kinetics: t1/2 increases with dose

- There are three fundamental pharmacokinetic parameters :
- Bioavailability (F)
- Volume of distribution (Vd), and
- Clearance (CL)

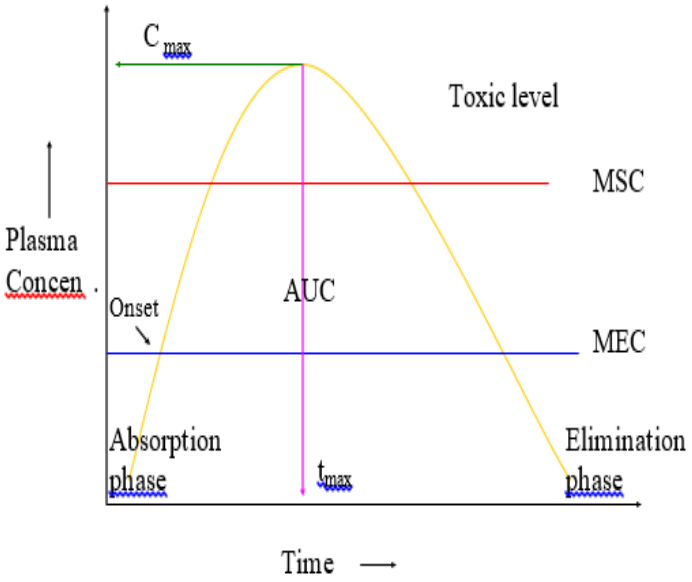
- Clearance (CL): It is the theoretical volume of plasma from which the drug is completely removed in unit time.
- Clearance = Rate of elimination/ Plasma concentration



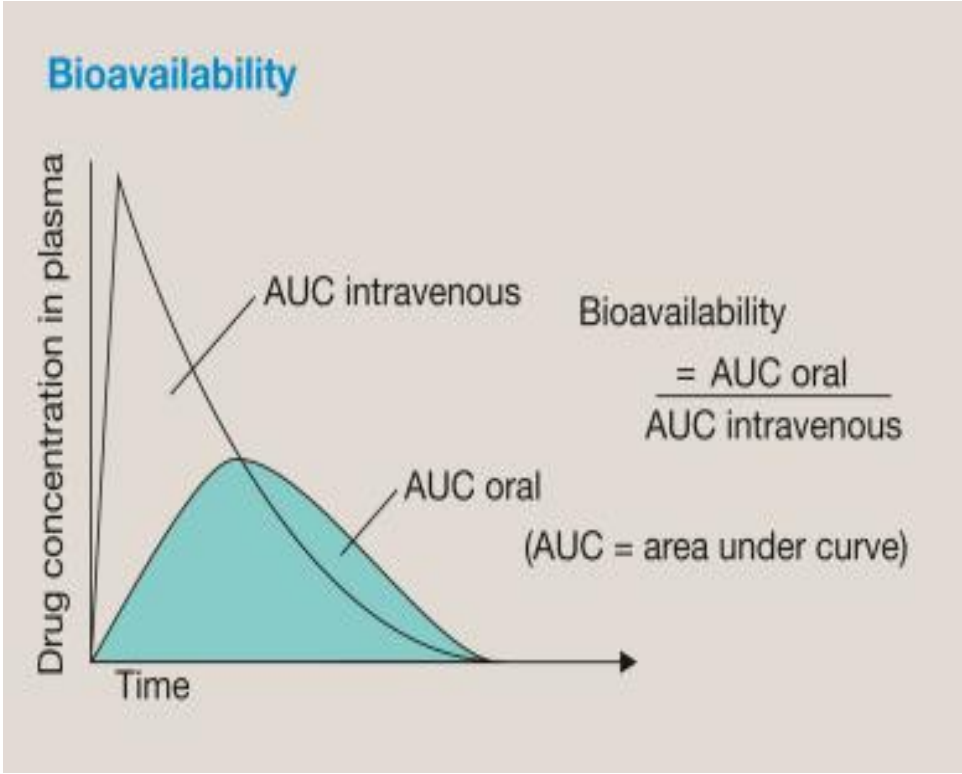
$$\text{Clearance} = \frac{500\ \mu g/min}{10\ \mu g/mL}$$

$$= 50\ ml/min$$

- **Bioavailability**: It is defined as the rate and extent to which a drug administered as a particular dosage form enters the systemic circulation intact. Therefore, bioavailability relates to rate of drug absorption and fraction of drug absorbed from site of administration.
- The bioavailability of drug administered through i/v route is taken as 100% and the bioavailability of the same dose of the drug when administered through different nonvascular routes is determined by comparing it with i/v route.
- Rate of absorption: It is given by the time at which the peak is reached on plasma concentration vs time curve



Plasma Concentration time profile



- Therefore, by comparing the AUC of the same dose of drug administered through different route one can determine the extent of absorption (F) of systemic availability or bioavailability.

$$F = \frac{(AUC)\ \text{oral}}{(AUC)\ \text{i.v.}}$$

- **Volume of distribution (Vd):** It is that volume of fluid which would be required to contain the amount of drug in the body if it was uniformly distributed at a concentration equal to that in plasma.
- **Apparent volume of distribution:** It gives an estimate of the extent of distribution of a drug. It is the sum of the volumes of the central and peripheral distribution compartment of the drug.
- Since all regions of the body which contain drug will not have equal concentrations so any volume determined by the drug concentrations in plasma can be only an apparent volume.
- Significance: A large value of AVD implies wide distribution of drug in the body or a high affinity binding (or selective binding) to tissues with restricted distribution or occurrence of both the possibilities.

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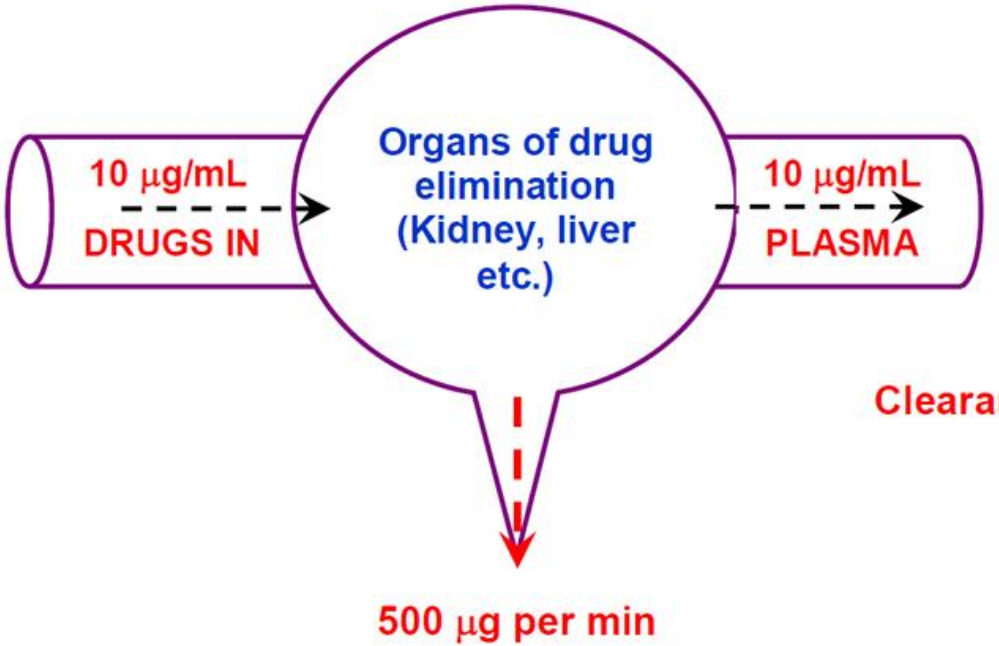
- Volume of Distribution (L) = Amount of drug in the body (mg) / Plasma concentration of drug (mg/L)

- **Half-life (hours) = 0.693 x (Volume of distribution (L) / Clearance (L/hr))**

- Significance: A large value of AVD implies wide distribution of drug in the body or a high affinity binding (or selective binding) to tissues with restricted distribution or occurrence of both the possibilities.

- Clearance (CL): It is the theoretical volume of plasma from which the drug is completely removed in unit time.
- Clearance = Rate of elimination/ Plasma concentration



$$\text{Clearance} = \frac{500\ \mu g/min}{10\ \mu g/mL}$$

$$= 50\ ml/min$$

Elimination rate constant

- The elimination rate constant describes the fraction of drug eliminated per unit of time or the rate at which plasma concentrations will decline during the elimination phase.
- t1/2= 0.693 / elimination rate constant (Ke)
- Ke = 0.693/t1/2

Pharmacodynamics

- Study of physiologic and biochemical effects and mechanism of action of drug is called pharmacodynamics. It focuses on mechanism of action, pharmacologic action and pharmacologic effects of drugs.
- *Mechanism of Action*: Drug induced changes in biochemical and physiological processes of the cellular organelles and tissues or organs
- *Drug actions*: Drug induced cascade of biochemical events of a particular component of the body where drug acts is called drug action.
- *Drug effect*: The battery of changes in the physiological functions of body subsequent to the drug action are called drug effects. e.g. antiemetic effect produced due to above action.
- Action: How and Where the effect is produced is called as Action.
- Effect: The type of response producing by drug.

Principles of Drug Action

- Drugs alter the pace of ongoing activity rather than imparting new function
- Basic types of drug action can be broadly classed as:
- Stimulation
- Depression
- Irritation
- Replacement
- Cytotoxic action

- Stimulation: Selective enhancement of the level of activity of specialized cells.
  - Adrenaline stimulates heart.
  - Pilocarpine stimulates salivary glands.
- Depression: Selective diminution of activity of specialized cells.
  - Barbiturates depress CNS
  - Quinidine depresses heart
  - Omeprazole depresses gastric acid secretion.

- IRRITATION: A non-selective, often noxious effect and is particularly applied to specialized epithelium, connective tissue etc.
- Mild irritation may cells like stimulate associated function like bitters increase salivary and gastric secretions and counterirritants increase blood flow to the site.
- But strong irritation results in inflammation, corrosion, necrosis and morphological damage. This may result in diminution or loss of function.

- REPLACEMENT: This refers to the use of natural metabolites, hormones or their congeners in deficiency states like insulin in diabetes and fluids in dehydration.
- CYTOTOXIC ACTION: Selective cytotoxic action for invading cancer parasites or cells, attenuating them without significantly affecting the host cells is utilized for cure or palliation of infections and neoplasms.

Basic Mechanisms of Drug Action

- NON-CELLULAR MECHANISMS OF DRUG ACTION

1. Physical effects: protective, adsorbent and lubricant properties of locally active agents that are applied to cutaneous and membrane surfaces.
2. Chemical reactions: A number of drugs produce their effects through a chemical union with an endogenous or foreign substance
3. Physicochemical mechanisms: Certain drugs act by altering the physicochemical or biophysical properties of specific fluids or even components of cells.
4. Modifications of the composition of body fluids: osmotically active agents like magnesium sulphate as a purgative, mannitol as a diuretic and use of dextran as plasma volume expander.

CELLULAR MECHANISMS OF DRUG ACTION

1**. Physicochemical and biophysical mechanisms**: Certain drugs appear to act by altering the physicochemical or biophysical characteristics of specific components of cells.

- Examples include the effect of general inhalant anaesthetics on the lipid matrix and perhaps the hydrophobic proteins in neuronal membranes within the CNS.

2. **Modification of cell membrane structure and function**: Various drugs may influence either the structure or specific functional components of cell membranes and thereby initiate their characteristic effects. These mechanisms of action may also involve enzyme systems or receptor mediated reactions.

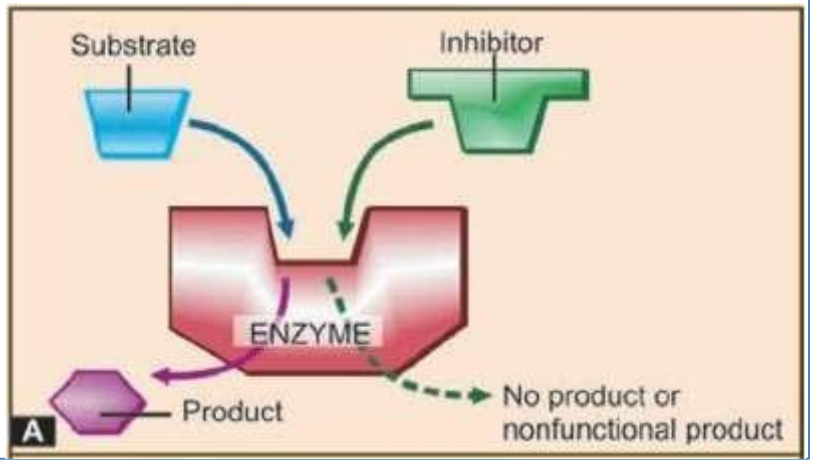
- A few examples include, local anaesthetics that bind to components of the sodium channels in excitable membranes and prevent depolarization, calcium channel blockers that inhibit the entry of calcium into cells.

- 3. Mechanisms associated with neurohumoural transmission: A number of drugs interfere with the synthesis, release, effects or re-uptake of neurotransmitters.
- Once again enzyme and/or receptor mediated effects may be responsible.
- For example, reserpine blocks the transport system of adrenergic storage granules, while amphetamine displaces norepinephrine from axonal terminals. Botulinum toxin prevents the release of acetylcholine

- Majority of drugs produce their effects by interacting with a discrete target biomolecule, which usually is a protein. Such mechanism confers selectivity of action to the drug.
- Functional proteins that are targets of drug action can be grouped into four major categories, viz.
- Enzymes,
- Ion channels,
- Transporters and
- Receptors.

Enzymes

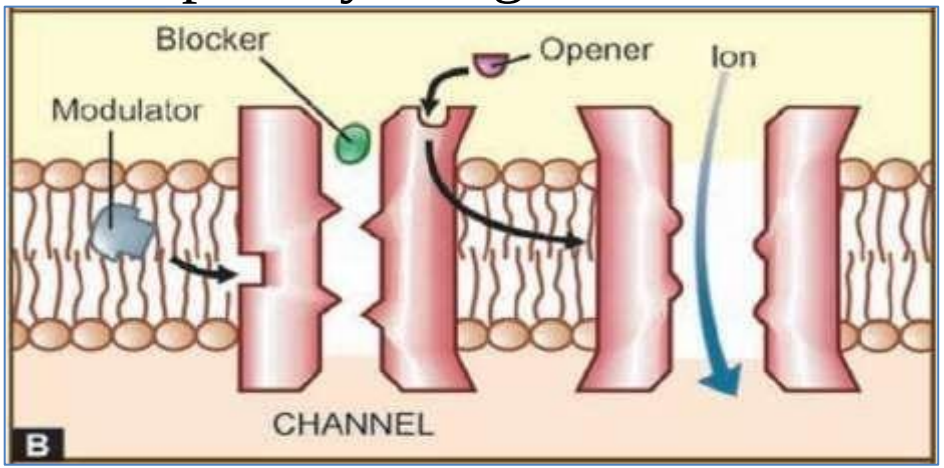
- Almost all biological reactions are carried out under catalytic influence of enzymes;
- Drugs can either increase or decrease the rate of enzymatically mediated reactions.
- Enzyme Inhibition:
  - Non-selective & Selective.
- Selective enzyme inhibition:
  - Competitive & Non-competitive.



Enzyme	Endogenous substrate	Competitive inhibitor
• Cholinesterase	Acetylcholine	Physostigmine, Neostigmine
• Monoamine-oxidase A (MAO-A)	Catecholamines	Moclobemide
• Dopa decarboxylase	Levodopa	Carbidopa, Benserazide
• Xanthine oxidase	Hypoxanthine	Allopurinol
• Angiotensin converting enzyme (ACE)	Angiotensin-1	Captopril
• 5α-Reductase	Testosterone	Finasteride
• Aromatase	Testosterone, Androstenedione	Letrozole, Anastrozole
• Bacterial folate synthase	Para-amino benzoic acid (PABA)	Sulfadiazine

Ion Channels

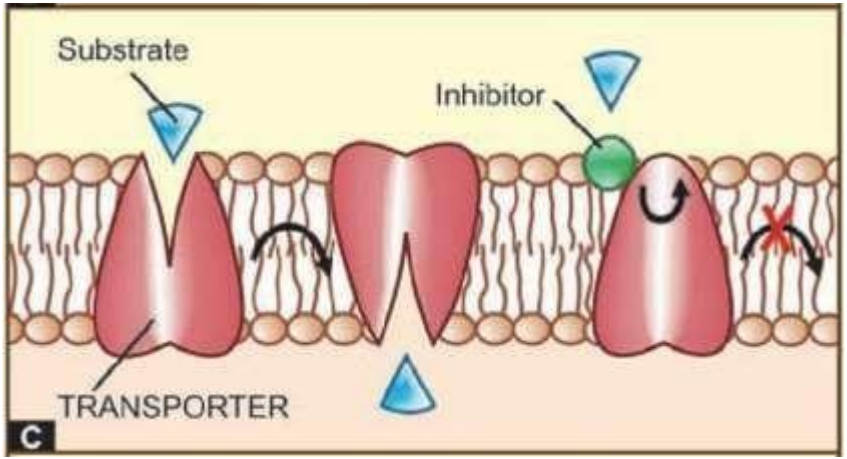
- Some ion channels (known as ligand gated channels) are directly linked to a receptor and they open only when the receptor is occupied by an agonist



- The simplest type of interaction involves the physical blocking action of local anaesthetics on the voltage gated sodium channels.
- Ion channel modulation by drugs, acting directly on the channel or indirectly is one of the most important mechanisms by which pharmacological effects are produced at the cellular level.

Carrier Molecules (Transporters)

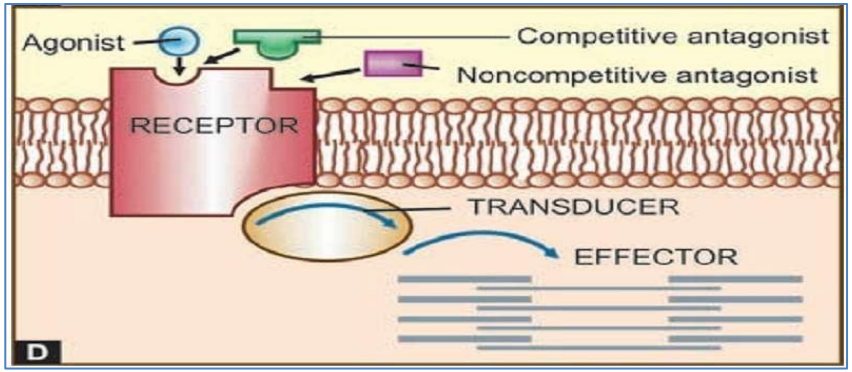
- The transport of ions and small organic molecules across cell membranes generally requires a carrier protein (transporter), the since permeating molecules are often polar, to penetrate lipid membranes on their own.



Receptors

- J.N. Langley (1878) introduced the concept receptor of . He used the term receptive substance.
- The term receptor was first used by Paul Ehrlich (1913) to describe the hypothetical specific chemical groupings of “side chains” on cells upon which the chemotherapeutic agents were postulated to act.
- A receptor is often defined in terms of the endogenous substance or ligand that produces a given effect upon interaction with a given biological substrate.

- Macromolecule or binding site located on the surface or inside the effector cell that serves to recognize the signal molecule/drug and initiate the response to it, but itself has no other function.

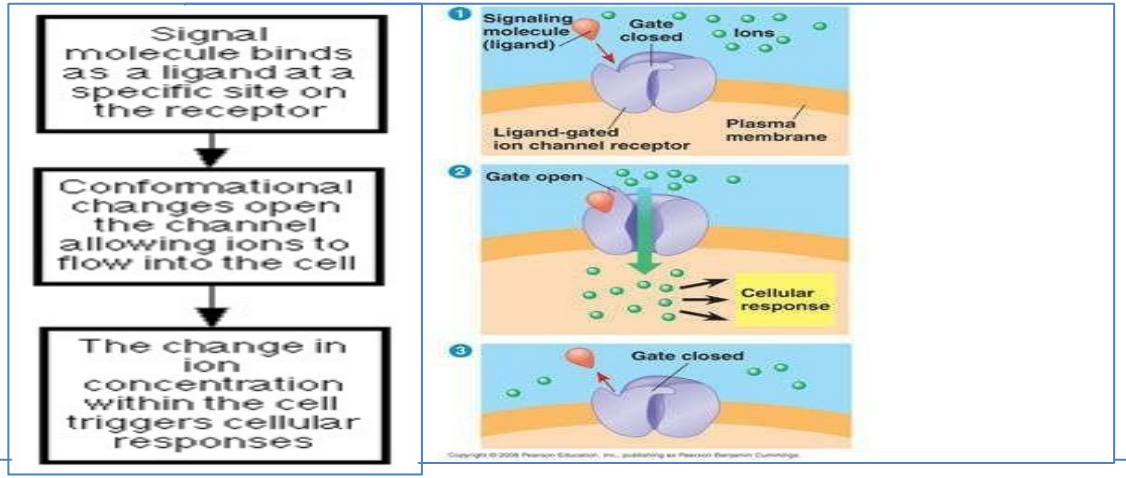


Properties of Receptors

- Saturability : A finite number of receptors per cell should be present.
- Specificity : The drug should be structurally complementary to the receptor.
- Reversibility : The drug should bind to the receptor and then dissociate in its non metabolized form

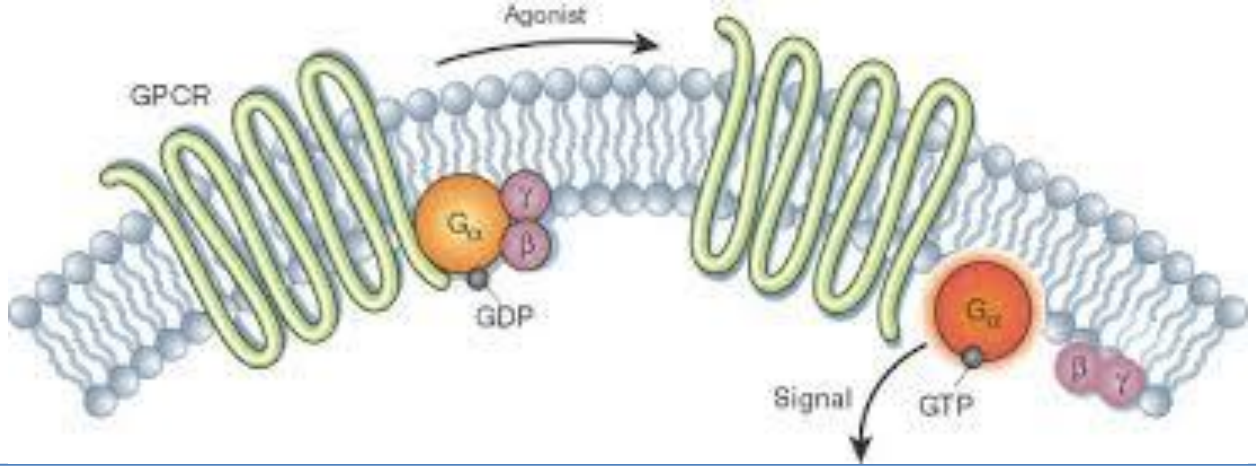
Types of Receptors

- **Ligand-gated ion channels (Ionotropic receptors):** Membrane receptors coupled directly to ion channels and are the receptors on which fast neurotransmitters act.
- Examples: the nicotinic acetylcholine receptor; GABAA receptor; and glutamate receptors.



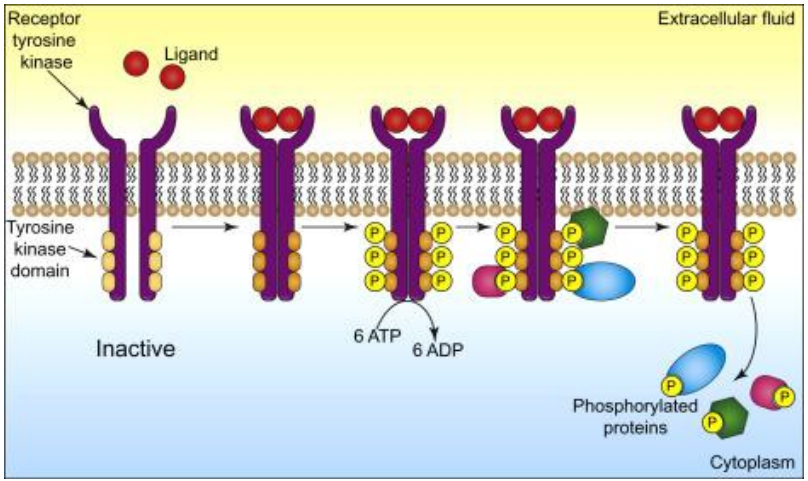
G-protein coupled receptors (GPCRs)

- Also known as metabotropic receptors or 7 transmembrane-spanning (heptahelical) receptors.
- Are membrane receptors that are coupled to intracellular effector systems via a G protein.
- Examples: Receptors for many hormones and slow transmitters, e.g. the muscarinic acetylcholine receptor and adrenergic receptors



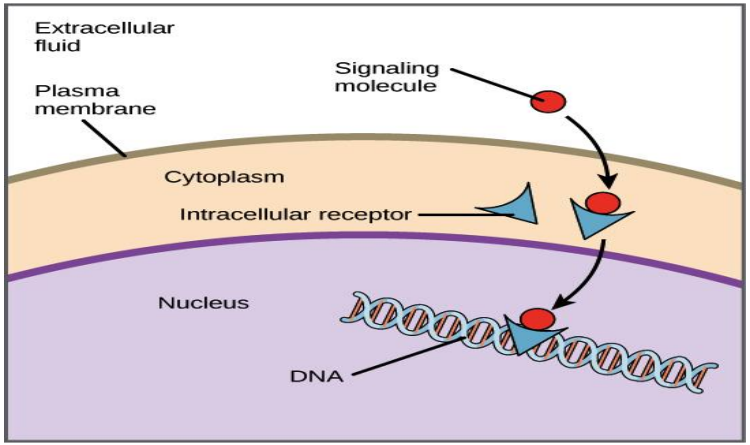
Kinase-linked and related receptors

- Are membrane receptors that incorporate an intracellular protein kinase domain within their structure.
- They include receptors for insulin, various cytokines and growth factors.



Nuclear receptors

- These are receptors that regulate gene transcription.
- They include receptors for steroid hormones, thyroid hormone, and other agents such as retinoic acid and vitamin D.



Drug Receptor Interactions

- Affinity: tendency of a drug to combine with a particular kind of a receptor.
- Efficacy (or intrinsic activity) of a drug refers to the maximal effect the drug can produce.
- Potency: It refers to the dose of a drug that must be administered to produce a particular effect of given intensity.
  - It is influenced by the affinity.
  - It varies inversely with dose.

- Specificity: When all the effects produced by a drug are due to a single mechanism of action, the drug is said to be specific or When the drug acts only on a single target (enzyme, receptor) it is said to be "specific.“
- Selectivity: It depends on the capacity of a drug to preferentially produce a particular effect. heparin has selective anticoagulant action

- **Agonist:** An agent which activates a receptor to produce an effect similar to that of the physiological signal molecule.
- **Inverse agonist:** An agent which activates a receptor to produce an effect in the opposite direction to that of the agonist.
- **Antagonist:** An agent which prevents the action of an agonist on a receptor or the subsequent response, but does not have any effect of its own.
- **Partial agonist:** An agent which activates a receptor to produce submaximal effect but antagonizes the action of a full agonist.

- **Agonists** have both affinity and maximal intrinsic activity (IA = 1), e.g. adrenaline, histamine, morphine.
- **Competitive antagonists** have affinity but no intrinsic activity (IA = 0), e.g. propranolol, atropine, chlorpheniramine, naloxone.
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Agonist

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Antagonist

- An antagonist is a drug that blocks the response produced by an agonist.
- Antagonists interact with the receptor or other components of the effector mechanism, but antagonists are devoid of intrinsic activity (Affinity=1, Efficacy=0).

Type of Drug Interaction

- **Addition:** when the combined effect of two drugs is equal in magnitude to the sum of the effect of each drug when given alone. i.e. 1+1 = 2. e.g. Combination of two organophosphorus insecticides produces additive effects.
- **Potentiation**: When one drug having no effect of its own increases the pharmacological action of another drug, the interaction is called as potentiation. i.e. 1+0 >1. e.g. Combination of penicillin and probenecid.
- **Synergism**: When the combined effect of two drugs is more in magnitude than the sum of effects of each drug when given alone. i.e. 1+1 >2 e.g. CCl_4 and ethanol when given together produce hepatotoxicity.
- **Antagonism**: When the combined effect of two drugs is less in magnitude than the sum of effects of each drug when given alone. i.e. 1+0 <1 where, 1 is agonist, 0 is antagonist or 1+2 <2 where, 1 is partial agonist, 2 is full agonist e.g. use of morphine and naloxone.

Antagonism

- **Competitive Antagonism**: It is completely reversible; an increase in the concentration of the agonist in the bio-phase will overcome the effect of the antagonist. Example: Atropine (Antimuscarinic agent) Diphenhydramine (H1 receptor blocker)
- **Non-competitive antagonism**: The agonist has no influence upon the degree of antagonism or its reversibility.
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1. Physical antagonism: Antagonism is based on physical property of drugs. i.e. charcoal adsorbs alkaloids and can prevent their absorption. This phenomenon is employed in alkaloidal poisonings.
2. Chemical antagonism: The two drugs react chemically and form an inactive product. Examples KMnO4 oxidizes alkaloids. Chelating agents (like BAL, CaNa2EDTA) complex with metals (like As, Pb etc.).

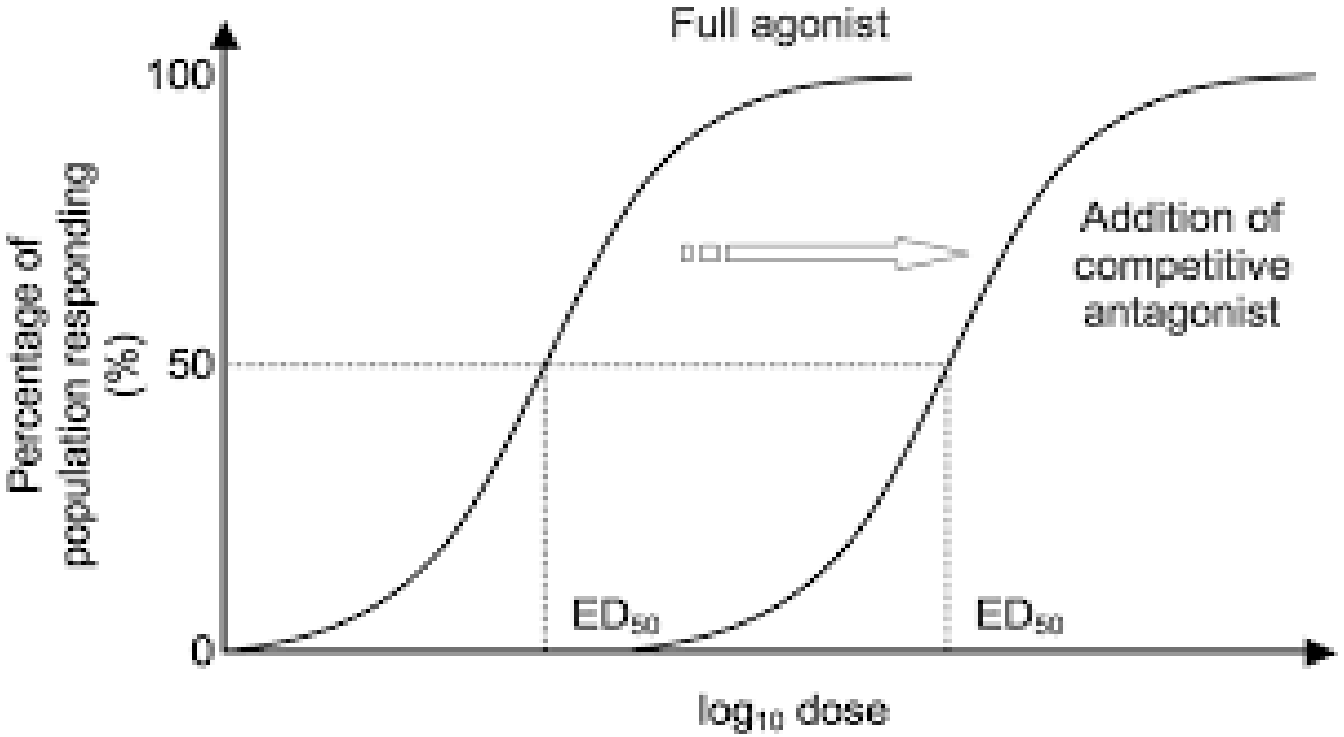
3. Physiological/ Functional antagonism: Two drugs act on different receptors, mechanisms or by different , have opposite overt effects on the same physiological function i.e. pharmacological effects in opposite direction.

* Examples have Histamine & adrenaline on bronchial muscles & B.P. Glucagon and Insulin on blood sugar level.

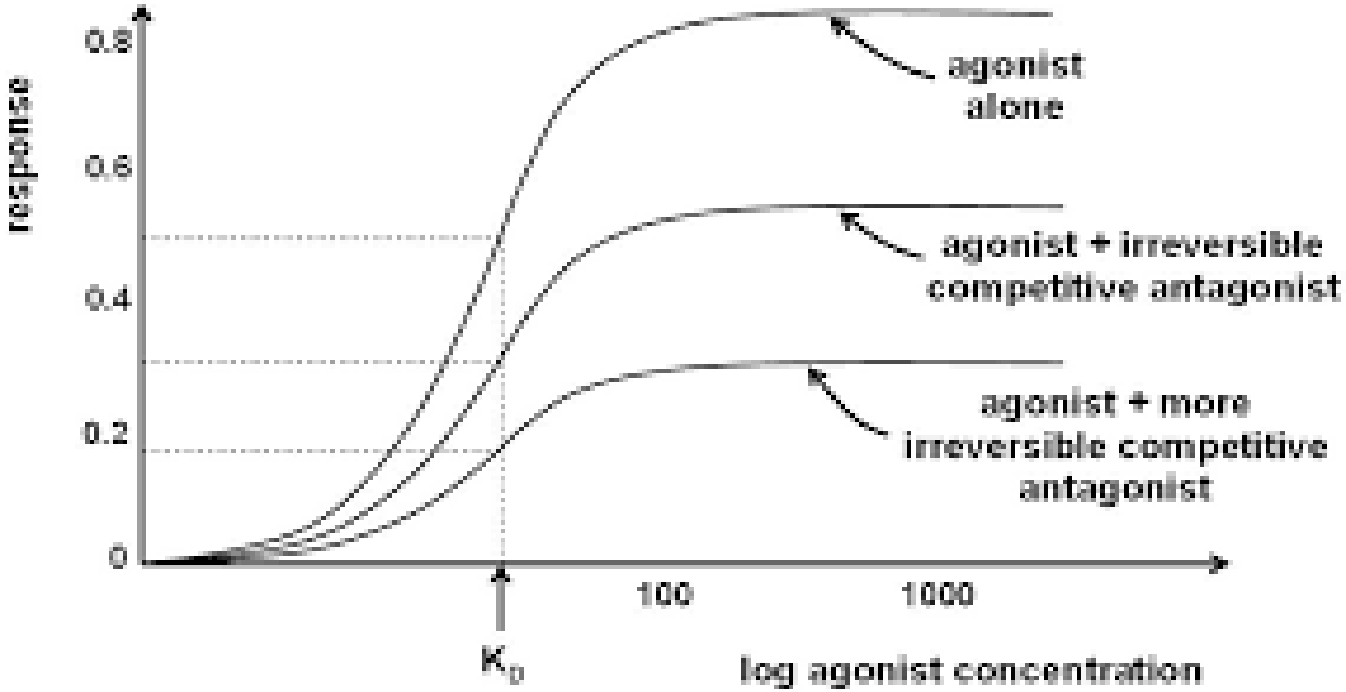
4. Antagonism by Receptor Block: The antagonist interferes with binding of the agonist with its receptor or inhibits the generation of response consequent to such binding.

- It may be competitive or non-competitive.

- **Competitive antagonism:** Here agonist and antagonist have a common binding site at receptor and the receptor can bind one drug molecule at a time.
- In the presence of competitive antagonist there is parallel shift of agonist log-conc. effect curve to the right without any reduction in maximal response. i.e. for the same response a higher concentration of drug (agonist) is required which shifts the curve to right. Such an antagonist is called surmountable.
- Examples ACh + Atropine, Morphine + Naloxone


Full agonist
100
50
0
Percentage of population responding (%)
Addition of competitive antagonist
ED50
ED50
log10 dose

- **<u>Irreversible or non equilibrium competitive antagonism</u>:**
- The antagonist bind with the receptor at the site where agonist binds. The dissociation of antagonist is very slow and is taken as irreversible in action.
- Antagonist after displacing the agonist occupy the receptors and increase in conc. of agonist further cannot displace the antagonist appreciably. The effect produced by the agonist is by acting on spare-receptors.


response
0.8
0.6
0.4
0.2
0
agonist alone
agonist + irreversible competitive antagonist
agonist + more irreversible competitive antagonist
100
1000
K_D
log agonist concentration

- **<u>Non competitive antagonism</u>:**
- The response produced in presence of antagonist is same as above. But antagonist does not act on the receptor site where agonist act. This type of drug produces its effect by binding a site on the receptor distinct from that of the primary agonist.

Type of receptors

- Spare receptors / reserve receptors: Formation of drug-receptor complex with some highly active drugs viz. adrenaline and histamine involve occupation of small fraction of receptors to produce maximal response and majority of receptors remain unoccupied, such receptors are called as spare receptors.
- Silent receptors: These are receptors to which drug binds with no production of pharmacological response. Such receptors are drug acceptors or binding sites.
- Orphan receptors: these receptors generally donot have endogenous ligands and are used as tool for search of new drugs.
- Putative receptors: These receptors are not fully characterized to behave as receptors.

Theories of receptor binding

- Drug-receptor theory: Paul Ehrlich and J. N. Langley in 1878 suggested that receptor-drug interaction takes place in a lock and key manner
- Receptor occupancy theory – given by A. J. Clarks (1923). Response is a function of occupancy of receptor molecule by agonist molecules. There is a linear relationship between occupation of number of receptor molecules and cellular response.
- Rate theory**:** Paton gave this theory in the end of 1950s. As per this theory, the response produced by drug molecules by binding to the receptors is based on the rate of association and dissociation of drugs to and from receptors which also determines intrinsic activity of the drug.
- Two state receptor theory: It suggests that a receptor exists in two interchangeable conformational forms, the active (Ra) and inactive (Ri) forms. Both forms are in equilibrium.

DOSE RESPONSE RELATIONSHIP

- The response to a drug varies according to its dosage i.e. the magnitude of the drug effect is a function of the dose administered.
- The relation between the response produced by different dosage is expressed by graphical representation called Dose Response Curve (DRCs). These are of two types:

(i) Graded dose response curve

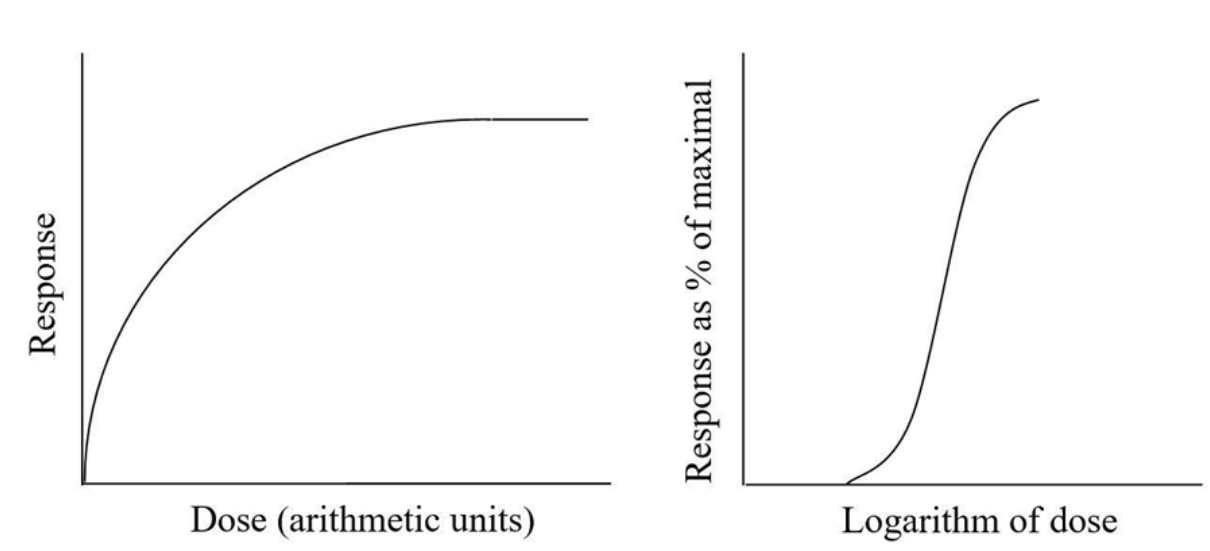
(ii) Quantal dose response curve

Graded Dose Response Curve

- It gives the relation between dose of a drug and the intensity of response in a single biological unit.
- The curve depicts that when the dose exceeds a critical level (threshold dose), the response also increases progressively until it reaches a steady level (ceiling effect-ceiling dose).
- The threshold dose may be defined as the minimum dose required to produce an observable response.
- The dose producing ceiling effect may be called as ceiling dose, which may be defined as the minimum dose producing the maximum response.

- Any further increase in the dose above the ceiling dose will not increase the level of response.
- The graded dose response represents the relationship between dose and response in a single unit or animal, but it does not indicate the normal biological individual variation on a population basis.
- When the graded response is plotted as a graph, a hyperbolic curve is obtained.
- When the response is expressed as a % of maximum instead of in absolute units, and is plotted against the logarithm of the dose, the curve adopts a sigmoid shape characteristic of a log-dose-percent response curve

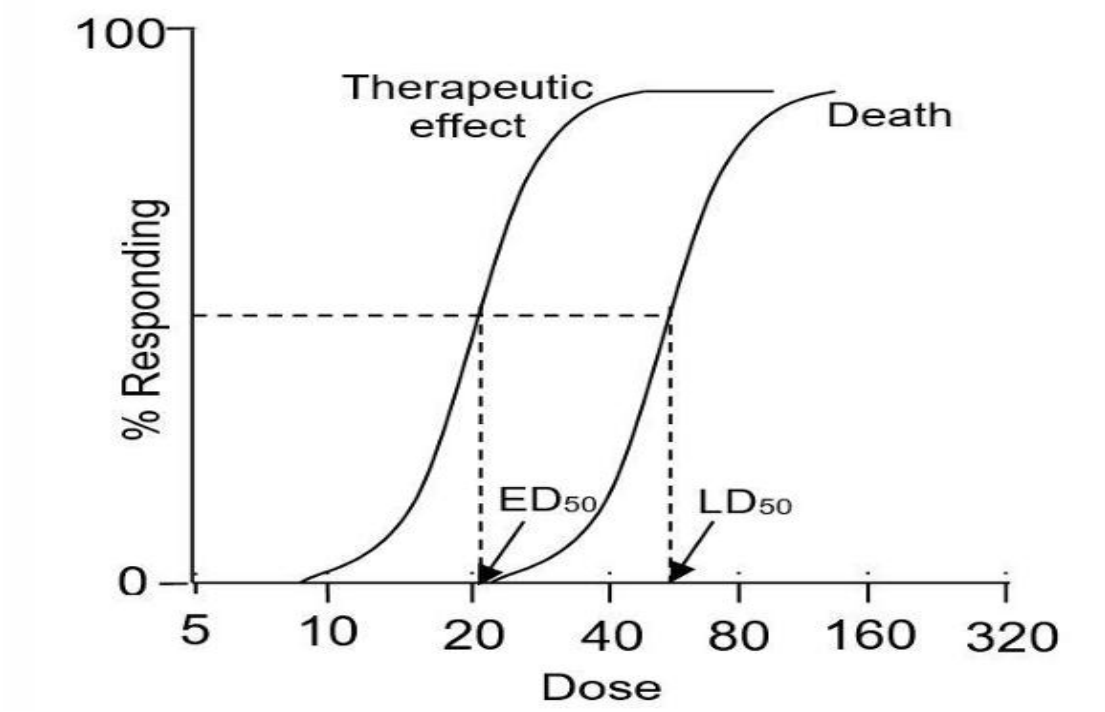
Graded Dose Response Curve



Quantal Dose Response Curve

- It represents the percent response of animals in a group of population to the doses of a drug.
- Each animal receiving a dosage is characterized as responding or non-responding. The percentages responding to each dose are recorded (i.e. 0% dead, 0% alive, % responded or % not responded etc.).
- The relation is based on all-or-non phenomenon, which cannot be quantitatively measured such as occurrence of death, convulsions, emesis, oestrous etc.
- This type of curve is used for estimating ED50 or LD50 values of a drug.
- For a quantal response, both the dose response and the log dose response curves are sigmoid

- LD50: It is called median lethal dose, which is defined as the dose which would be expected to kill 50% of the exposed population.
- ED50: It is called median effective dose, which is defined as the dose which would be expected to produce a desired therapeutic response among 50% of the exposed population.
- Therapeutic index = LD50/ED50.
- Larger is the value of T.I. more is the safety of drugs.


100
0
% Responding
Therapeutic effect
Death
ED50
LD50
5
10
20
40
80
160
320
Dose

Altered Receptor Functions

- **Tolerance**: The effect of a drug often diminishes when it is given repeatedly. The term used to describe a gradual decrease in responsiveness to chronic drug administration (days, months) is *tolerance.*
- **Tachyphylaxis or Desensitization**: Tachyphylaxis is an acute form of tolerance. Here the effect of drug that follows continued or subsequent exposure to the same conc./dose of drug is altered
- **Drug Resistance**: generally used to describe the loss of effectiveness of an antimicrobial drug.
- **Idiosyncratic response**: Individual variation in responsiveness to a drug is called idiosyncratic response.

Factors modifying Drug Action

1. Species of animal: Effect of a drug may be variable in different species of animals due to difference in pharmacokinetic of a drug in different species of animals. e.g.

i) Rabbits are resistant to atropine due to presence of atropinase enzyme in liver.

ii) Morphine produces CNS depression in human beings, monkeys and dogs but causes CNS excitation in cats.

2. Breeds: Occasionally there can be variation in effect of drugs depending on breeds. e.g. Greyhounds are more susceptible to thiobarbiturates as this breed has less s/c fat and are lean in body weight so there is less redistribution of thiobarbiturates.
3. **Sex**: Generally female animals are more sensitive to the effects of drugs than the males.

4. Age: Young and very old animals are more susceptible to harmful effect of drugs when compared with adults. Young animals have inefficient metabolic and excretory processes. Chloramphenicol induces grey-baby syndrome in human infants due to inadequate conjugation of chloramphenicol with glucuronic acid.
5. Pregnancy: There are marked; hormonal and metabolic changes during pregnancy which affects effect of certain drugs.
   - Volume of distribution increases
   - Drug may cross placental barriers and affect foetus
   - High progesterone level during pregnancy may increase hepatic microsomal enzymes that cause increase in drug metabolism.
6. Lactation: There may be increase in excretion of some lipophilic drugs and toxicants (e.g. DDT, polychlorinated biphenyls)

7. Hormonal status: Hyperthyroidism, elevated thyroid hormones activate some Cyps (e.g. hydroxylation) while activities of others are decreased (e.g. N-demethylation)
8. Body weight and composition: In obese animals, lipid soluble drugs are more distributed in adipose tissues so plasma conc. is less while water soluble drugs are less distributed in adipose tissue and concentration is high plasma. e.g. thiopentone is rapidly redistributed in obese animals.
9. Genetic Status: Genetic variations may lead to genetic tolerance, intolerance or idiosyncratic reactions in susceptible individuals. e.g. individuals with Glucose-6-phosphate dehydrogenase deficiency are more susceptible to haemolytic effect of drugs like sulphonamides, aspirin and acetanilide.
10. Nutritional status: In malnourished animals, absorption, distribution, metabolism and excretion may be impaired.

- Decrease protein deficiency → decrease plasma protein → decrease protein binding
- Decrease microsomal enzymes → decrease metabolism → increased toxicity.

11. Pathological status: Liver diseases can reduce synthesis of protective binding molecules eg. glutathione

- Kidney diseases: Excretion of drugs → usual dose may result in accumulation of drug in body which is excreted through renal route.

- Route of administration
- Time of administration
- Drug interaction: Drug interaction may modify drug effect in various ways as discussed already.

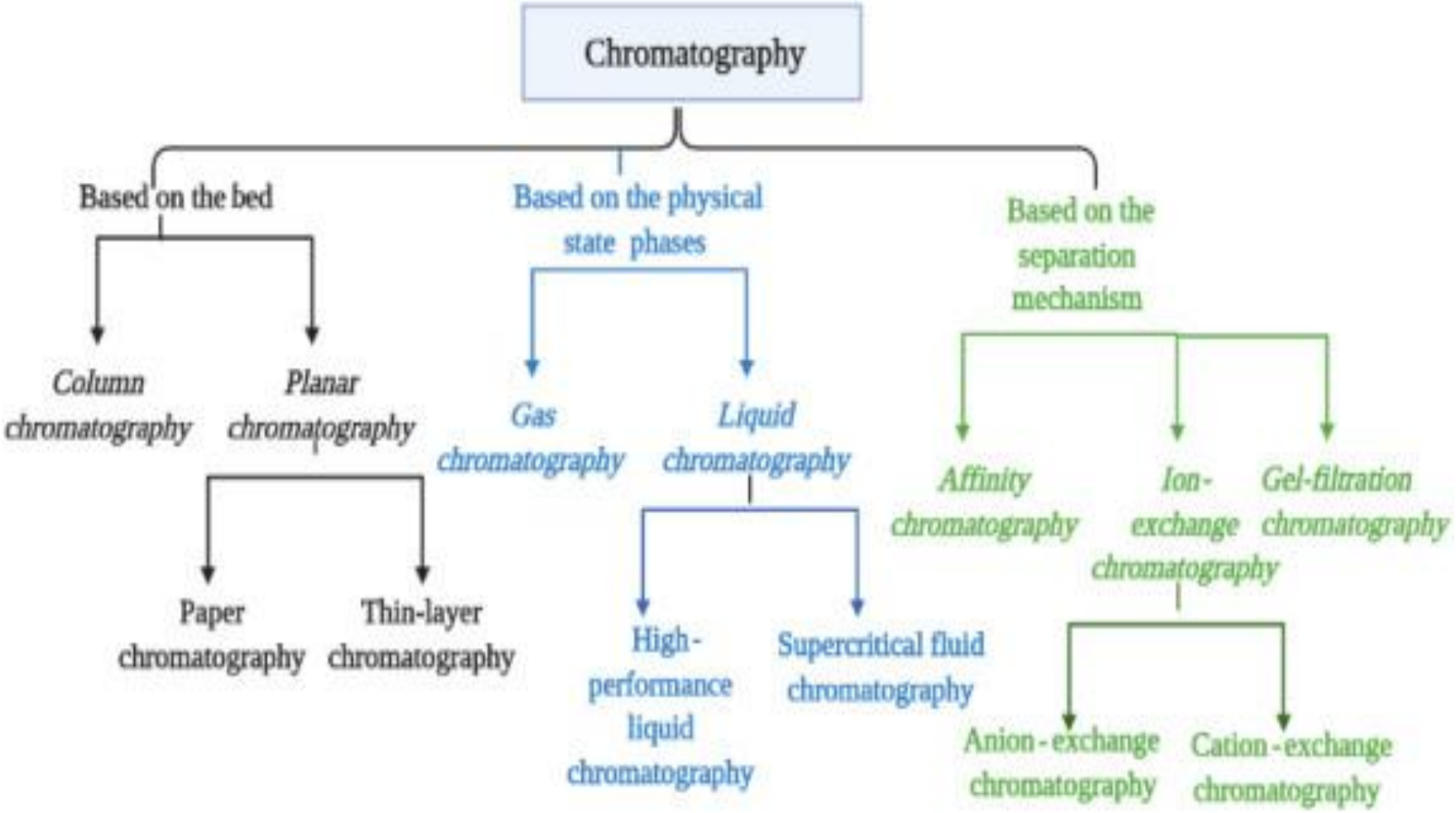
1. Drug interactions may be due to chelation of drugs by nutrients e.g. tetracyclines in presence Ca^{+2} ions.
2. Interactions may be at the level of absorption, distribution (less distribution due to more protein binding). Metabolism (induction of microsomal enzymes), excretion (Penicillin in presence of probenecid) and at the site of action.

Assay of drugs

- Assaying of drugs is the measurement of concentration or potency of drugs, metabolites or other biologically active chemical in biological material or drug preparations. It is done by utilizing two methods – bioassay and chemical assay.
- **Bioassay** or **biological assay** or **biological standardisation** is measurement of concentration or potency of substance by comparing its effect with that of a standard preparation on a test organism.
- Chemicals assay is defined as the measurement of concentration or potency of a substance by chemical/Physico-chemical methods. At most of the places, chemical assays have largely replaced bioassays.

Chemical assay

- Chromatography:- This is the most useful and powerful technique for the separation, purification and identification of closely related compounds in the mixture.
- Principle:- a mobile phase passes over a stationery phase and transports components of the mixture of different speeds in the direction of flow of the mobile phase. Separation occurs because the stationary phase either selectively binds or selectively excludes the specific chemical substance flowing in mobile phase.


Chromatography
Based on the bed
Based on the physical state phases
Based on the separation mechanism
Column chromatography
Planar chromatography
Gas chromatography
Liquid chromatography
Affinity chromatography
Ion-exchange chromatography
Gel-filtration chromatography
Paper chromatography
Thin-layer chromatography
High-performance liquid chromatography
Supercritical fluid chromatography
Anion-exchange chromatography
Cation-exchange chromatography

- Mass spectrometry:- In this technique, molecule of a substance is converted to vapours or gas & introduced in a chamber and then ionized by an electronic beam that removes one or more electrons of their orbital ions. The resulting ions (having positive charge) are then forced to move in a particular direction in the form of a beam by negatively charged electrode. Then a magnetic field separates the beam depending on the mass of ion. These separated beams are then measured by detectors.
- Spectrophotometry:- In this technique, a monochromatic light is allowed to pass through a solution of fixed length and then fraction of light absorbed by the sample is estimated. The fraction of light absorbed depends on the type of compound and its concentration. In this technique measurement can be made at any point in electromagnetic spectrum (200 to 750 nanometre).

- Colorimetry:- Principle is same as spectrophotometry but colorimeter cannot measure compounds which are colourless but absorb radiation in UV region. Wavelength range of this technique is 300-750 nanometre.
- Fluorimetry:- also called as fluorescence spectrophotometry. In this technique principle of fluorescence is used. A molecule in solution is energised by a light of short wave length. By the effect of light, electron in the molecule will move to a higher energy orbit. But after sometime, electron will fall back to its original orbit after emitting a light of a wavelength typical and specific for the molecule. The emitted light is detected as fluorescence by a sensitive wavelength selective multiplier tube. The intensity of fluorescence is proportional to the concentration of the fluorescing substance.

Adverse Drug Effects

- Adverse drug effects are unwanted or unintended effects of the drug that is harmful to the patient. These can occur even at normal therapeutic doses and vary in severity form mere inconvenience to organ dysfunction or even death.
- Pharmacological or type A adverse drug effects
- Exaggerated desirable effects, Side effects, Secondary effects, Drug interactions
- Non-pharmacological or type B adverse effects
- Hypersensitivity, Idiosyncrasy, Photosensitization , Intolerance
- Miscellaneous adverse effects
- Carcinogenicity, Mutagenicity, Teratogenicity, Iatrogenic disease

- **Exaggerated desirable effects:**
- These are high magnitude primary or desirable pharmacological effects and are observed either with over dosage or prolonged use of drug. Such effects can be avoided by administering appropriate dose.
- Haemorrhage → due to over dosage of anticoagulants.
- Dehydration and electrolyte depletion → over dosage of diuretics.
- **Side effects:**
- These are unwanted but unavoidable pharmacological effects of drug occurring at therapeutic dose. These can be predicted by pharmacological profile of a drug and after minimized by adjusting dosage.
  - Phenathiazine antihistamines → drowsiness
  - Anticholinergics → constipation
  - Antihypertensive agent → postural hypotension

- **Secondary effects:** These are indirect consequence of primary actions of drugs and usually cannot be controlled by dosage adjustment.
- e.g. Prolonged corticosteroid therapy may lead to activation of latent infections e.g. latent T.B.
- Broad spectrum antibiotics administered orally for longer duration cause diarrhea due to suppression of gut microflora.
- Prolonged NSAIDs therapy (like Aspirin) may lead to GIT bleeding or ulcerations.
- **Drug Interactions:** Drug interaction is a condition in which a drug (or food0 affects activity of other drug. Most drug interactions are well known & can be easily predicted. Adverse drug interactions usually occur by wrong prescriptions.

E.g. (i) Theophylline toxicity in the presence of Erythromycin because Erythromycin is a potent inhibitor of microsomal enzymes.

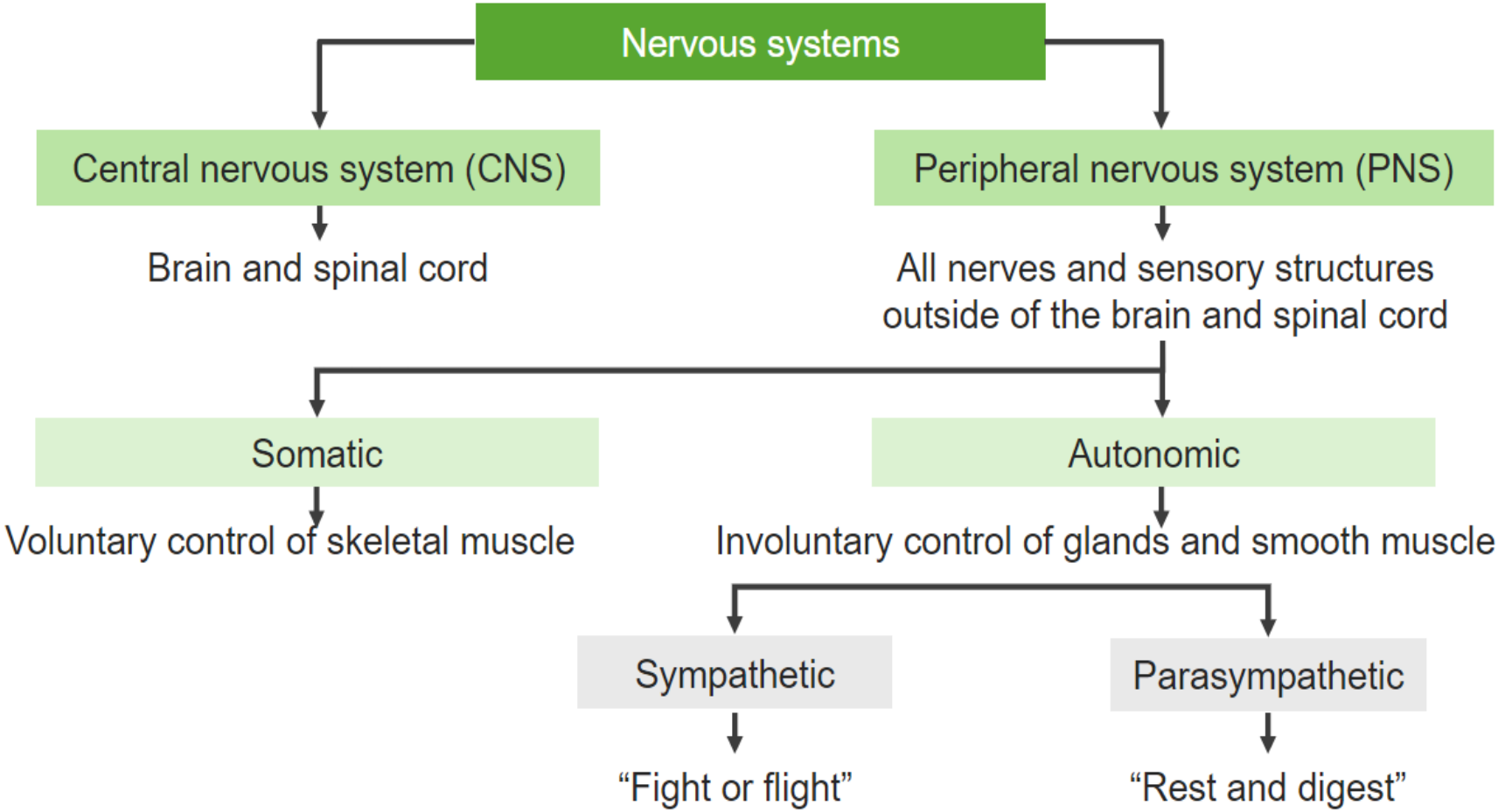
(ii) Warfain toxicity in the presence of Aspirin.

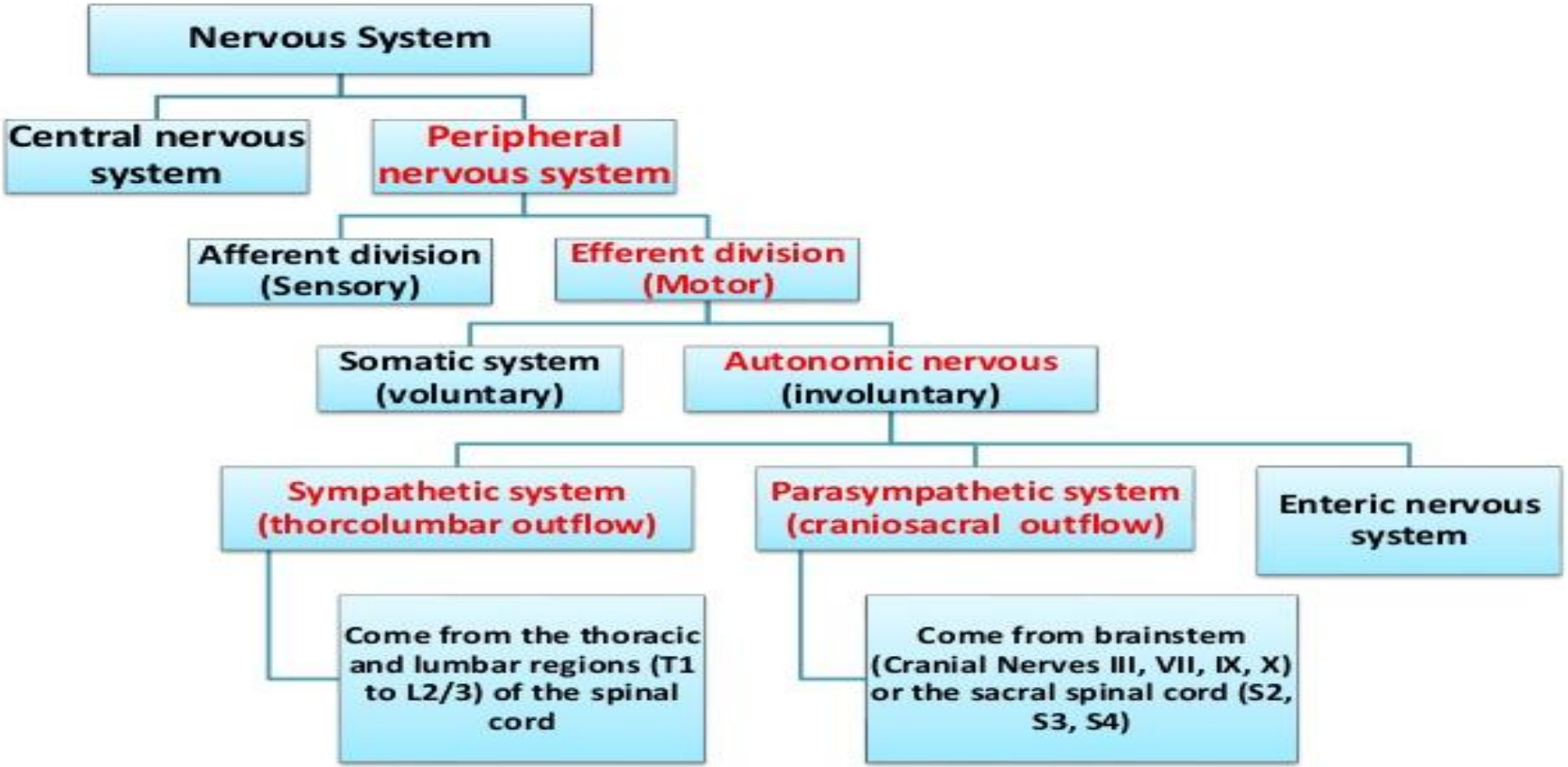
- **Hypersensitivity/ Drug Allergic reactions:**
- These are immunologically mediated untoward drug effects and are unrelated to pharmacodynamic profile of drugs.
  - These reactions are not dose-related and exposure of little amount of drug can lead to severe manifestations. These reactions are generally related to parenteral administration of drugs.
  - These drugs generally act as haptens and become complete antigen after combining with a body protein.
  - First exposure lead to sensitization of the body and subsequent exposure lead to hypersensitivity reactions.
  - A latent period of 1-2 weeks is required after the first exposure.
  - Gross reactions are shown by chemically related drugs e.g. Penicillin.

- **Idiosyncrasy:** These reactions occur in some individuals of a population. These are not immune related but are genetically determined. It is not related to the dose or pharmacology of the drug. e.g. 1. Sulphonamide produces haemolytic anaemia in some individuals. Halothane produces malignant hyperthermia & hepatitis.
- **Photosensitization/Photosensitivity**: These reactions occur due to presence of photodynamic agents in peripheral circulation and skin that absorb light and initiate chemical reactions. Here tissue injury occurs due to production of highly reactive oxygen intermediates and alteration cell membrane permeability. Examples of drugs producing Photosensitization are phenothiazine, sulphonamides, tar products etc.
- **Intolerance:** Here these are exaggerated pharmacological effects (desirable and undesirable) in an individual at therapeutic dose. Intolerance is shown by those patients who are very sensitive to the drug. Example:-Some people are extremely sensitive to NSAIDS because of variation in metabolism of arachidonic acid.

- **Carcinogenicity**: capacity of a drug to induce cancer. e.g. Alkylating agents (cyclophosphamide), androgens, oestrogens, metronidazole etc.
- **Mutagenicity**: It refers to capacity of a drug to cause abnormalities of genetic material (gene, chromosomes) of a cell so that a mutation occurs.
- **Teratogenicity/Dysmorphogenicity:** Refers to capacity of drug to cause foetal malformations when administered to a pregnant animal. e.g. thalidomide.
- **Iatrogenic Diseases**: are drug induced diseases which occur occasionally after the therapy is terminated or sometimes even during the course of therapy. These diseases also include nosocomial (acquired in hospital) diseases, medical negligence and contravention of contra-indications.
- e.g.1. Prolonged use of NSAIDs causes gastric ulceration. 2. Fluoroquinolones produce cartilage and joint damage in foals & pups. 3. Chloramphenicol produces myelosuppression and aplastic anaemia in humans.

Drugs Acting On Autonomic Nervous System


Nervous systems
Central nervous system (CNS)
Brain and spinal cord
Peripheral nervous system (PNS)
All nerves and sensory structures outside of the brain and spinal cord
Somatic
Voluntary control of skeletal muscle
Autonomic
Involuntary control of glands and smooth muscle
Sympathetic
"Fight or flight"
Parasympathetic
"Rest and digest"


Nervous System
Central nervous system
Peripheral nervous system
Afferent division (Sensory)
Efferent division (Motor)
Somatic system (voluntary)
Autonomic nervous (involuntary)
Sympathetic system (thorcolumbar outflow)
Parasympathetic system (craniosacral outflow)
Enteric nervous system
Come from the thoracic and lumbar regions (T1 to L2/3) of the spinal cord
Come from brainstem (Cranial Nerves III, VII, IX, X) or the sacral spinal cord (S2, S3, S4)

Sr. no.	Sympathetic Nervous System	Parasympathetic Nervous System
1.	Thoracolumbar in origin. All thoracic spinal nerves and first 2/3 lumbar spinal nerve give rise to symp. nerves.	Craniosacral in origin.
2.	Acts as sympathizer to animal i.e. it prepares the animals to fight or fly in stressful condition. Dissipation of energy is there.	Acts for conservation of energy
3.	Sympathetic ganglia are located parallel to spinal cord and on either side of spinal cord.	Ganglia are located near the organ or on the organ itself.
4.	Preganglionic sympethatic fiber is shorter than post ganglionic fiber	The preganglionic fiber is longer than postganglionic fiber
5.	In symp. nervous system, ratio of pre and post ganglionic fiber is 1:20 so stimulation results in wide-spread action	Ratio is 1:1 except Auerbach's and Meissner's plexus where it is 1:8000. Stimulation results into discrete response
6.	N.T. is NE in mammals, Epi in Amphibian. NE and Epi in avians.	ACh is N.T.

Organization of ANS

- ANS functions below the level of consciousness
- Also called Visceral, vegetative and involuntary nervous system
- complex set of neurons that mediate internal homeostasis without conscious intervention or voluntary control
- two main branches of efferent segment of ANS – the sympathetic nervous system and the parasympathetic nervous system
- sympathetic and parasympathetic outflow comprises two neurons- Preganglionic and postganglionic
- Majority of the organs supplied by systems which have opposite effects

- Consist of two division
- 1. Sympathetic/ Thoracolumbar outflow
- 2. Parasympathetic/ craniosacral outflow
- Visceral efferent pathway from CNS to visceral organ is unique in that it is composed of two multipolar neurons
- The first neuron in pathway has cell body in the CNS(brain and spinal cord) (Preganglionic fibre)
- The cell body of second neuron is located within the autonomic ganglion in peripheral nervous System(Post ganglionic fibre)

- Afferent (Sensory): Nerves that convey flow of impulse from peripheral to CNS.
- Efferent (Motor): Nerves that convey impulses from the brain and spinal cord (CNS) to muscles, glands and other organs.
- Ganglion: It is an aggregation of synapses.
- Neuroeffector junction: The junction of a post-ganglionic axonal terminal with its effector cell is termed a neuroeffector junction.
- Nerve plexus: It is a network of nerve fibres.

TYPES OF AUTONOMIC FIBRES:

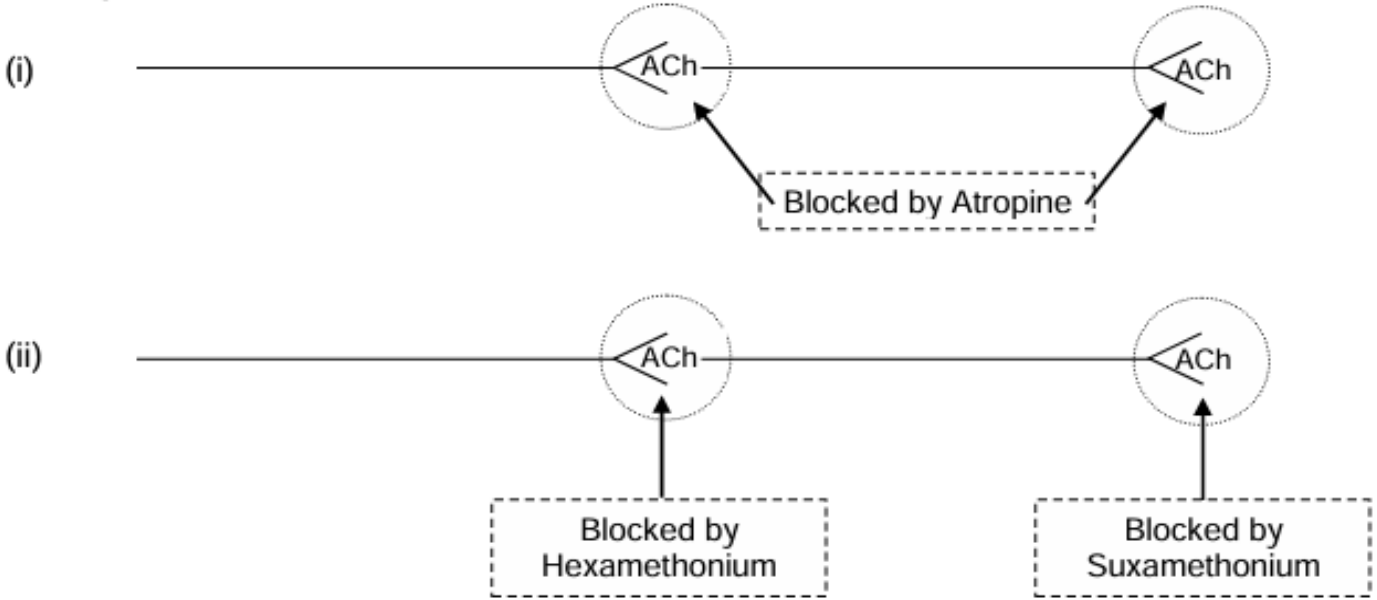
Sympathetic Fibres:

(i) Sympathetic adrenergic:

(ii) Sympathetic cholinergic: Supplies to salivary, bronchial and sweat glands of all animals except sheep and horses.

(iii) Sympathetic splanchnic cholinergic or sympathetic preganglionic fibre : Supplies to adrenal gland.

Parasympathetic Fibres:



- Cholinergic Fibre: Neuron liberate Ach as a major neurotransmitter
- All Preganglionic autonomic fibre (sympathetic as well as parasympathetic)
- All Postganglionic Parasympathetic fibres and a few post ganglionic sympathetic fibre(sweat gland in human)
- Adrenergic Fibre: Neuron liberate norepinephrine as a neurotransmitter. Example: Majority of Postganglionic sympathetic fibre.
- The term adrenergic and cholinergic are given by Dale
- Noradrenergic Norcholinergic fibres(NANC) release nitric oxide as their neurotransmitter substance. These fibres innervate GI tract, vasculature and external genitalia. Nitric Oxide is a noradrenergic norcholinergic neurotransmitter responsible for penile erection.

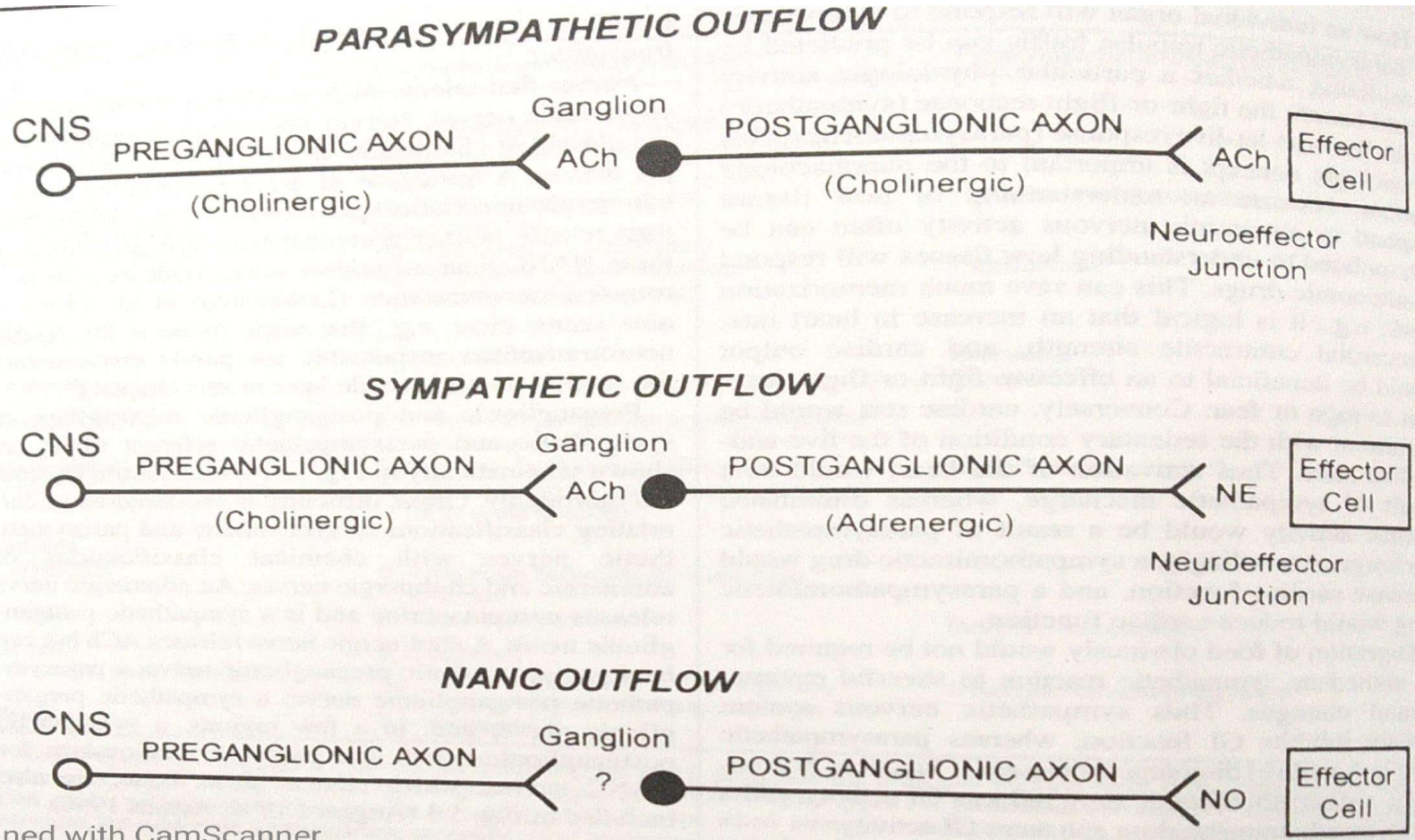


FIG. 5.3—Schematic representation of the preganglionic and

Sympathetic nervous system

- **Thoracolumbar system**

- not essential to life in a controlled environment but under the circumstances of stress prepares body for fight or flight as symapthomedullary system

- Adrenal medulla differs from sympathetic ganglia in that it releases epinephrine (adrenaline) whereas norepinephrine is released from post ganglionic sympathetic fibre.

Parasympathetic nervous system

- **craniosacral outflow.**
- tendency to slow down body processes except digestion and absorption of food and the functions of the genitourinary systems
- preganglionic fibre originate in three area of CNS - the midbrain, medulla oblongata and the sacral part of the spinal cord
- Post ganglionic supply the ciliary muscle, the salivary and lacrimal gland and the mucous gland of nose, mouth and pharynx, the fibre also include vasodilator nerve to the organ mentioned

Enteric Nervous System

- Enteric Nervous system does not have unique connection to CNS
- While under the influence of parasympathetic preganglionic fiber, Release of transmitter is usually is dominated by local control
- Enteric neurons located in Auerbach's and Meissner's Plexus releases different neurotransmitters such as VIP, NO, nucleotide which causes relaxation of intestinal muscle.

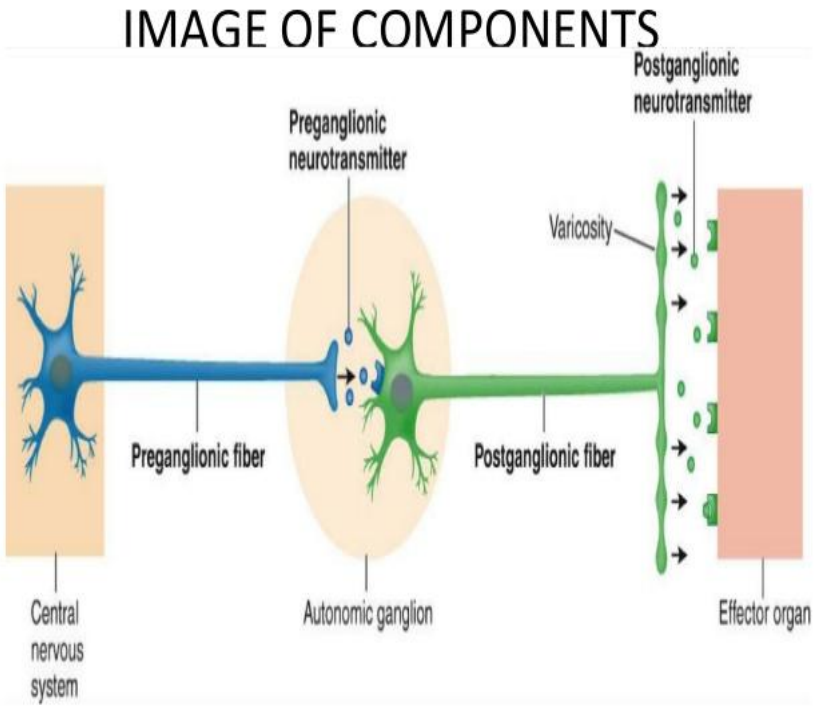
Effector tissues	*Sympathetic-mediated responses*[1]	*Parasympathetic -mediated responses*[2]
Heart	General excitation	General inhibition
Sinoatrial (SA) node	β_1 – increase heart rate	Decrease heart rate
Atria	β_1 – increase contractile force, conduction velocity	Decrease contractile force
Atrioventricular (AV) node	β_1 – increase automaticity, conduction velocity	Decrease conduction velocity; AV block
His-Purkinje system		…
Ventricles	β_1 – increase automaticity, conduction velocity	
	β_1 – increase contractile force, conduction velocity, irritability[3]	Decrease contractile force[4]
Blood vessels		
Coronary	α_1 – constriction; β_2 – dilation[5]	Dilation[6]; constriction[6]
Cutaneous, mucosal	α_1 – constriction	Dilation[7]
Cerebral	α_1 – constriction; β – dilation	Dilation[7]
Skeletal muscle	α_1 – constriction; β_2 – dilation[8]	Dilation[7]
Splanchnic	α_1 – constriction; β_2 – dilation[9]	Dilation[7]
Renal	α_1 – constriction; β_2 – dilation[9]	Dilation[7]
Genital	α_1 – constriction	Dilation[10]
Veins	α_1 – constriction	
Endothelium	α_2 – dilation	
GI tract	General inhibition	General excitation
Smooth muscle	β_1 – relaxation; α – relaxation[11]	Increase motility and tone
Sphincters	α – contraction	Relaxation
Secretions	Decrease (usually)	Increase
Gall bladder & ducts	Relaxation	Contraction
Bronchioles		
Smooth muscle	β_2 – relaxation	Contraction
Glands	Inhibition (?)	Stimulation

Eye Radial muscle, iris Sphincter muscle, iris Ciliary muscle	 α_1 – contraction (mydriasis) … β – relaxation; far vision	 … Contraction (miosis) Contraction; near vision
Urinary bladder Fundus Trigone, sphincter	Urinary retention β_1 – relaxation α – contraction	Urination Contraction Relaxation
Splenic capsule	α – contraction, β_2 – relaxation	…
Sweat glands	Secretion (cholinergic); [12]β_2 – Secretion (horse)	
Salivary glands	α_1 – scant, viscous secretion	Profuse watery secretion
Piloerector muscles	α – contraction	…
Kidney rennin release	α_2 – decrease; β_1 – increase	…
Uterus[13]	α_1 – contraction, β – relaxation (non-pregnant > pregnant)	Contraction[14]
Genitalia Male Female	 α – ejaculation …	 Erection[15] Erection[15]
Adrenal medulla	Secretion of epinephrine > norepinephrine (cholinergic)	…
Autonomic ganglia	Ganglionic discharge (cholinergic)	Ganglionic discharge[16]
Liver	β_2 – glycogenolysis and gluconeogenesis (α in some species)	…
Pancreas Islet cells Acini	 α_2 – decrease; β_2 – increase secretion α – decrease secretion	 … Increase secretions
Fat cells	β_1 – lipolysis	…
Adrenergic nerve terminals	α_2 – decrease release of norepinephrine β_2 – increase release of norepinephrine	± Release of norepinephrine[17]
Platelets	α_2 – aggregation	…

NEUROHUMOURAL TRANSMISSION

- Neurohumoral transmission implies that nerves transmit their message(in the form of Action Potential) across synapses and neuroeffector junctions by the release of humoral (chemical) messengers.

- Most of the autonomic drugs used clinically exert primary pharmacological activities by altering some essential step in neurohumoral transmission.



Criteria/Evidence For Being a Neurohumoural Transmitter

- Following criteria should be met before a chemical can be accepted as neurotransmitter –

  - It should be present in the presynaptic neuron
  - It should be released in the medium following nerve stimulation.
  - Demonstration that its application should produce responses identical to those produced by nerve stimulation.
  - Its effects should be antagonized or potentiated by other substances which similarly alter effects of nerve stimulation.

Steps involved in Transmission

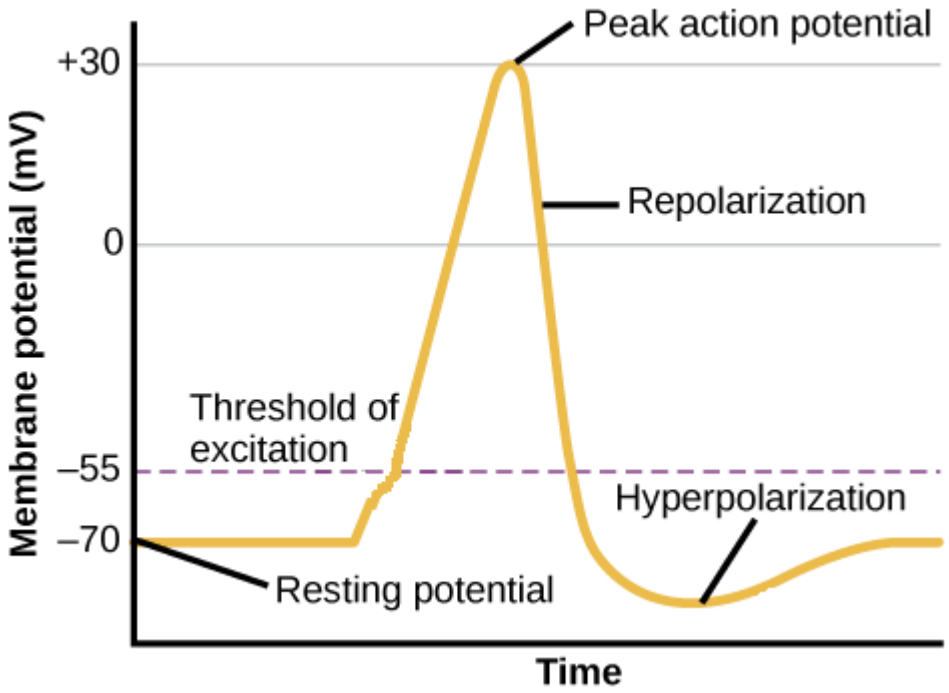
1. Axonal conduction
2. Junctional Transmission

- The conduction refers to passage of impulse along an axon or muscle fibre
- Transmission refers to passage of impulse across the synaptic or neuroeffector junction.
- Except Local anaesthetic very few drug modify the axonal conduction

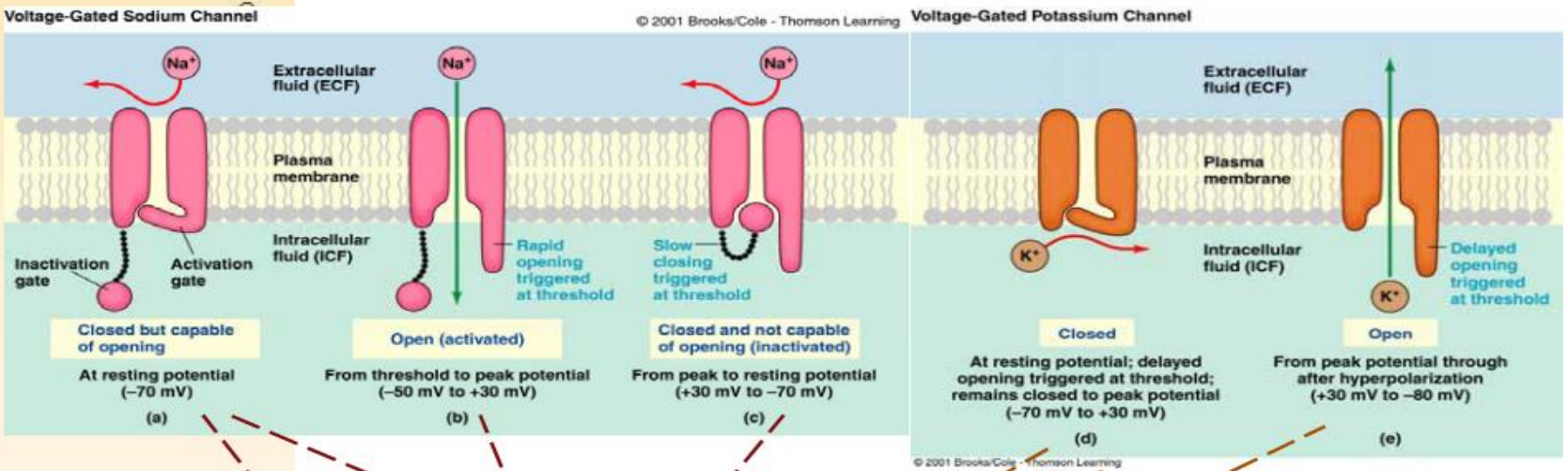
AXONAL CONDUCTION

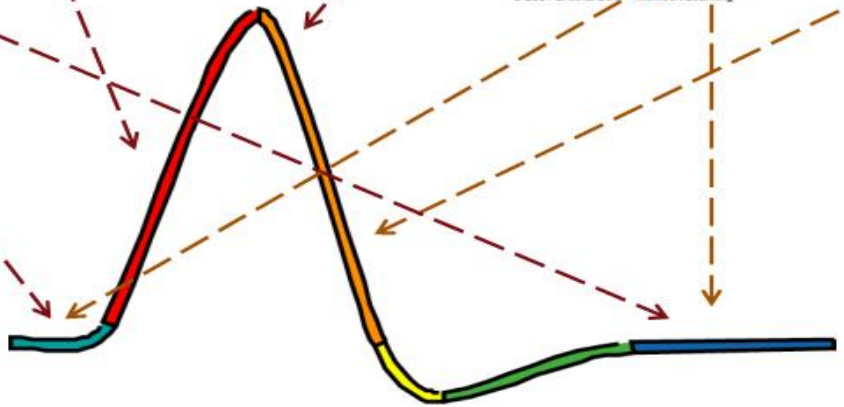
- Axonal conduction: passage of an impulse along a nerve fibre. It is dependent upon selective changes in the permeability of the axonal membrane to electrolytes.
- **Action Potential** or nerve impulse reflects a reversal of polarisation state present at rest (negative- inside and positive-outside) and is the result of permeability change that occur at the axonal surface as an impulse is propagated along the nerve fibre.
- At rest, membrane potential within mammalian axons is approximately -70 mV.

- In normal conditions Na+ ions are in higher concentration in extracellular than in intracellular fluid, whereas K+ ions are in greater concentration in intracellular than in extracellular fluid.
- During generation of action potential, permeability of the fibre to Na+ ion is greatly increased in relation to K+; Na+ moves inward in the direction of its large electrochemical gradient.
- The movement is detected by an instantaneous change in the membrane potential in a positive direction.
- The positively charged Na+ increases in concentration within the axon; the membrane potential moves from – 70 mV toward zero and then overshoots to the extent that momentarily the inside of the fibre is positive in relation to the exterior of the cell.


Peak action potential
+30
Repolarization
0
Threshold of
excitation
–55
Hyperpolarization
–70
Resting potential
Membrane potential (mV)
Time

- The axonal conduction is blocked by certain toxins such as Tetradotoxin (puffer fish poison) and Saxitoxin (shell fish toxin), which interfere with the Na+ entry across the neuronal membrane during depolarization.
- Batrachotoxin, a steroidal alkaloidal toxin elaborated by a type of South American frogs, paralyses the nerves by persistent depolarization as a result of increase in Na+ influx.
- Local anaesthetics act by preventing the Na+ influx and depolarization of the nerve.





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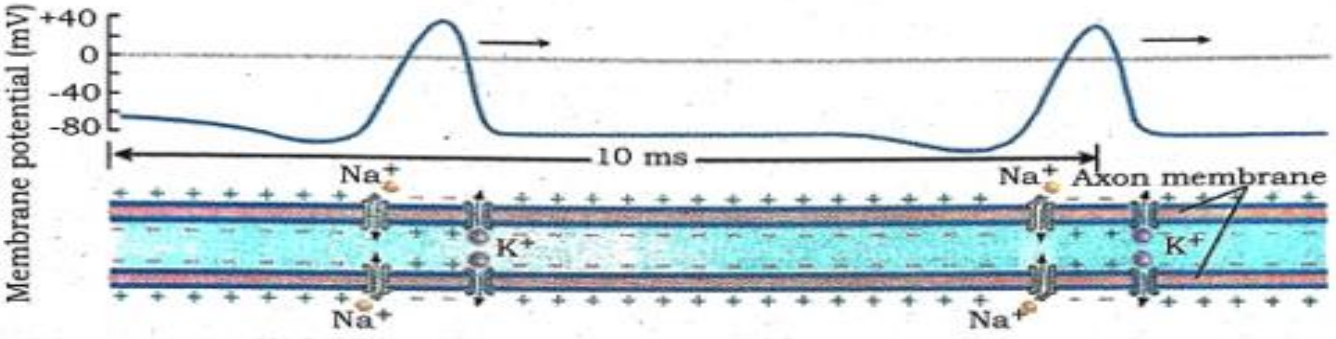
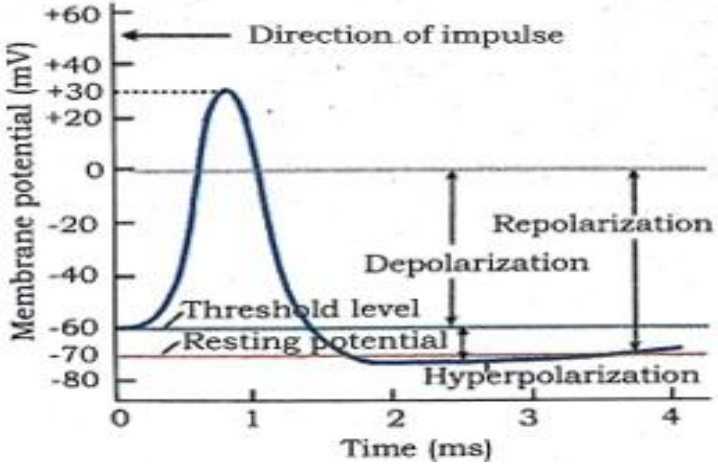
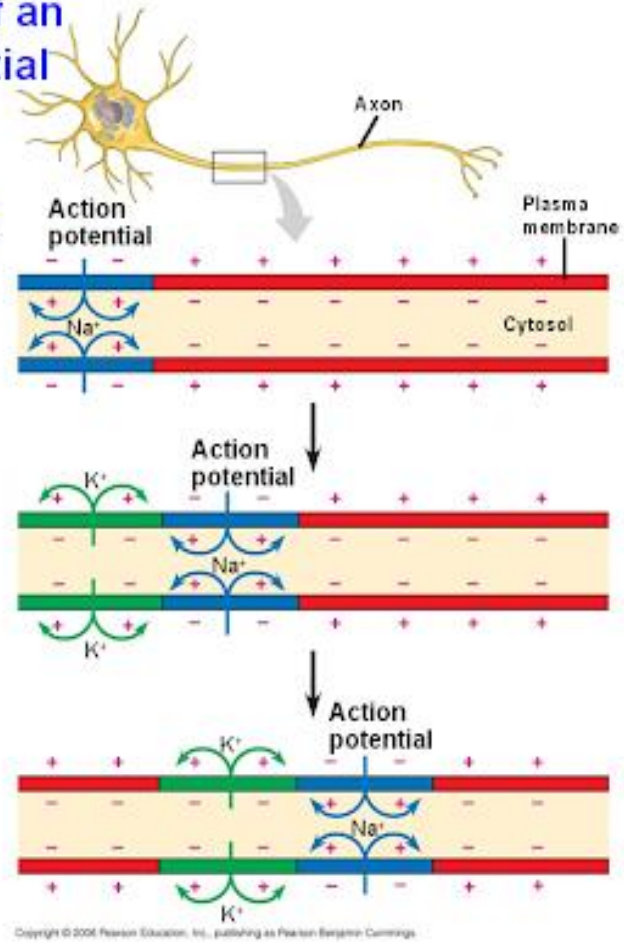

Membrane potential (mV)
+40
0
-40
-80
10 ms
Na+
K+
Axon membrane

(a)


Membrane potential (mV)
+60
+40
+30
+20
0
-20
-40
-60
-70
-80
Direction of impulse
Repolarization
Depolarization
Threshold level
Resting potential
Hyperpolarization
0
1
2
3
4
Time (ms)

Conduction of an Action Potential

Signal Transmission



Junctional transmission

- The arrival of action potential at the axonal terminal initiates a series of events

1. Storage and the release of transmitters
2. Combination of transmitter with postjunctional receptor and production of post junctional potential
3. Initiation of post junctional activity
4. Destruction/ Dissipation of transmitter

Storage and the Release of transmitters

- Nonpeptide neurotransmitter synthesised in axonal terminal and stored in synaptic vesicle while peptide NT synthesised in cell body and transported in vesicle to axon terminal.
- During the resting state there is continual slow release of isolated quanta of the transmitter;(Ach vesicle spontaneously leak into neuromuscular junction in resting condition)
- This produces electrical responses at post junctional membrane(miniature end plate potential or mepps) that are associated with maintenance of physiological responsiveness of effector organ.

- A low level of motor activity within the motor units of skeletal muscle is particularly important since muscle lacks inherent tone.
- The action potential causes the synchronous release of several hundred quanta of neuro transmitter.
- Depolarisation of axonal membrane triggers the influx of Ca ion through voltage gated calcium channel at axonal terminal
- This promotes the fusion of axoplasmic membrane to those of vesicles in close proximity of it.
- The content of vesicles including enzyme and other proteins, then are discharged to the exterior by a process termed exocytosis.

Combination of transmitter with postjunctional receptor and production of post junctional potential

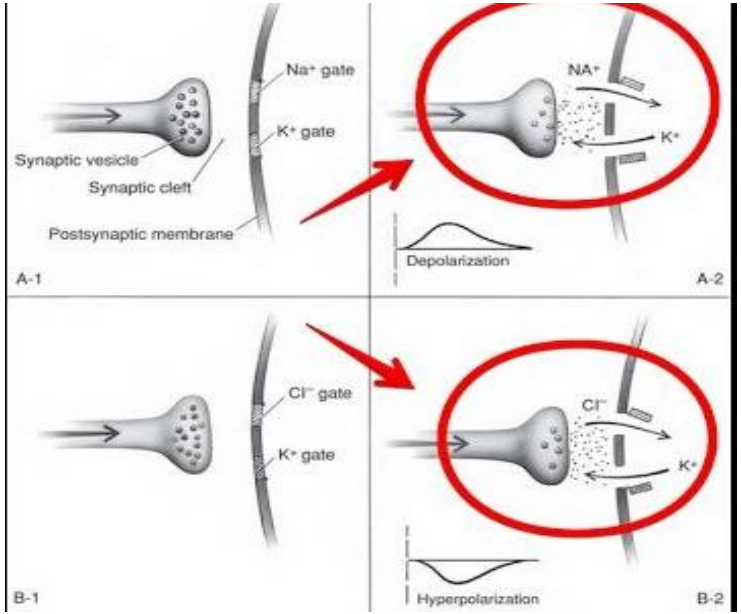
- Transmitter diffuse across the synaptic and junctional cleft
- combine within specialised receptors on post junctional membrane
- this result in localised increase in ionic permeability or conductance of the membrane.
- Following permeability change may occur depending on the type of receptor

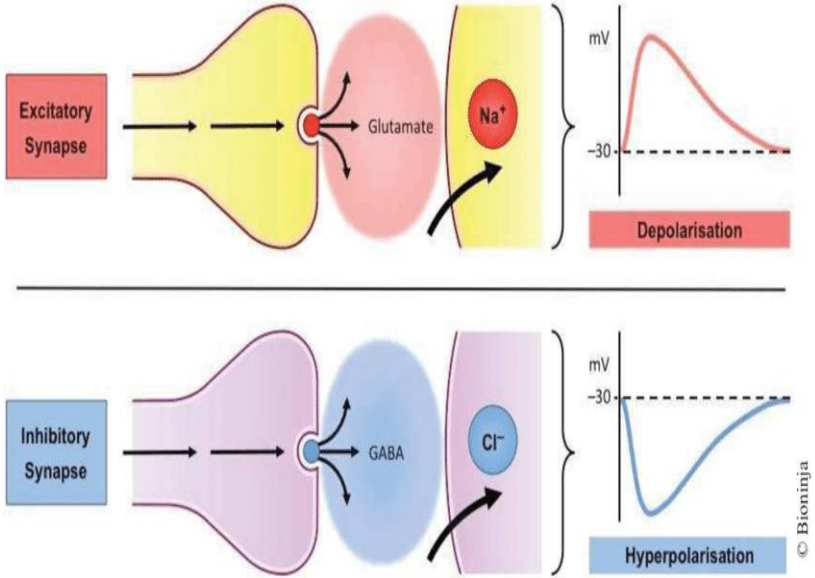
  i) A generalised increase in permeability to cation(notably Na but occasionally Ca++ resulting in localised depolarisation of the membrane(EPSP: Excitatory Post Synaptic Potential)

ii) A selective increase in permeability to anion, usually Cl-, resulting in hyperpolarisation and actual stabilisation of membrane which constitute the **inhibitory post synaptic potential(IPSP)**

iii) An increase permeability to potassium, because K gradient directed outside the cell, hyperpolarisation and stabilisation of the membrane potential occur.

- **Initiation of Post-Junctional Activity**
- If EPSP exceeds a certain threshold value, it initiates a propagated action potential in post synaptic neuron or a muscle action potential in skeletal and cardiac muscle by activating a voltage sensitive channel in the immediate vicinity.
- In gland EPSP increase secretion through ca2+ mobilisation


Na+ gate
K+ gate
Synaptic vesicle
Synaptic cleft
Postsynaptic membrane
NA+
K+
Depolarization
A-1
A-2
Cl− gate
K+ gate
Cl−
K+
Hyperpolarization
B-1
B-2

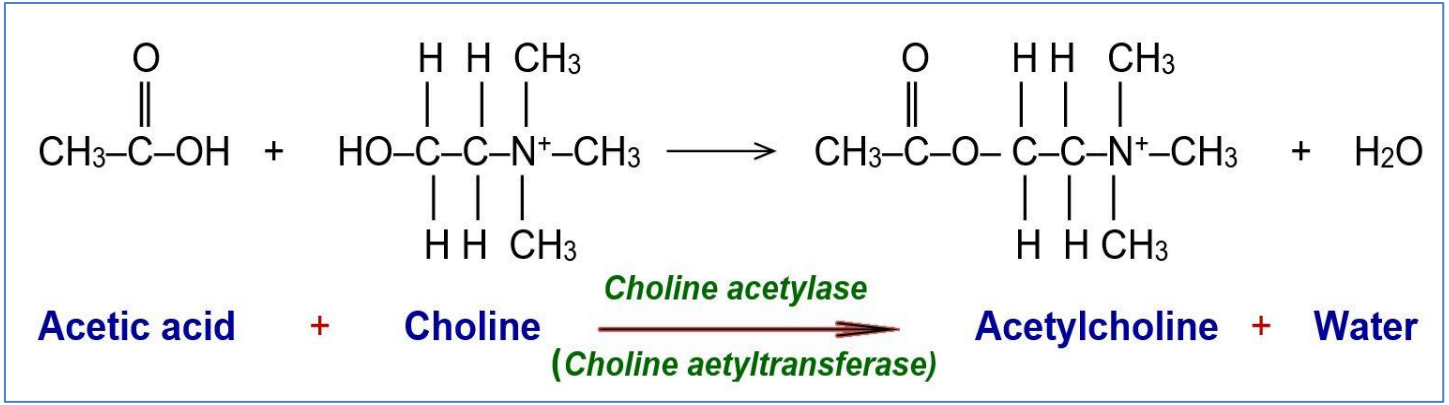

Excitatory Synapse
Glutamate
Na+
mV
-30
Depolarisation
Inhibitory Synapse
GABA
Cl−
mV
-30
Hyperpolarisation
© Bioninja

Destructions/ Dissipation of transmitter

- A high and localised concentrations of acetylcholine esterase are available at cholinergic synapse involved in very rapid neurotransmission
- Acetylcholine esterase is responsible for very rapid termination of action of acetylcholine at the cholinergic synapse or neuroeffector junction
- Rapid termination of cholinergic transmitters occur by the process of simple diffusion and and reuptake by the axonal terminals of most of the released norepinephrine.
- Termination of action of aminoacid transmitter mostly occurs by active transport into neuron and surrounding glia cells.

Cholinergic Transmission

- The impulse transmission on nerve or neuroeffector junction that is mediated by acetylcholine (ACh) is called cholinergic transmission.
- SYNTHESIS, STORAGE, RELEASE AND CATABOLISM OF ACETYLCHOLINE:



- ✓ **Hemicholinium** - competitively blocks choline uptake
- ✓ Uptake of choline is the rate limiting step in the biosynthesis of ACh.
- ✓ **Storage**: After synthesis in the cytoplasm, ACh is transferred to axonal vesicles in the nerve terminals where it is stored for release whenever necessary.
- ✓ Stored in form of complex with ATP, Ca^{2+}, Mg^{2+} and Vesiculin.(Ach: ATP – 10:1)
- ✓ Transport of ACh into synaptic vesicles is blocked by **Vesamicol** (storage blocker).
- ✓ **Release:** Two toxins interfere with cholinergic transmission by affecting release –

    1. **Botulinum toxin** (release blocker) inhibits release
    2. **Black widow spider toxin** induces massive release and depletion.

Destruction of ACh

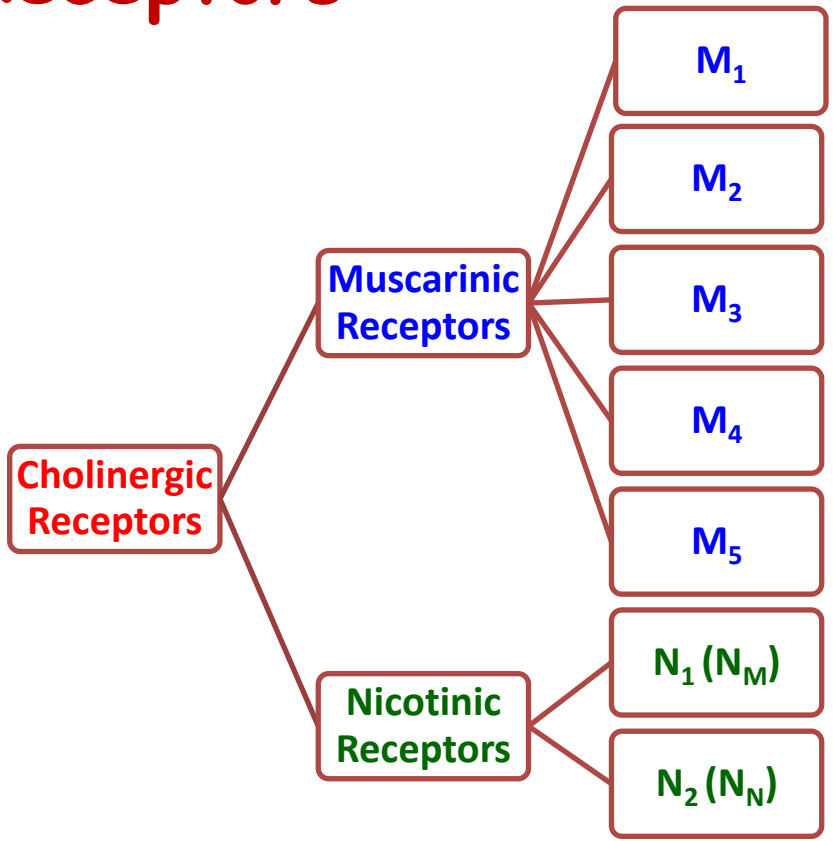
- ✓ After serving the transmitter function, ACh within the junctional space is rapidly inactivated by hydrolysis by a specific enzyme, acetylcholine esterase (AChE).
- ✓ AChE is present in cholinergic nerves, autonomic ganglia and neuromuscular & neuroeffector junctions.

- ✓ A somewhat similar enzyme, butyrylcholinesterase (a pseudocholinesterase) is present in serum and other body tissues. It is primarily synthesized in the liver and its likely vestigial physiological function is the hydrolysis of ingested esters from plant sources.

Cholinergic Receptors

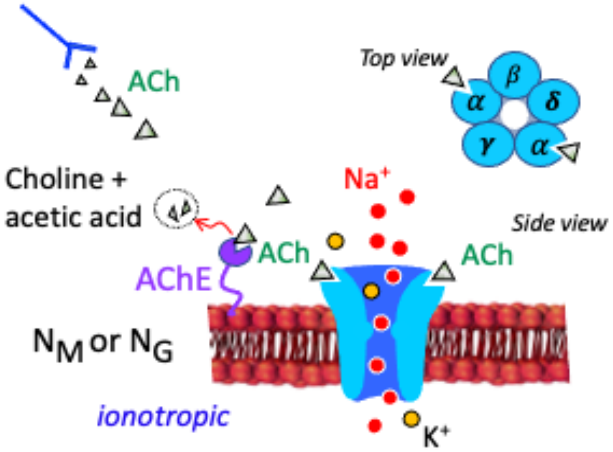
- ✓ **Muscarinic receptors (G-protein coupled receptors)**
- ✓ Selective affinity for alkaloid, muscarine (*Amanita muscaria*) - mimic the activity of ACh at the parasympathetic neuroeffector junctions.

- ✓ **Nicotinic receptors (Ligand gated cation channels)**
- ✓ Small doses of nicotine mimicked certain actions of ACh and large doses inhibited the same ACh responses.



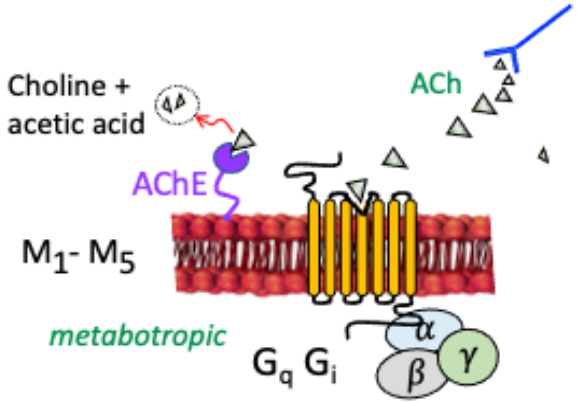
Nicotinic

- Responsive to nicotine
- Ionotropic (ion channel)
- **SkM, Ganglionic,** CNS
- Drugs affecting:
  - ACh (NT)
  - **SkM Relaxants (curare)**
  - **Ganglionic blockers**
  - CNS Partial agonists
  - **Inhibitors of AChE**



Muscarinic

- Responsive to muscarine
- Metabotropic (GPCRs)
- **Glands, Heart**, Vascular endothelial, **Smooth Muscle** (e.g. Eye, Gut, Lung), **CNS**
- Drugs affecting:
  - ACh (NT)
  - **Antimuscarinics (atropine, antihistamines…)**
  - Methacholine & Pilocarpine
  - **Inhibitors of AChE**



Muscarinic Receptors

	M_1	M_2	M_3
Location and function served	**Autonomic ganglia: Depolarization** **Gastric glands: Histamine release and acid secretion**	• **Heart - ionotropic and chronotropic effect** • **Cholinergic nerve endings: Decreased ACh release** • **(** Auto receptors: receptor that regulates, via positive or negative feedback processes, the synthesis and/or release of its own physiological ligand. **)**	**Visceral smooth muscles: Contraction** **Exocrine glands: Secretion** **Vascular endothelium: Release of nitric oxide (NO) → vasodilatation**
Agonist	**Oxotremorine**	**Methacholine**	**Bethanechol**
Antagonist	**Pirenzepine, Telenzepine**	**Methoctramine**	**Hexahydrosiladifenidol, Darifenacin**

Nicotinic Receptors

	N_M or N_1	N_N or N_2
Location and function subserved	Neuromuscular junction: Depolarization of muscle end plate ⇨ contraction of skeletal muscle.	Autonomic ganglia: Depolarization ⇨ post-ganglionic impulse. Adrenal medulla: Catecholamine release. CNS: Site specific excitation or inhibition.
Agonists	PTMA, Nicotine	DMPP, Nicotine
Antagonists	Tubocurarine, a-Bungarotoxin	Hexamethonium, Trimethaphan

Actions of Acetylcholine

[I]. Muscarinic actions:

1. Heart: SA node: Hyperpolarization, Rate of impulse generation reduced and bradycardia.

AV node & His-Purkinje fibres : Conduction slowed.

Atria : The force of atrial contraction is markedly reduced.

Ventricles : Contractility also reduced but not marked.

2. Blood vessels: Vasodilatation ⇨ Fall in B.P. Vasodilatation is primarily mediated through EDRF (NO).

3. Smooth muscles:

- ✓ Smooth muscles contracted. Tone and peristalsis in the GI tract is increased and sphincters relax ⇨ abdominal cramps and evacuation of bowel.

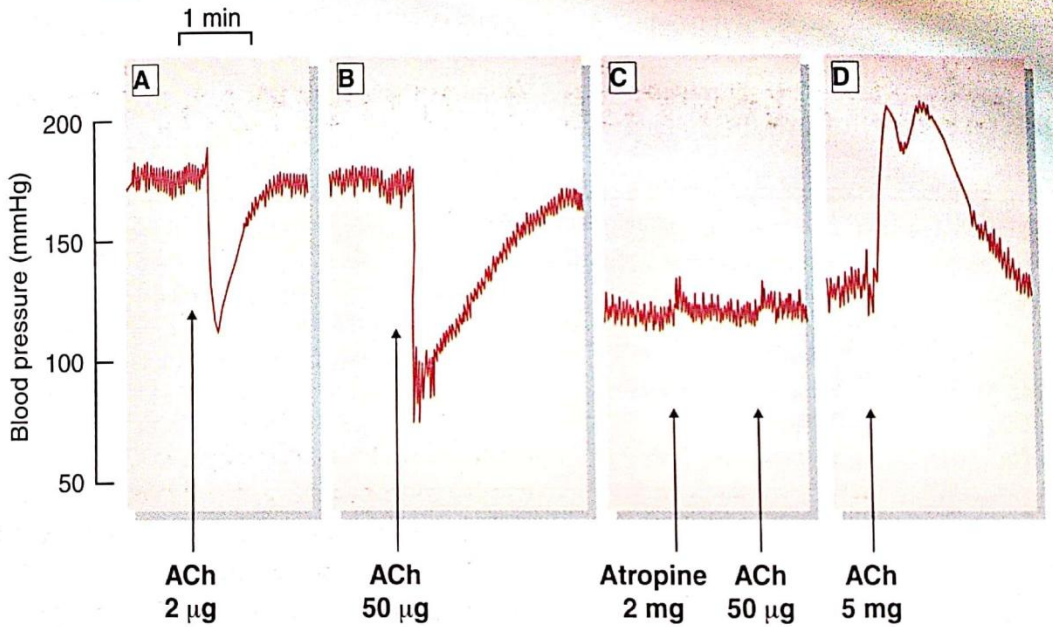
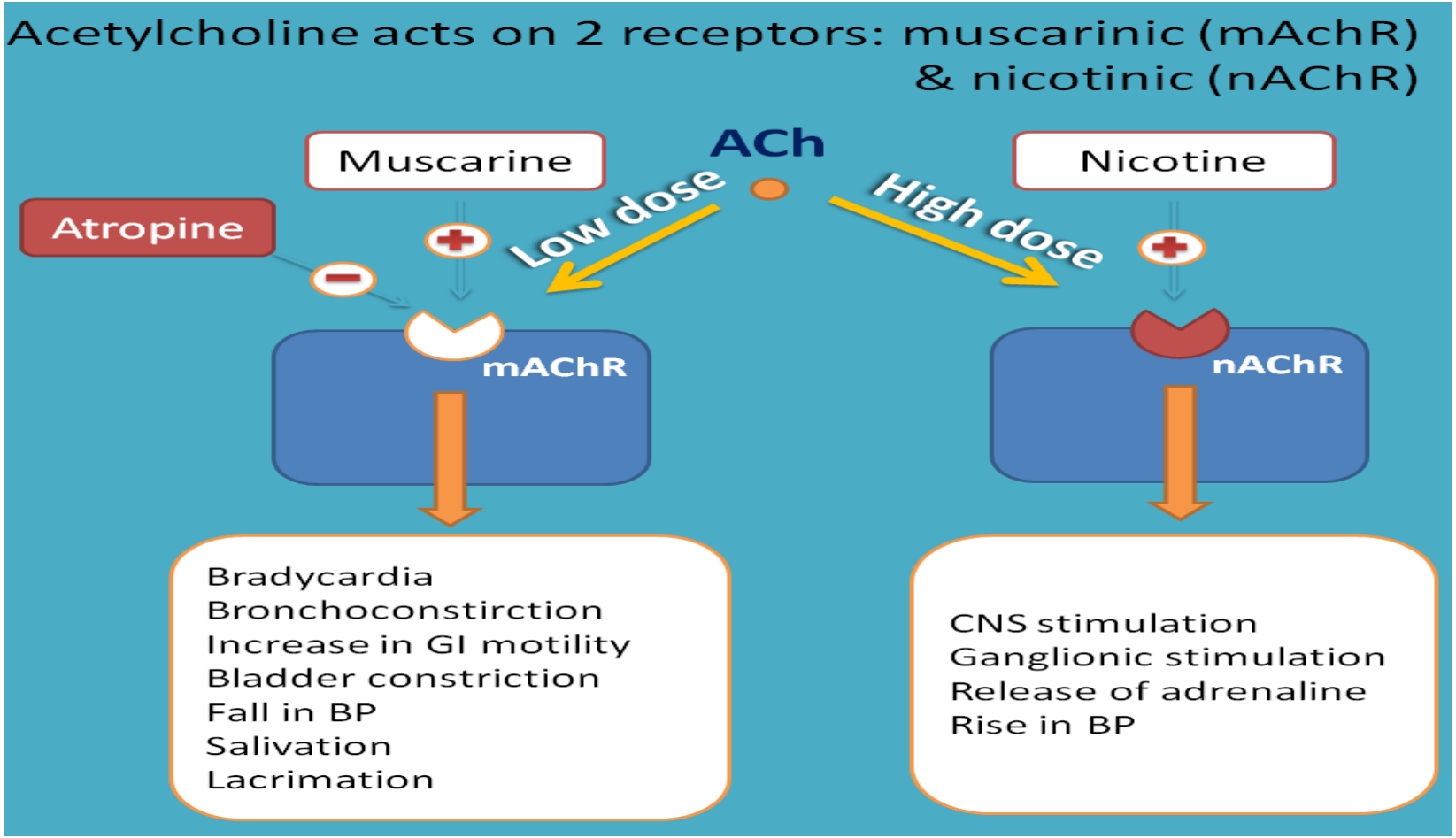
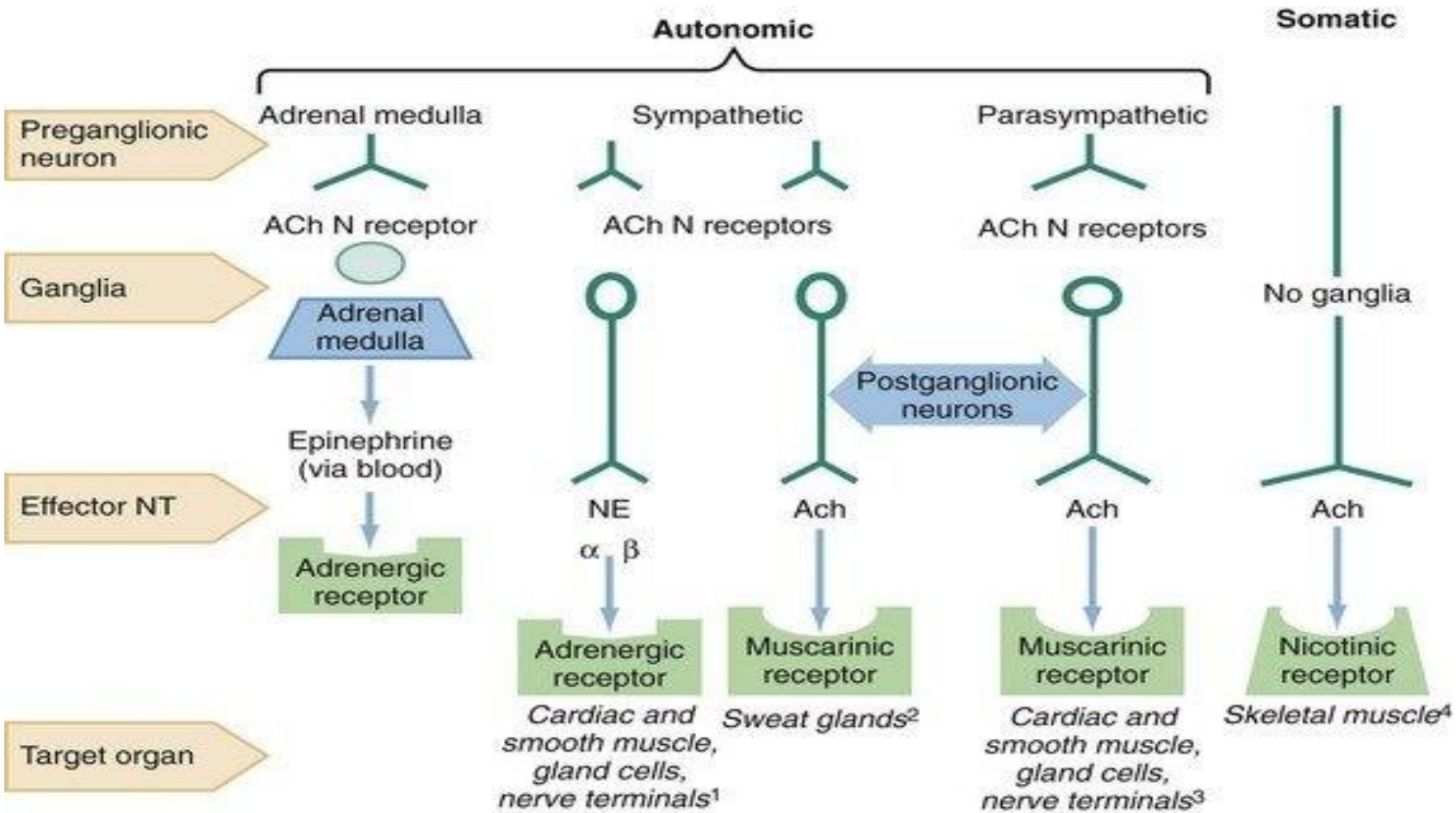


Fig. 10.1 Dale's experiment showing that acetylcholine (ACh) produces two kinds of effect on the cat's blood pressure. Arterial pressure was recorded with a mercury manometer from a spinal cat. A ACh causes a fall in blood pressure owing to vasodilatation. B A larger dose also produces bradycardia. Both A and B are muscarinic effects. C After atropine (muscarinic antagonist), the same dose of ACh has no effect. D Still under the influence of atropine, a much larger dose of ACh causes a rise in blood pressure (by stimulation of sympathetic ganglia), accompanied by tachycardia, followed by a secondary rise (owing to release of adrenaline from the adrenal gland). These effects result from its action on nicotinic receptors. (From: Burn J H 1963 Autonomic pharmacology. Blackwell, Oxford.)

Dale's Experiment

- After a muscarinic effect is blocked by atropine, larger dose of Ach produced another set of effect, closely similar to those of nicotine.
- They include:
  - Stimulation of All autonomic ganglia
  - Stimulation of voluntary muscle
  - Secretion of adrenaline from the adrenal medulla.
- Experiment of Dale formed the basis of classification of Ach receptor
- There are two type of Ach receptor in body muscarinic(M) and Nicotinic(N)
- Capacities of tubocurarine and atropine to block nicotinic and muscarinic effect of Ach, respectively, provided further support for the proposal of two distinct type of cholinergic receptor.


Acetylcholine acts on 2 receptors: muscarinic (mAchR) & nicotinic (nAChR)
Muscarine
ACh
Nicotine
Atropine
Low dose
High dose
mAChR
nAChR
Bradycardia
Bronchoconstirction
Increase in GI motility
Bladder constriction
Fall in BP
Salivation
Lacrimation
CNS stimulation
Ganglionic stimulation
Release of adrenaline
Rise in BP


Autonomic
Somatic
Preganglionic neuron
Adrenal medulla
Sympathetic
Parasympathetic
ACh N receptor
ACh N receptors
ACh N receptors
Ganglia
Adrenal medulla
No ganglia
Postganglionic neurons
Epinephrine (via blood)
Effector NT
NE
Ach
Ach
Ach
α β
Adrenergic receptor
Adrenergic receptor
Muscarinic receptor
Muscarinic receptor
Nicotinic receptor
Target organ
Cardiac and smooth muscle, gland cells, nerve terminals1
Sweat glands2
Cardiac and smooth muscle, gland cells, nerve terminals3
Skeletal muscle4

Nicotinic Receptor

- typical of ligand gated ion channel(fast action)
- activation always causes a rapid(millisecond) increase in cellular permeability to Na+ and Ca2+
- depolarisation and excitation

- **Nicotinic Muscle Ach receptor(Nm):**confined to the skeletal neuromuscular junction
- selectively stimulated by Phenyl Trimethyl Ammonium (PTMA). It is selectively blocked by tubocurarine

- **Nicotinic neuronal Ach receptor(Nn):** These are present on ganglionic cell, adrenal medullary cells and in spinal chord and in certain area of brain
- selectively stimulated by Dimethyl Phenyl Piperazinium(DMPP) and blocked by Hexamethonium.

Nicotinic Receptors

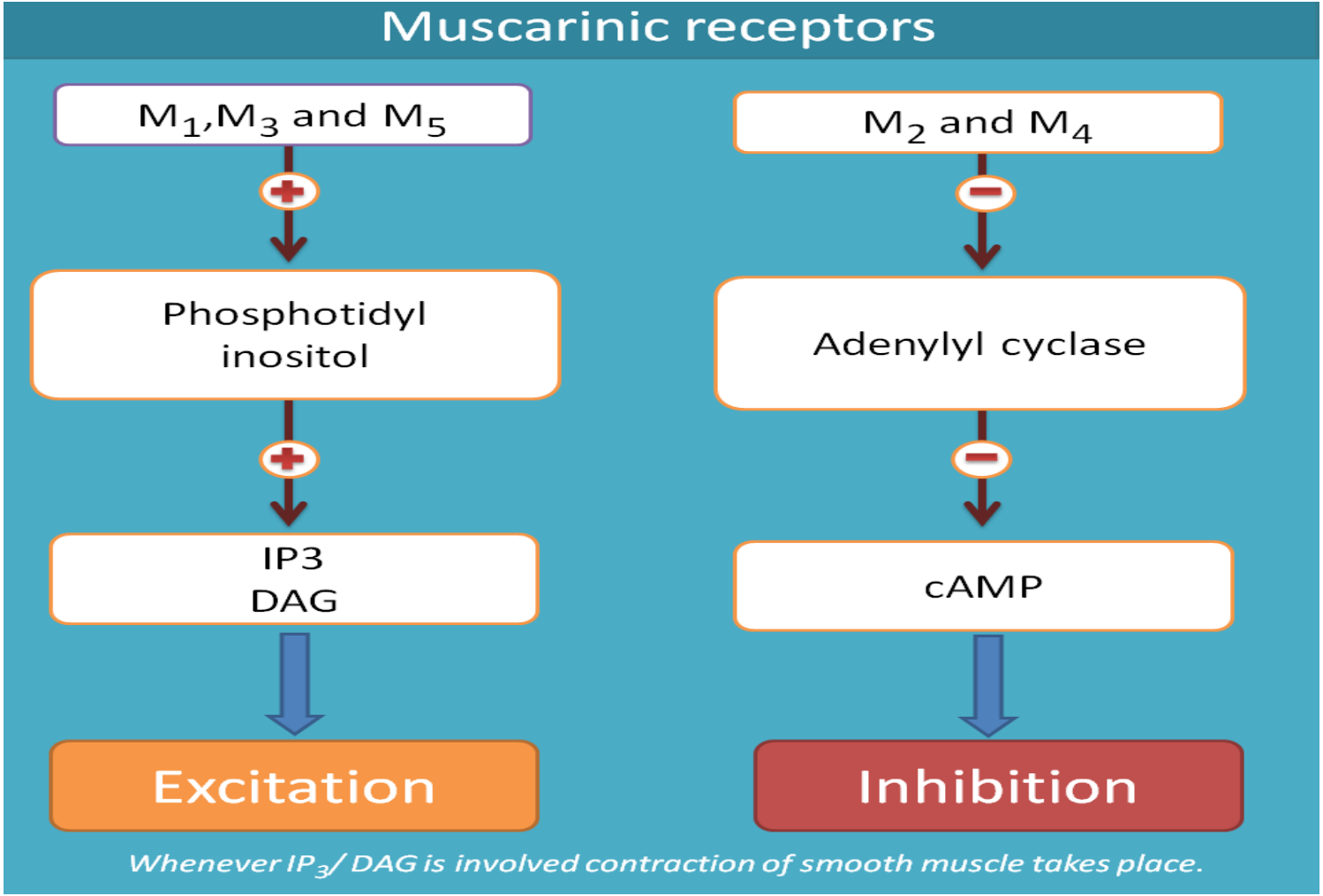
	N_M	N_N
1.Location and function subserved	Neuromuscular junction: Depolarization of muscle end plate ⇨ contraction of skeletal muscle.	Autonomic ganglia: Depolarization ⇨ post-ganglionic impulse. Adrenal medulla: Catecholamine release. CNS: Site specific excitation
2.Transducer mechanism/ membrane response	Opening of cation(Na+) channel-**Excitatory**	Opening of cation(Na+ , K+, ca2+) **channel-Excitatory**
Agonists	PTMA(Selective), Nicotine	DMPP(Selective), Nicotine
Antagonists	Tubocurarine, a-Bungarotoxin	Hexamethonium, Trimethaphan

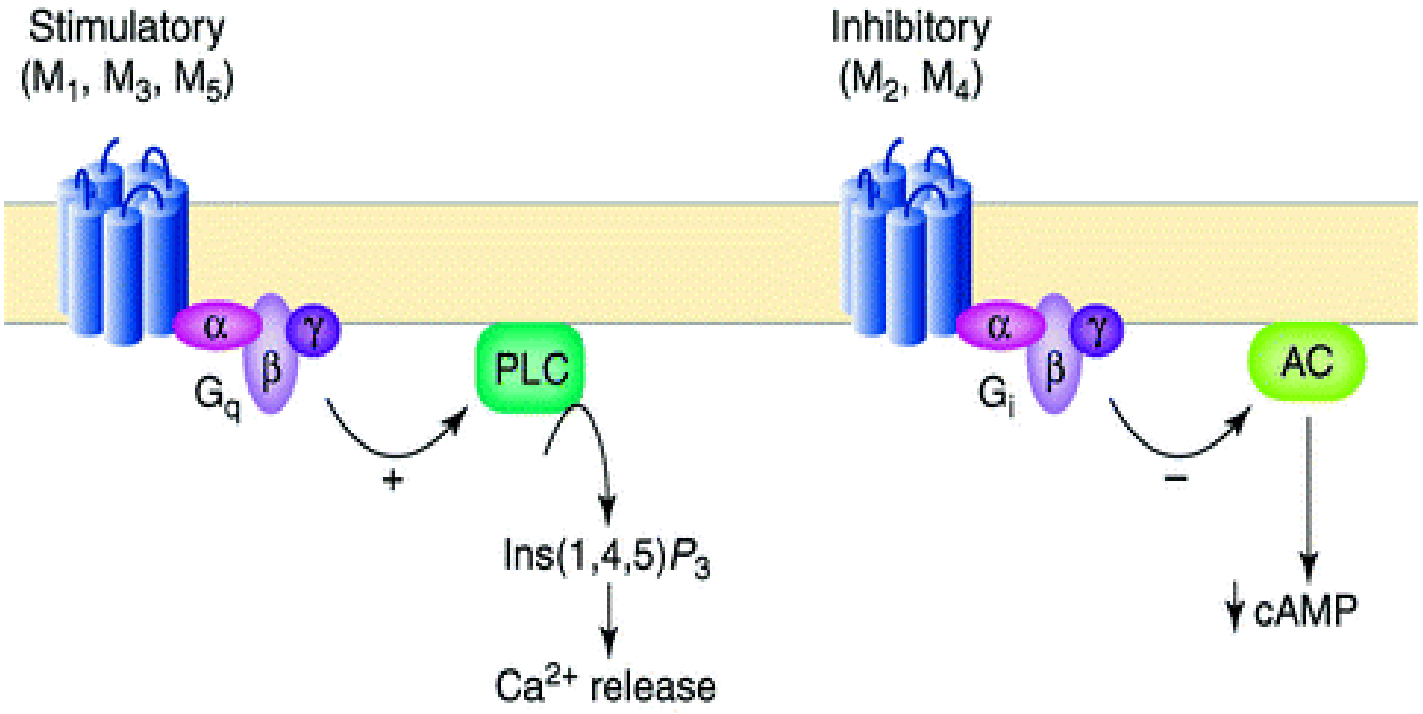
Muscarinic receptor

- There are five subtypes of muscarinic receptor**: M1, M2, M3, M4 and M5**
- First three are major subtype that are present on effector cells as well as on prejunctional nerve endings and are expressed in both peripheral organ as well as in the CNS
- M4 and M5 - mainly in certain area of brain & regulate the release of other neurotransmitter
- Functionally, M1, M3 and M5 fall in one class while M2 and M4 fall in another class

Muscarinic Receptors

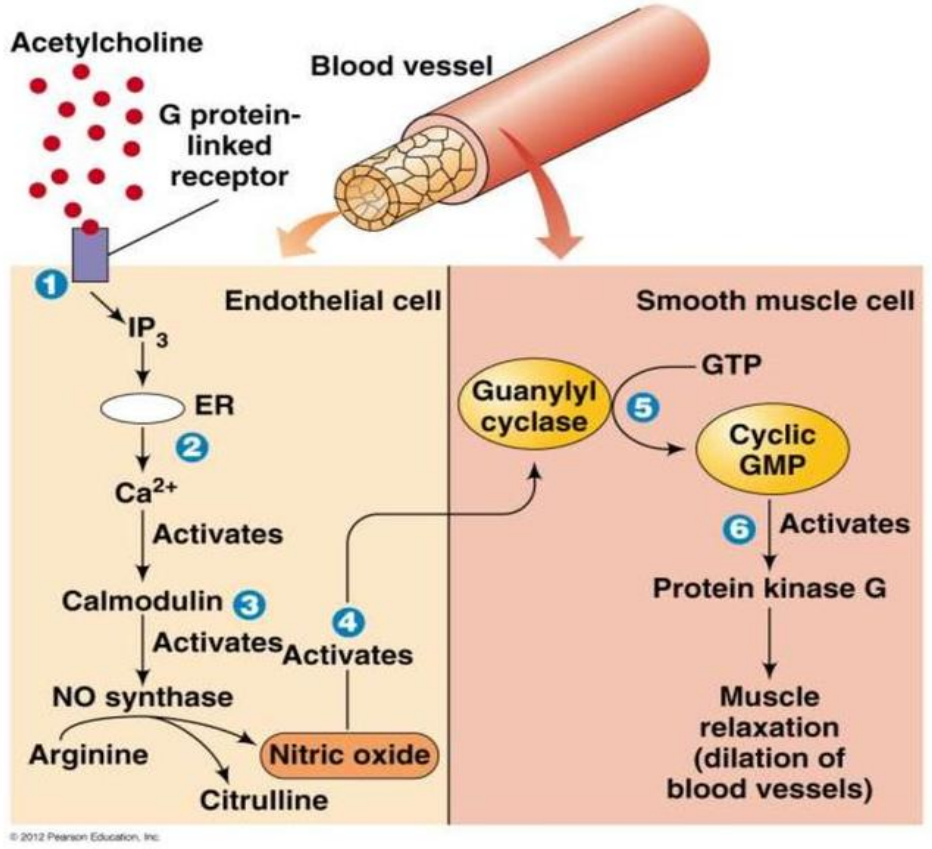
	M_1	M_2	M_3
Transducer mechanism	IP3/DAG-increased cytosolic ca2+ ion, PLA2 stimulation-PG synthesis	K channel opening, decrease in cAMP level	IP3/DAG-increased cytosolic ca2+ ion, PLA2 stimulation-PG synthesis
Agonist	Oxotremorine	Methacholine	Bethanechol
Antagonist	Pirenzepine, Telenzepine	Methoctramine	Hexahydrosiladifenidol


Muscarinic receptors
M1,M3 and M5
Phosphotidyl inositol
IP3
DAG
Excitation
M2 and M4
Adenylyl cyclase
cAMP
Inhibition
Whenever IP3/ DAG is involved contraction of smooth muscle takes place.

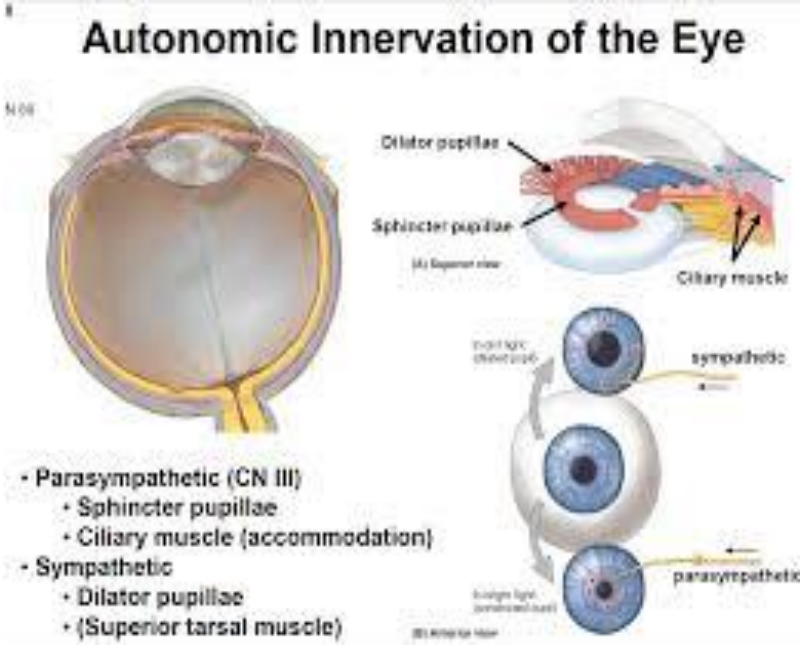

Stimulatory
(M1, M3, M5)
Inhibitory
(M2, M4)
α
β
γ
Gq
Gi
PLC
AC
+
−
Ins(1,4,5)P3
Ca2+ release
cAMP
TRENDS in Pharmacological Sciences

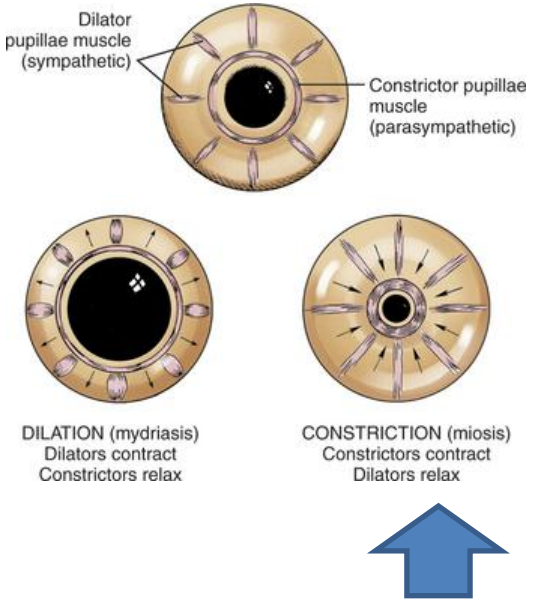
Action of Ach on Blood Vessels

- **All blood vessels are dilated, though only few vessels (skin of face, neck, salivary gland) receive cholinergic innervation**.
- **Fall in BP occurs**
- Ach binds with M3 receptor on vascular endothelial cell------- **Release of NO from endothelial cell**---Act on smooth muscle cell ----Activation of Guanyl cyclase enzyme-----Relaxation of BV---hypotension



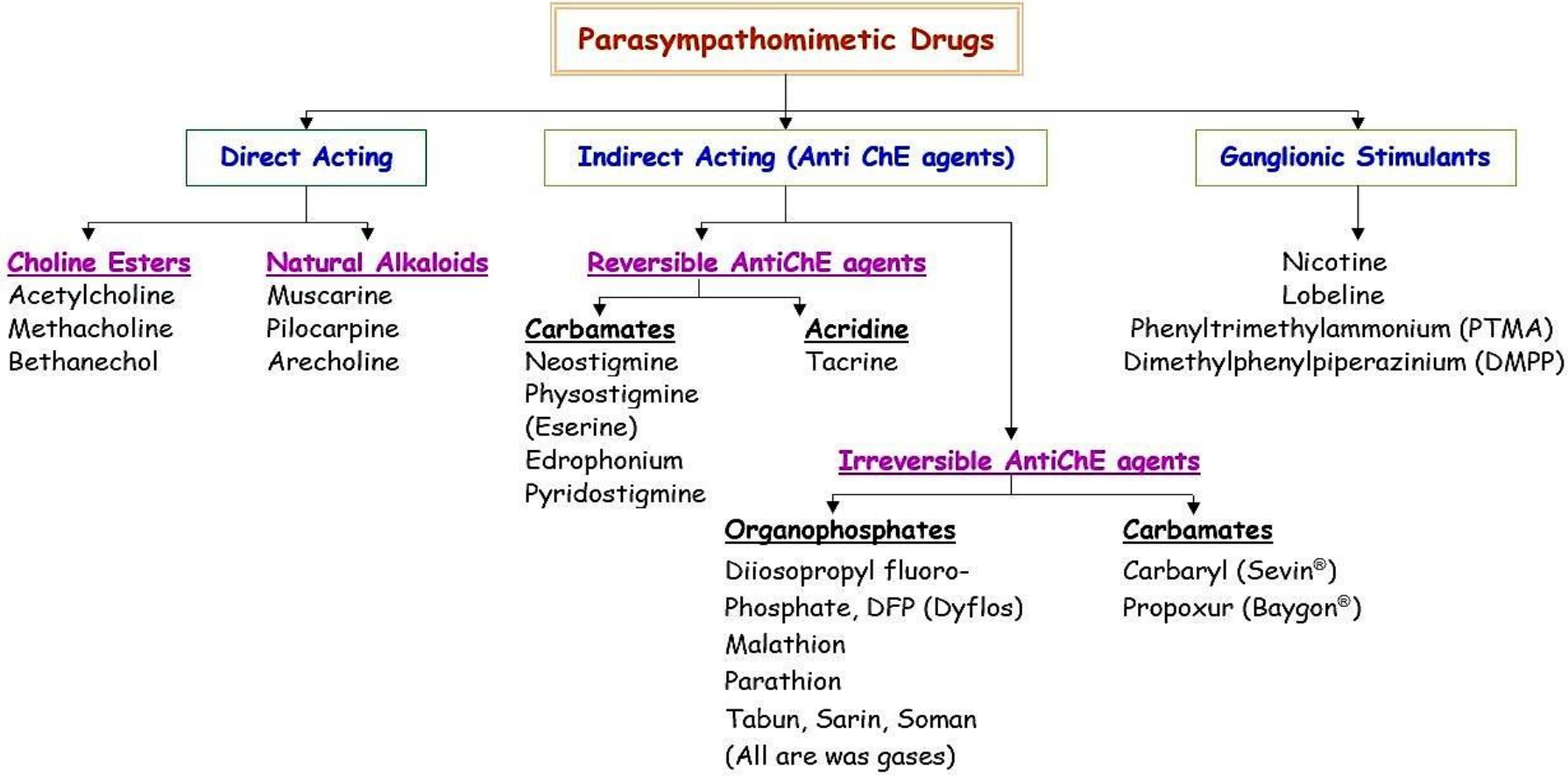
Autonomic innervation of eye and effect of sympathetic and parasympathetic stimulation





Effect of Ach on pupil Size: Miosis

Classification of Parasympathomimetic Drugs



Natural Alkaloids

1. Pilocarpine:

- ✓ leaves of Brazilian shrubs *Pilocarpus jaborandi* and *P. microphyllus*.
- ✓ Prominent muscarinic actions

2. Arecholine:

- ✓ An alkaloid found in the beetle nut, the seed of the beetle palm (*Areca catechu*).
- ✓ Has muscarinic as well as nicotinic actions including those on skeletal muscle end plate.
- ✓ Clinically, solutions of 0.5 to 2% of pilocarpine are used for instillation into the conjunctival sac for treatment of glaucoma.
- ✓ Other uses of pilocarpine as a miotic agent.

Cholinesterase Inhibitors

- ✓ These are indirect acting parasympathomimetic agents.
- ✓ They inactivate or inhibit AChE and thereby intensify the activity of endogenous ACh.

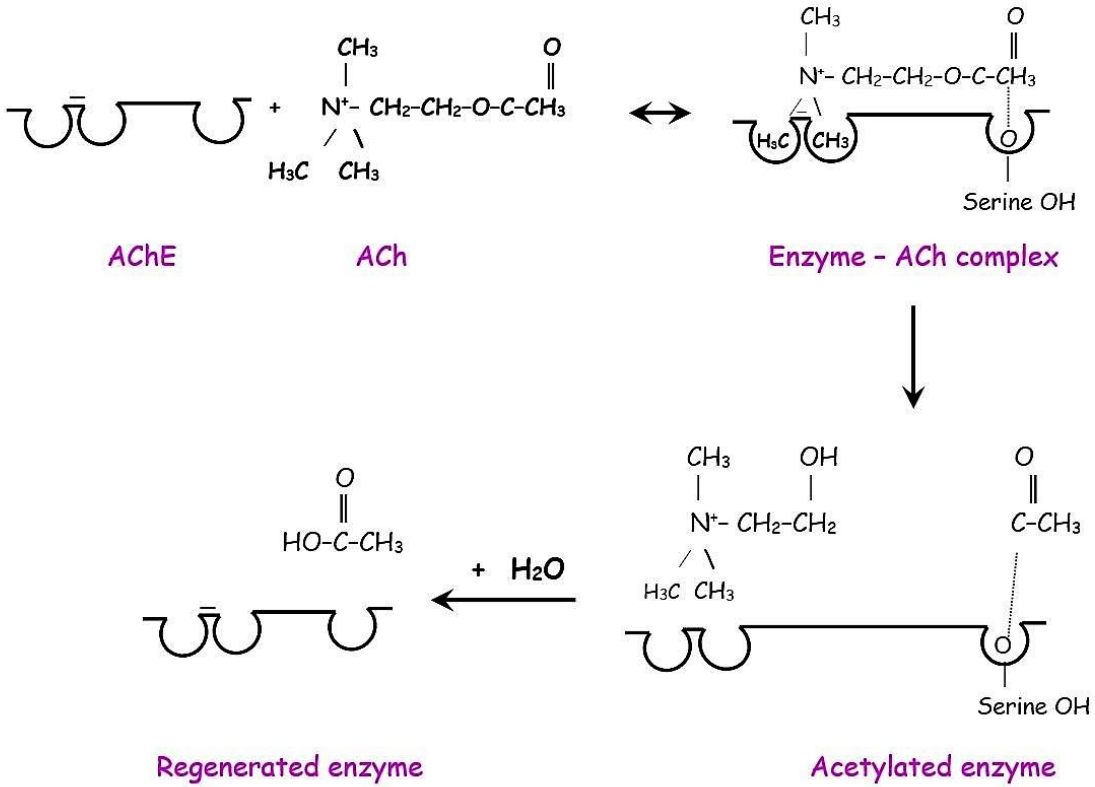
- **Acetylcholinesterase (AChE):**

- **Anionic site:** Active region of AChE formed by tryptophan
- **Esteratic site:** Formed by serine, glutamate and histidine

Cholinesterase Inhibitors

Hydrolysis of ACh by AChE:

- Involves electrostatic attraction of +ly charged N^+ of ACh to the aromatic pocket and nucleophilic attack by serine –OH which is activated by the adjacent histidine leading to acetylation of the serine.
- The acetylated enzyme reacts with water to produce acetic acid and choline.



Reversible Cholinesterase Inhibitors:

- **Mechanism of action:**
  - reversibly bind to the active sites of the enzyme
  - Edrophonium and Tacrine attach only to the anionic site of the enzyme and tacrine - action is brief.
  - Physostigmine and Neostigmine bind to both anionic and esteratic sites ---So, the carbamylation of the enzyme (with neostigmine and physostigmine) is of longer duration than the inhibition by edrophonium.
  - during the period where the enzyme inhibitor complex exists, the enzyme will not hydrolyze its natural substrate ACh.

III. Cholinesterase Inhibitors

[A]. Reversible Cholinesterase Inhibitors:

1. Physostigmine:

- ✓ An alkaloid extracted from the dried ripe seeds of a vine, *Physostigma venenosum*
- ✓ physostigmine is used for its ability to constrict the pupil or as miotic and in the **treatment of deadly nightshade poisoning**.

2. Neostigmine:

- ✓ synthetically produced
- ✓ It is used as purgative and in the treatment of atony of urinary bladder.

- **[B]. Irreversible Cholinesterase Inhibitors:**

- **Mechanism of action:**

  - Organophosphates act as irreversible inhibitors of the cholinesterases in mammals.

  - These compounds irreversibly phosphorylate the esteratic site of AChE

  - Endogenous ACh is not inactivated and the resulting effects are due to the excessive preservation and accumulation of endogenous ACh.

- **Effects & Toxicity:**
  - Muscarinic effects: Profuse salivation, vomiting, defaecation, hypermotility of the GI tract, urination, bradycardia, hypotension, severe bronchoconstriction and excess bronchial secretions.
  - Nicotinic effects: Skeletal muscle fasciculations, twitching and subsequently muscle paralysis.
  - CNS symptoms: Convulsions and frequently death due to the penetration of the agents into the CNS and subsequent intensification of the activity of ACh at CNS sites.

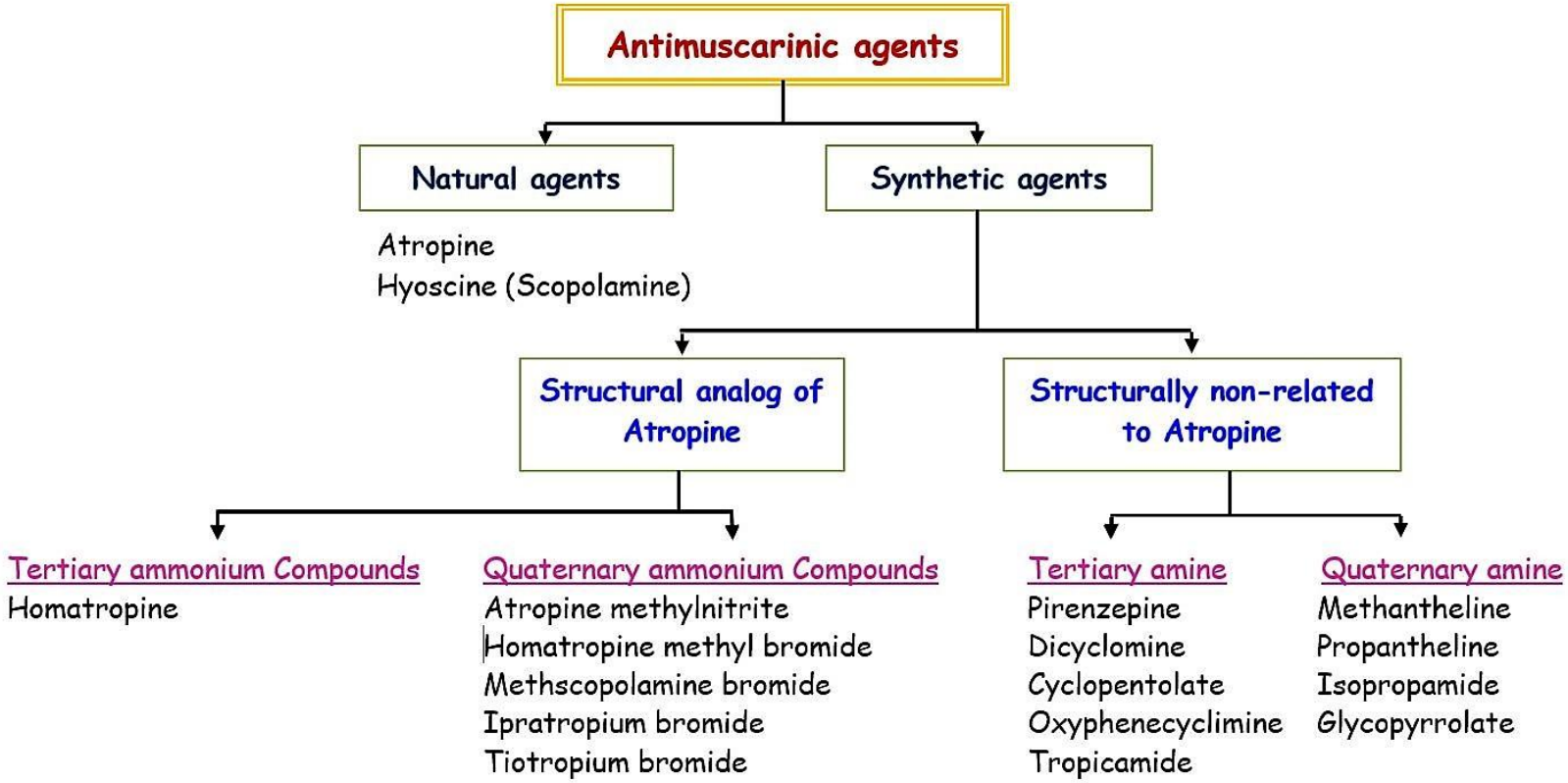
Anticholinergic (Parasympatholytic) Drugs

✓These drugs block muscarinic receptors only, so better known as **antimuscarinic agents**.

- **Mechanism of action of antimuscarinic agents:**
  - Atropine and related drugs block the cholinergic muscarinic receptors by acting as competitive antagonists of ACh or other direct acting cholinergic drugs.

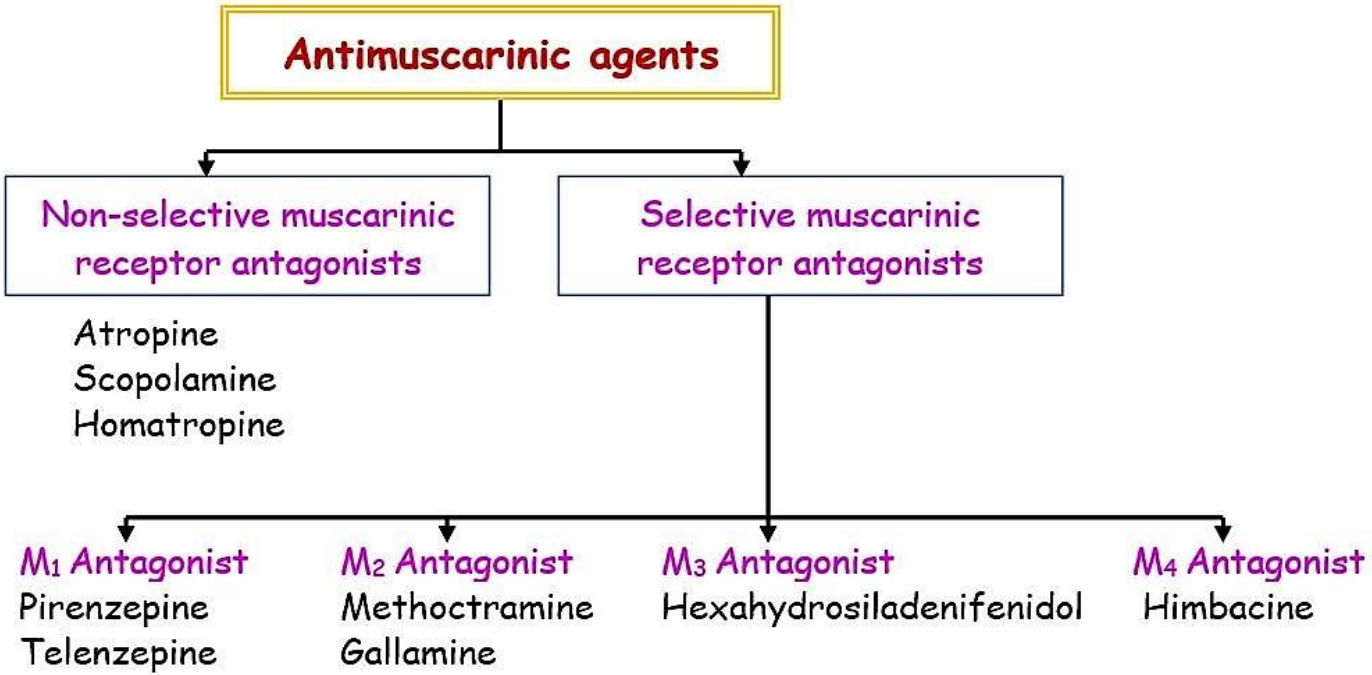
Classification of Parasympatholytic Drugs

Classification based on Origin & Structure:



Classification of Parasympatholytic Drugs

Classification based on Mode of Action:



Atropine & Scopolamine

- ✓ **Atropine** is an alkaloid extracted from the leaves of belladonna plants *Atropa belladonna* (deadly nightshade), *Datura stramonium* (Jimson weed) and *Hyoscyamus niger* (Henbane).
- ✓ **Scopolamine** is also an alkaloid extracted from the leaves *Hyoscyamus niger* and *Scopolia carniolica*

Atropa belladonna

Datura stramonium

Hyoscyamus niger

Scopolia carniolica

Atropine

Atropine is a racemic mixture of d-hyoscyamine and l-hyoscyamine. The laevo form of hyoscyamine is biologically active.

- **Atropine poisoning**: Physostigmine is used as it is better able to enter CNS than other parasympathomimetics. It is the central effects of atropine which is lethal.

- **Rabbits** possess an esterase (**atropinase**) which hydrolyses atropine

- **Atropine:**
  (i) As preanaesthetic
  (ii) As antidote in organophosphate and carbamate poisoning (0.2 to 0.5 mg/kg : $1/4^{th}$ of the total dose should be given i.v. and rest by i.m. route).
  (iii) For relief of heaves in horses.
  (iv) Eye drops (1%) – during eye examination.
- **Homatropine:** 2 – 5 % solution topically in the eye for ophtalmological use (mydriatic or cycloplegic). Its effects are of shorter duration as compared to those of atropine which causes persistent mydriasis and cycloplegia.
- **Glycopyrrolate:** Preanaesthetic.

Adrenergic Transmission

- The impulse transmission that is mediated by norepinephrine (post-ganglionic sympathetic nerve terminals and CNS), dopamine (CNS) and epinephrine (adrenal medulla) is in general called as adrenergic transmission. All these transmitters are also called as catecholamines.

- **CATECHOLAMINES:**
- Norepinephrine: It acts as transmitter at most peripheral sympathetic neuroeffector junctions and in the CNS.
- Epinephrine: It is the major hormone released from adrenal medulla.
- Dopamine: It is believed to transmit impulse information in specific areas within the CNS (basal ganglia, limbic system, CTZ, anterior pituitary etc.).

Synthesis of Catecholamines

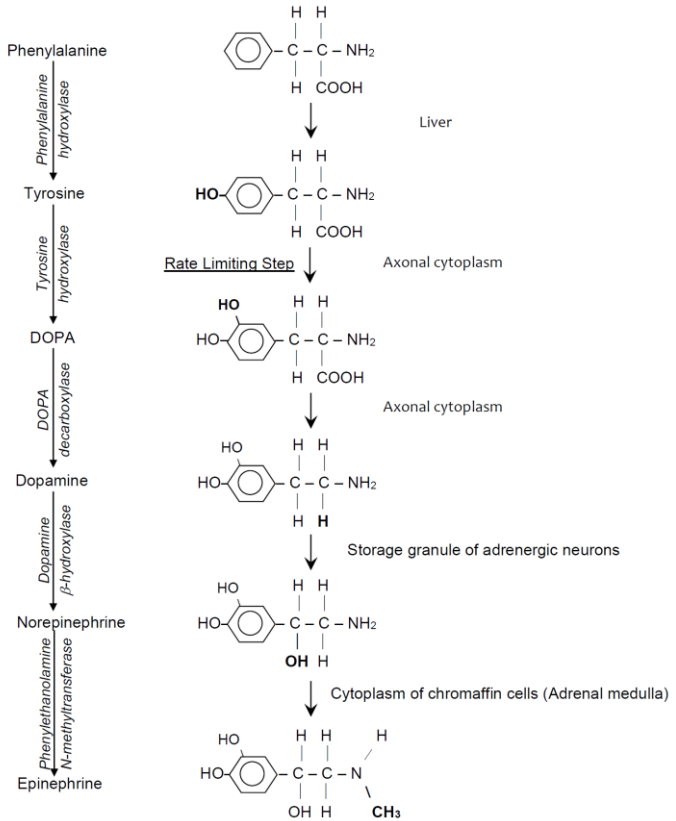


Fig.: Steps involved in the synthesis of catecholamines

Step I: Phenylalanine → Tyrosine

Step II: Tyrosine → DOPA

(Rate Limiting Step)

Step III: DOPA → Dopamine

Step IV: Dopamine → Norepinephrine

Step V: Norepinephrine → Epinephrine

- ✓ Catecholamines are taken up from the cytoplasm into vesicles or granules by an active transport system which is ATP and Mg^{2+} dependent.
- ✓ Storage within the granular vesicles is accomplished by complexation of the catecholamines with ATP (in molecular ratio of 4:1) which is adsorbed on a protein, chromogranin

- **Release of Catecholamines:**

- ✓ The nerve impulse coupled release of catecholamines from adrenergic nerve terminals takes place by **exocytosis** and is dependent upon an inward movement of **Ca^{2+}**.
- ✓ **Bretylium** inhibits norepinephrine release.

Uptake of Catecholamines

- ✓Neuronal Reuptake into nerve terminals: 60% disposed by reuptake
- ✓Extraneuronal uptake: enzymatic degradation by Monoamine oxidase (MAO) and Catechol-O-methyl transferase (COMT), Aldehyde reductase, aldehyde dehydrogenase
- ✓1. COMT→ MAO→ Al.reductase and dehydrogenase
- ✓2. MAO→ Al. reductase and dehydrogenase-→ COMT

Axonal uptake (Uptake - 1)	Extraneuronal uptake (Uptake -2)
(i) The adrenergic neuronal uptake is referred to as **uptake.** This uptake is the most important mechanism for terminating the action post-junctional action of NE.	(i) It signifies the extraneuronal uptake of catecholamines into surrounding tissue.
(ii) Uptake-1 is saturable and operates at very low physiological concentrations of transmitter.	(ii) Uptake-2 has very large capacity and accumulation operates most effectively at high concentrations of NE.
(iii) Uptake-1 requires Na^+ ions, K^+ ions and ATP and is blocked by cocaine, desipramine & its congeners guanethidine and many H_1 antihistaminics.	(iii) Uptake-2 is less selective, and is not blocked by cocaine but is sensitive to cortisol. It is not of pharmacological importance.

- ✓ The duration of action of catecholamines can be terminated either by reuptake mechanisms or metabolism by **enzymes monoamine oxidase (MAO) and catechol o-methyl transferase (COMT)**.
- ✓ Cytoplasmic NE is attacked by MAO.
- ✓ The extraneuronal NE which diffuses into circulation is destroyed by COMT in liver and other tissues like kidney, brain etc.
- ✓ However, metabolism does not play an important role in terminating the action of endogenous catecholamines.

Adrenergic neurohumoral transmission

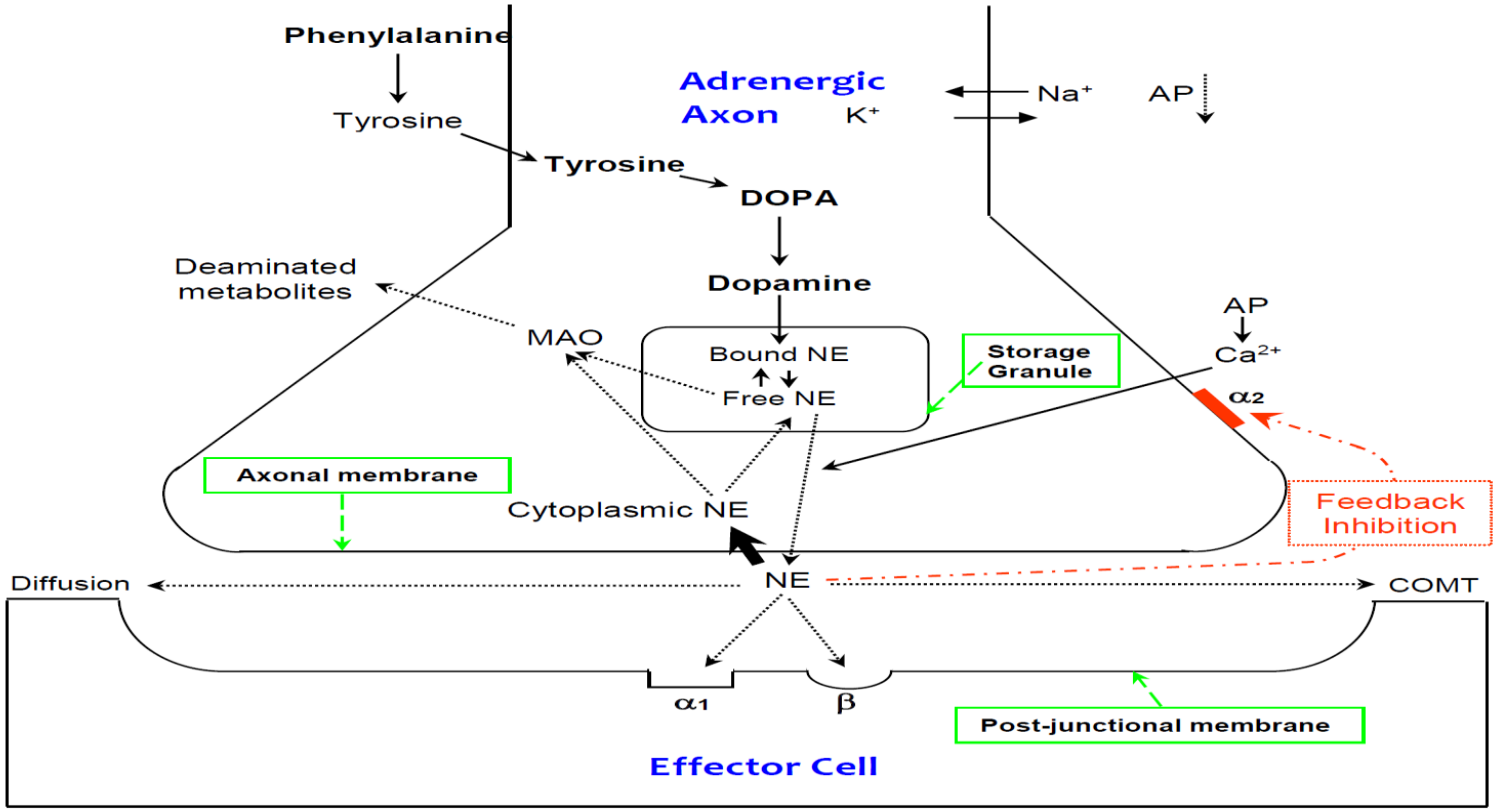


Fig.: Showing neurohumoural transmission at the adrenergic neuroeffector junction

Adrenergic Receptors

- ✓ Adrenergic receptors have been classified into two types based on rank order of potencies of adrenergic agonists – **α and β receptors**.
- ✓ ***Catecholamines produce excitatory (except GIT) and inhibitory (except CVS) responses on smooth muscles upon activation of α and β receptors, respectively***.
- ✓ α receptors have been further classified into two subtypes – **α_1 and α_2**. Molecular cloning have further identified three subtypes of **α_1 (α_{1A}, α_{1B} & α_{1D})** and three subtypes of **α_2 (α_{2A}, α_{2B} & α_{2C})** receptors.
- ✓ β receptors can be classified in three subtypes – **β_1, β_2 and β_3** based on relative organ specificity of selective agonists and antagonists.

Characteristics of sub-types of Adrenergic Receptors

Receptor	Agonist	Antagonist	Tissue distribution & Responses
α_1	Epi≥NE>>Iso Phenylephrine	Prazosin	• Vascular smooth muscle: Contraction • Genitourinary smooth m.: Contraction • Liver: Glycogenolysis, gluconeogenesis • Intestinal smooth m.: Relaxation • Heart: Increased contractile force
α2(auto Receptor)	Epi≥NE>>Iso Clonidine	Yohimbine	• Pancreatic islets: ↓ insulin secretion • Platelets: Aggregation • Nerve terminals: Decreased release of NE • Vascular smooth muscle: Contraction

β_1	Iso> Epi=NE Dobutamine	Metoprolol Atenolol	• Heart: ↑ force & rate of contraction & AV nodal conduction velocity. • Juxtaglomerular cells: ↑ renin secretion
β_2	Iso>Epi>>NE Terbutaline Salbutamol	a-methyl propranolol	• Smooth muscles: Relaxation [vascular, bronchial, GI & genitourinary] • Skeletal muscles: Glycogenolysis. • Liver: Glycogenolysis, gluconeogenesis.
β_3	Iso=NE>Epi	-	• Adipose tissue: Lipolysis.

- EPI ≥ NE >> isoproterenol for α adrenergic receptors.
- Isoproterenol > EPI ≥ NE for β adrenergic receptors.

Important:

- **Epinephrine:** $\alpha_1 + \alpha_2 + \beta_1 + \beta_2$ and weak β_3 action.
- **Norepinephrine:** $\alpha_1 + \alpha_2 + \beta_1 + \beta_3$ but no β_2 action.
- **Isoproterenol:** $\beta_1 + \beta_2 + \beta_3$ but no α action.

Adrenergic Drugs (Sympathomimetics)

- ✓ These are drugs which mimic the effects of sympathetic stimulation or those of catecholamines.

- ✓ Their effects are due to stimulation of adrenergic receptors (directly or indirectly) on the effector cells, hence also called as adrenergic drugs.

Classification of Adrenergic Drugs

(I) Classification based on chemical structure:

(1) Catecholamines : Epinephrine, Norepinephrine, Dopamine and Isoproterenol.

(2) Non-catecholamines : Phenylephrine, Ephedrine, Amphetamine, Tyramine etc.

(II) Classification based on mechanism of action:

1. **Directly acting agents:** They act directly as agonists on a and/ or b-adrenergic receptors. e.g. Epinephrine, NE, Isoproterenol.
2. **Indirectly acting agents:** They act on adrenergic neurons to release noradrenaline which then acts on the adrenergic receptors. e.g. Tyramine.
3. **Mixed acting agents:** They act directly as well as indirectly. e.g. Ephedrine.

Classification of Adrenergic Drugs

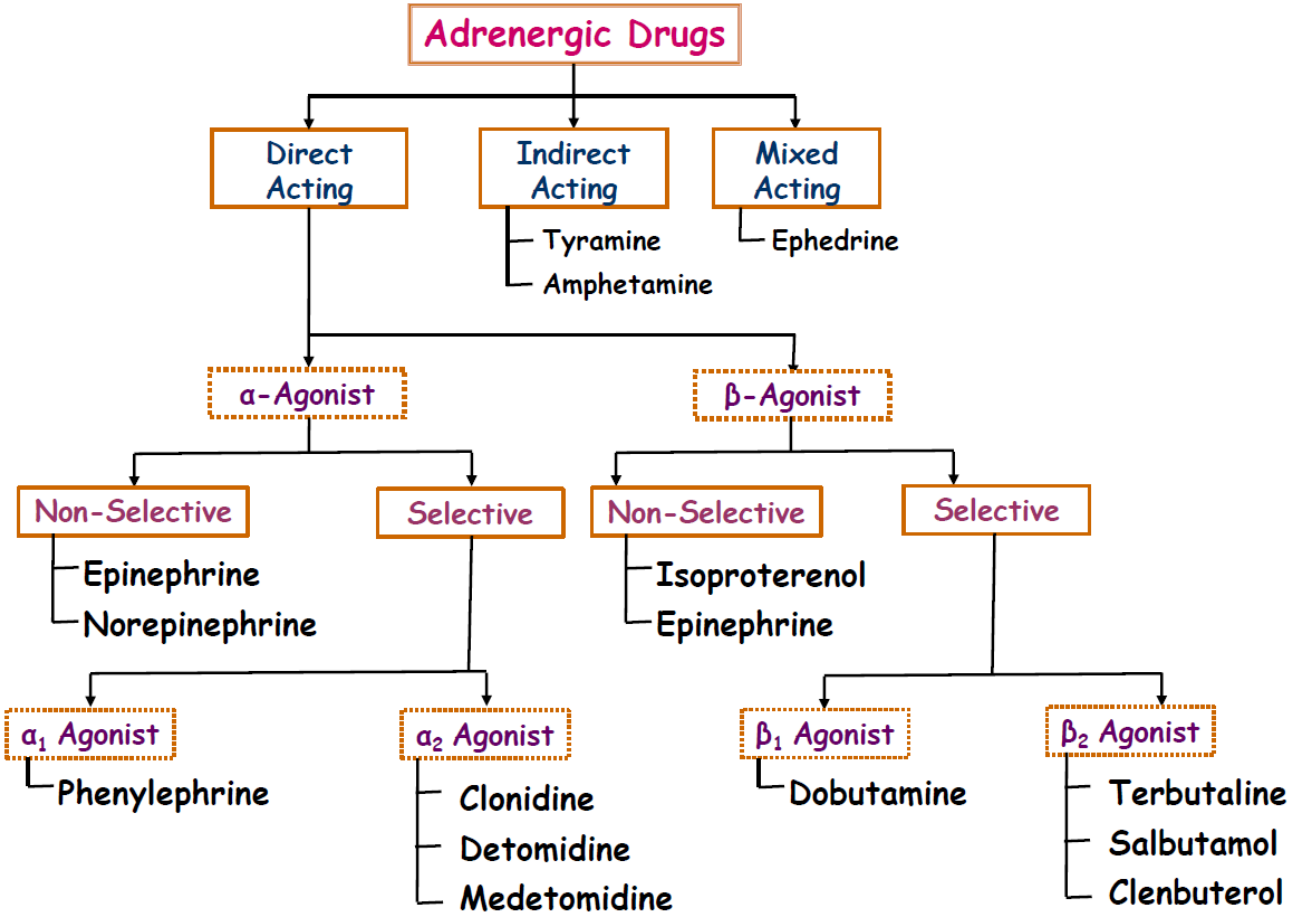


TABLE 5.1—Typical responses of effector tissues to sympathetic and parasympathetic nerve impulses

Effector tissues	Sympathetic-mediated responses[1]	Parasympathetic-mediated responses[2]
Heart	General excitation	General inhibition
Sinoatrial (SA) node	β_1—increase heart rate	Decrease heart rate
Atria	β_1—increase contractile force, conduction velocity	Decrease contractile force
Atrioventricular (AV) node	β_1—increase automaticity, conduction velocity	Decrease conduction velocity; AV block
His-Purkinje system	β_1—increase automaticity, conduction velocity	. . .
Ventricles	β_1—increase contractile force, conduction velocity, irritability[3]	Decrease contractile force[4]
Blood vessels		
Coronary	α_1—constriction; β_2—dilation[5]	Dilation[6]; constriction[6]
Cutaneous, mucosal	α_1—constriction	Dilation[7]
Cerebral	α_1—constriction; β—dilation	Dilation[7]
Skeletal muscle	α_1—constriction; β_2—dilation[8]	Dilation[7]
Splanchnic	α_1—constriction; β_2—dilation[9]	Dilation[7]
Renal	α_1—constriction; β_2—dilation[9]	Dilation[7]
Genital	α_1—constriction	Dilation[10]
Veins	α_1—constriction	
Endothelium	α_2—dilation	
GI tract	General inhibition	General excitation
Smooth muscle	β_1—relaxation; α—relaxation[11]	Increase motility and tone
Sphincters	α—contraction	Relaxation
Secretions	Decrease (usually)	Increase
Gallbladder and ducts	Relaxation	Contraction
Bronchioles		
Smooth muscle	β_2—relaxation	Contraction
Glands	Inhibition (?)	Stimulation
Eye		
Radial muscle, iris	α_1—contraction (mydriasis)	. . .
Sphincter muscle, iris	. . .	Contraction (miosis)
Ciliary muscle	β—relaxation; far vision	Contraction; near vision
Urinary bladder		
Fundus	Urinary retention	Urination
Trigone, sphincter	β_1—relaxation	Contraction
	α—contraction	Relaxation

continued

TABLE 5.1—*continued*

Effector tissues	Sympathetic-mediated responses[1]	Parasympathetic-mediated responses[2]
Splenic capsule	α—contraction, β_2—relaxation	. . .
Sweat glands	Secretion (cholinergic);[12] β_2—secretion (horse)	
Salivary glands	α_1—scant, viscous secretion	Profuse, watery secretion
Piloerector muscles	α—contraction	. . .
Kidney renin release	α_2—decrease; β_1—increase	. . .
Uterus[13]	α_1—contraction; β—relaxation (nonpregnant > pregnant)	Contraction[14]
Genitalia		
Male	α—ejaculation	Erection[15]
Female	. . .	Erection[15]
Adrenal medulla	Secretion of epinephrine > norepinephrine (cholinergic)	. . .
Autonomic ganglia	Ganglionic discharge (cholinergic)	Ganglionic discharge[16]
Liver	β_2—glycogenolysis and gluconeogenesis (α in some species)	. . .
Pancreas		
Islet cells	α_2—decrease secretion; β_2—increase secretion	. . .
Acini	α—decrease secretion	Increase secretions
Fat cells	β_1—lipolysis	. . .
Adrenergic nerve terminals	α_2—decrease release of norepinephrine β_2—increase release of norepinephrine	± Release of norepinephrine[17]
Platelets	α_2—aggregation	. . .

Pharmacological Effects of Adrenergic Drugs

1. Heart (α_1,β_1):

- ✓ Increase in heart rate (**positive chronotropic effect**) and
- ✓ Increase in force of cardiac contraction (**positive inotropic effect**).

2. Blood vessels (Mainly α_1 but also β_2):

- ✓ Both vasoconstriction (α_1 mediated) and vasodilatation (β_2 mediated).
- ✓ There is dilatation of blood vessels in skeletal muscles, lungs and mesentery (β_2 action).

Dale's Reversal Phenomenon

- ✓ Blood vessels → More α and less β_2 receptors. β_2 receptors → more powerful and sensitive.
- ✓ Epinephrine causes increase which is followed by decrease in blood pressure.
- ✓ The initial rise in B.P. is mediated by α receptors which are more in number.
- ✓ As the concentration of epinephrine decreases by metabolism or elimination, it dissociates first from the less sensitive α receptors. So, at later stage, the number of activated β_2 receptors remains more than the activated α receptors which cause decrease in blood pressure.
- ✓ Presence of α receptor blockers like ergot etc. inhibits the rising phase of epinephrine induced B.P. But, β_2 receptor mediated action (i.e. fall in blood pressure) predominates.
- ✓ As the effect of epinephrine is reversed by the presence of α receptor blockers and this phenomenon was first observed by Dale, the phenomenon is called as Dale's Reversal Phenomenon.

3. **Respiratory tract (β_2):** Relaxation of smooth ms. Of bronchi and trachea. Epinephrine and isoproterenol (but not norepinephrine) are potent bronchodilators.

4. **Gastrointestinal tract (Both α_1 & β_2):** Decrease in tone and motility.

5. **Eye (α_1):** Mydriasis due to contraction of radial muscles.

Decreased Intraocular Pressure by enhancing both β_2-receptor mechanism

6. **Sex organ (α_1):** Ejaculation of male sex organ.

7. **Metabolism:** Metabolic effects like hyperglycaemia (**α_1 & β_2**) due to glycogenolysis and hyperlipaemia (**β_3**) due to lipolysis.

8. **Splenic capsule:** Contracts (**α**) and more RBCs are poured into circulation.

Clinical Uses

[I]. Adrenaline (Epinephrine) and Noradrenaline (Norepinephrine): These agents reverse hypotension, hence, called **'pressoramines'**.

- ✓ **Noradrenaline :** Best i.v. infusion. It causes generalized vasoconstriction with increased peripheral resistance and increased systolic and diastolic B.P.
- ✓ **Adrenaline :** Myocardial stimulation & disordered rhythm of the heart.
- ✓ **Uses:**
  - With local anaesthetics: Potentiate local anaesthetic action by decreasing absorption of local anaesthetics.
  - As local haemostatic: Arrests bleeding due to local vasoconstriction.
  - In allergic/ anaphylactic reactions and acute bronchial asthma
  - As cardiac stimulant: Used in the treatment of acute cardiac arrest AV blocks.

[II]. Ephedrine: It is a naturally acting alkaloid obtained from Ephedra vulgaris.

- ✓ Mixed acting - Mainly acts indirectly but also has some direct action on α & β receptors also.
- ✓ It is resistant to MAO and COMT.
- ✓ It is 100 times less potent than adrenaline but longer lasting (4 - 6 hour).
- ✓ It was the first agent to be used clinically in management of asthma.

[III]. Amphetamine (CNS stimulant): It is a synthetic, orally active, largely indirect acting α & β agonist having euphoriant & habit forming properties in man. It has been used by athletes and given to race horses to improve performance illegally (**Doping**).

[IV]. Phenylephrine (Vasoconstrictor): α_1 agonist (less potent but more long lasting than noradrenaline)

[V]. Isoprenaline (Isoproterenol) {Bronchodilator & Cardiostimulant}:

- ✓ It is a synthetic, mixed b agonist. The drug is resistant to MAO but metabolized by COMT.
- ✓ Bronchodilator (β_2) action to asthma in man.
- ✓ Powerful cardiostimulatory action (β_1) to accelerate ventricular rate in heart block.

[VI]. Salbutamol (Albuterol) {bronchodilator}:

- ✓ It is a selective β_2 agonist (*i.e.* acting on bronchial muscle, vasculature and the uterus). β_2 selectivity is only relative
- ✓ Salbutamol has β_2: β_1 action ratio of 10:1
- ✓ resistant to MAO and COMT and is having longer duration of action as compared to isoprenaline.

[VII]. Terbutaline {bronchodilator}:

- ✓ It is similar to salbutamol in properties and use.
- ✓ Inhaled salbutamol and terbutaline are currently the most popular drugs.

[VIII]. Isoxuprine {Tocolytic or uterine relaxant}:

- ✓ Selective β_2 agonist.
- ✓ Depresses smooth muscle contraction in gravid uterus. So, useful in threatened abortion.

[IX]. Clenbuterol: Selective β_2 agonist. It is having tocolytic and bronchodilator actions.

Ganglionic Transmission

- ✓ Acetylcholine (ACh) is the primary excitatory neurotransmitter in both sympathetic and parasympathetic ganglia.
- ✓ principal pathway of impulse transmission through the ganglia involves release of ACh from the preganglionic nerve endings
- ✓ and the stimulation of nicotinic receptors by ACh on the post-junctional membrane (EPSP)
- ✓ causing rapid depolarization and subsequent propagation of the impulse through the post-ganglionic nerve fibre.

Diagrammatic representation of Ganglionic Transmission

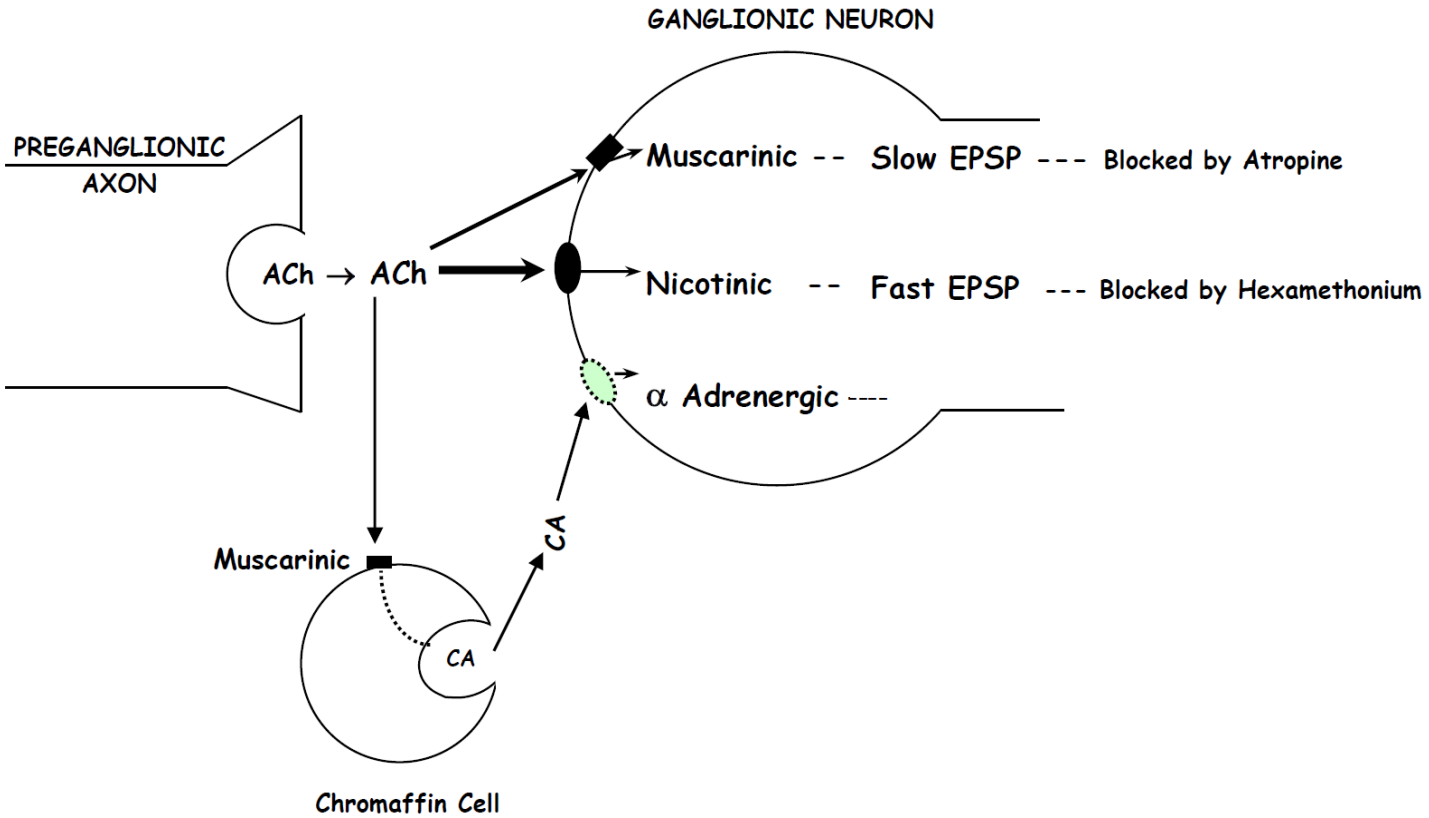


Fig.: Impulse transmission in sympathetic autonomic ganglia.

Ganglionic Stimulants

[I]. Natural Alkaloids:

1. Nicotine:

- ✓ leaves of *Nicotiana tabacum*.
- ✓ Nicotine can stimulate the sympathetic and parasympathetic ganglia in small doses. In large doses, it blocks ganglia.
- ✓ GI tract : Due to stimulation of parasympathetic ganglia → Salivation, increase in tone and motility of GI tract and defaecation.

2. Lobeline: It is obtained from the leaves of *Lobelia inflata*.

[II]. Synthetic Compounds:

(a) Trimethylammonium (TMA)

(b) Tetraethylammonium (TEA)

(c) Dimethylphenylpiperazinium (DMPP)

Ganglionic Blockers

- ✓ competitively antagonize the action of ACh on the nicotinic receptors on the post-ganglionic membrane and thus block ganglionic transmission.
- ✓ Ganglionic blockers are all synthetic compounds.
  - (i) Hexamethonium
  - (ii) Pentolinium
  - (iii) Trimethaphan
  - (iv) Mecamylamine

Pharmacological effects of Ganglionic Blockers

CVS: Vasodilatation, increased peripheral blood flow, venous pooling, decreased cardiac output, hypotension and tachycardia.

GI tract: Reduced tone and motility.

Eye: Mydriasis and cycloplegia.

Bladder: Relaxation and urine retention.

Sweat glands: Anhydrosis.

Salivary glands: Xerostomia (dry mouth).

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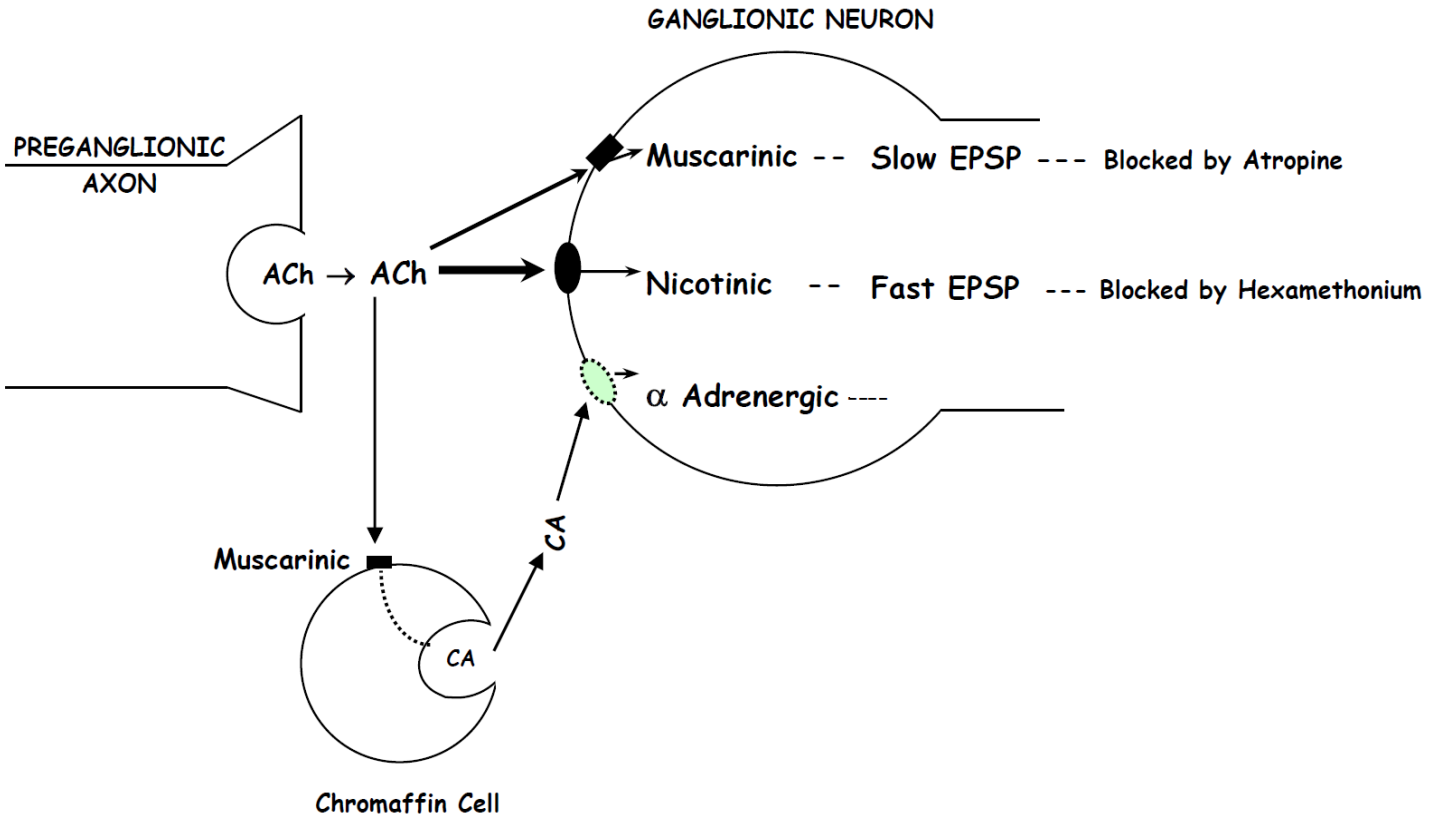

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Autacoids

- ✓‘autacoid’ meaning remedy or healing substance
- ✓Autacoids are locally acting hormone like substances produced by a wide variety of cells in the body, having intense biological activity which act briefly at the site of synthesis and release (i.e. on adjacent cells).

- ✓ Autacoids are also known as **tissue hormones** or **local hormones**. These are formed, released and inactivated within tissues.
- ✓ They are usually vasoactive and **mediators of inflammation**.
- ✓ Autacoids differ from hormones in following ways:
  - (i) Hormones are produced by specific cells; and
  - (ii) They are transported through circulation to act on distant target tissues.

Classification

(I) Classification based on chemical structure:

(1) **Amine autacoids:** Histamine, 5-Hydroxytryptamine (5-HT) or Serotonin.

(2) **Lipid derived autacoids:** Eicosanoids {Prostaglandins, Leucotrienes (LTs) and Thromboxanes (TXs)}, Platelet activating factor (PAF).

(3) **Peptide autacoids:** Plasma kinins (Bradykinin and Kallidin), Angiotensin, Vasoactive Intestinal Polypeptide (VIP) and Substance P.

Classification based on origin

1. **Precursor molecules in plasma**: Bradykinin, Kallidin and Angiotensin.
2. **Preformed & stored in the cell**: Histamine, 5-HT, VIP and Substance P.
3. **Precursor molecules in cell membrane phospholipids**: Prostaglandins, LTs and PAF.

Histamine (Tissue Amine)

- ✓ It is an amine present in a variety of **animal tissues, venoms, bacteria and certain plants** (e.g. stinging nettle). The amine is involved in **inflammations, anaphylaxis, allergies** and **certain types of drug reactions**, and it **regulates gastric secretion**.
- ✓ Chemically, histamine is β-imidazolylethylamine.
- ✓ synthesized from the decarboxylation of amino acid histidine by a specific enzyme, **histidine decarboxylase**.
- ✓ This enzyme is present in all cell types that contain histamine.
- ✓ Histamine is **widely distributed throughout mammalian tissues**.

Histamine Receptors

Selective Agonist	H_1	H_2	H_3
	2-methylhistamine	4-methylhistamine	a-methylhistamine
Selective Antagonist	Chlorpheniramine	Ranitidine	Thioperamide
Distribution In The Body And Actions Mediated	▪ Smooth muscle (GIT, RT & uterus): Contraction. • Blood vessels: Endothelium-Vasodilatation & increased capillary permeability. • Afferent nerve endings: stimulation (itching & pain) • Ganglionic cell: Stimulation. • Adrenal medulla: Release of catecholamines	• Gastric glands: Acid secretion. • Blood vessels: Dilatation. • Heart: + ve inotropy & + chronotropy • Brain: Transmitter function.	• Brain: Inhibition of histamine release • Lung, spleen, skin, gastric mucosa: ↓ histamine content. • Primarily serves as autoreceptors controlling histamine release from neurons in brain.

Pathophysiological Functions of Endogenous Histamine

- ✓ **HCl secretion** in the stomach.
- ✓ Released from mast cells following Ag - Ab interactions during hypersensitive reactions (**Type-1 hypersensitivity**).
- ✓ **Neurotransmitter in CNS:** Regulates water intake, body temperature, release of ADH, blood pressure and pain perception.
- ✓ **Regulates GI tone and motility** : helps to maintain normal peristalsis.
- ✓ **Released in extensive tissue damage:** Mediates local circulatory response to injury and inflammatory reactions.
- ✓ Play an essential role in the process of **tissue growth** and **repair** because these tissues contain high concentrations of histamine.

Pharmacological Effects of Histamine

- **[1]. Blood Vessels:**

✓ Marked dilatation of smaller blood vessels including arterioles, capillaries and venules. Constrictor effect on large blood vessels.

✓ In rabbits, histamine is a "pressor agent" as a result of pronounced constriction of blood vessels.

- **Histamine Shock:**

✓ Intense dilatation of capillary bed → Increase in capillary permeability.

✓ The dilated arterioles, capillaries and venules that tag large volumes of blood and reduce venous return to heart and thus the cardiac output.

✓ Histamine release during allergic or anaphylactic reactions.

✓ The condition may cause death due to vascular shock as seen in acute surgical or haemorrhagic shock.

- **Triple Response:** Histamine produces a characteristic triple response in skin following intradermal injection. It consists of the following:-

1. **A localized red spot** : due to intense capillary dilatation developing within a few seconds and attaining maximum hue within a minute.
2. **Wheal**: Localized oedema fluid forming a wheal in about 90 seconds due to exudation of fluid from capillaries and venules; and
3. **Flare (Diffuse redness)**: redness in the surrounding area due to arteriolar dilatation mediated by axonal reflex.

Classification of H_1 antagonists

Drug	Trade Name
First Generation	
(1) Ethanolamines : Diphenhydramine HCl	Benadryl (Parke-Davis)
(2) Ethylene diamines : Pyrilamine maleate	Histosol
(3) Alkylamines : Chlorpheniramine maleate	Jeet (Alembic),
Pheniramine maleate	Avil (Intervet)
(1) Piperazines : Hydroxyzine HCL	Atarax (UCB Pharma)
(2) Phenothiazines : Promethazine HCl	Phenergan (Rhone Poulenc)
(3) Piperidines : Cyproheptadine HCl	Practin (Merind)
Second Generation	
(1) Piperazines : Cetirizine HCl	Cetzine (Glaxo)
(2) Piperidines : Loratadine HCl	Loridin (Cadila)
: Fexofenadine HCl	Allegra (Hoechst)
: Terfenadine HCl	Terin (Wockardth)

- ✓ **Highly Sedative** : Diphenhydramine, Promethazine & Hydroxyzine.
- ✓ **Moderately Sedative** : Pheniramine and Cyproheptadine.
- ✓ **Mildly Sedative** : Chlorpheniramine and pyrilamine
- ✓ **Non- Sedative** : Second generation antihistaminics.

H_1 antihistaminics

- **Cyclizine, Meclizine, Promethazine, Diphenhydramine (Anti-motion sickness):**

✓ These agents have prophylactic value in **milder types of motion sickness**; should be taken one hour before starting journey.

✓ Promethazine can also be used in **morning sickness, drug induced and post-operative vomiting, radiation sickness**.

✓ **H_1 receptors mediate emesis in emetic centre**.

H_2 antihistaminics

- ✓ These drugs block the effects of histamine that are mediated through H_2 receptor stimulation, such as increase in **gastric acid secretion** and increase in **heart rate** and **automaticity of auricles and ventricles**.
- ✓ The H_2 antagonists also act as competitive antagonists of histamine for H_2 receptors.
- ✓ The H_2 antagonists : **Cimetidine**, **Ranitidine**, **Famotidine**, **Roxatidine**, **Nizatidine** etc.
- ✓ These drugs are of value in the treatment of **peptic ulcer** in man and animals.

5-Hydroxytryptamine (5-HT) or Serotonin

- ✓ 5-HT is synthesized from dietary tryptophan in a two stage chemical reaction: Tryptophan is hydroxylated by the enzyme tryptophan-5-hydroxylase to give 5-hydroxytryptophan (5-HTP).
- ✓ 5-HTP is then decarboxylated to yield 5-HT.
- ✓ Like catecholamines, 5-HT is also stored in storage granules and its uptake is also inhibited by **Reserpine**.
- ✓ Enzymes like MAO, dehydrogenase and aldehyde reductase help to metabolize 5-HT.
- ✓ In the pineal gland, 5-HT is converted to melatonin

- ✓ 5-HT is formed and localized in three essential pools in the body:
    - i. **Enterochromaffin cells** of intestine (about 90%).
    - ii. Small number of neurons in **CNS** and **mast cells** of rodents (rat, mice, hamsters) along with histamine and heparin.
    - iii. **Blood platelets**.

Synthesis and Destruction of 5-HT

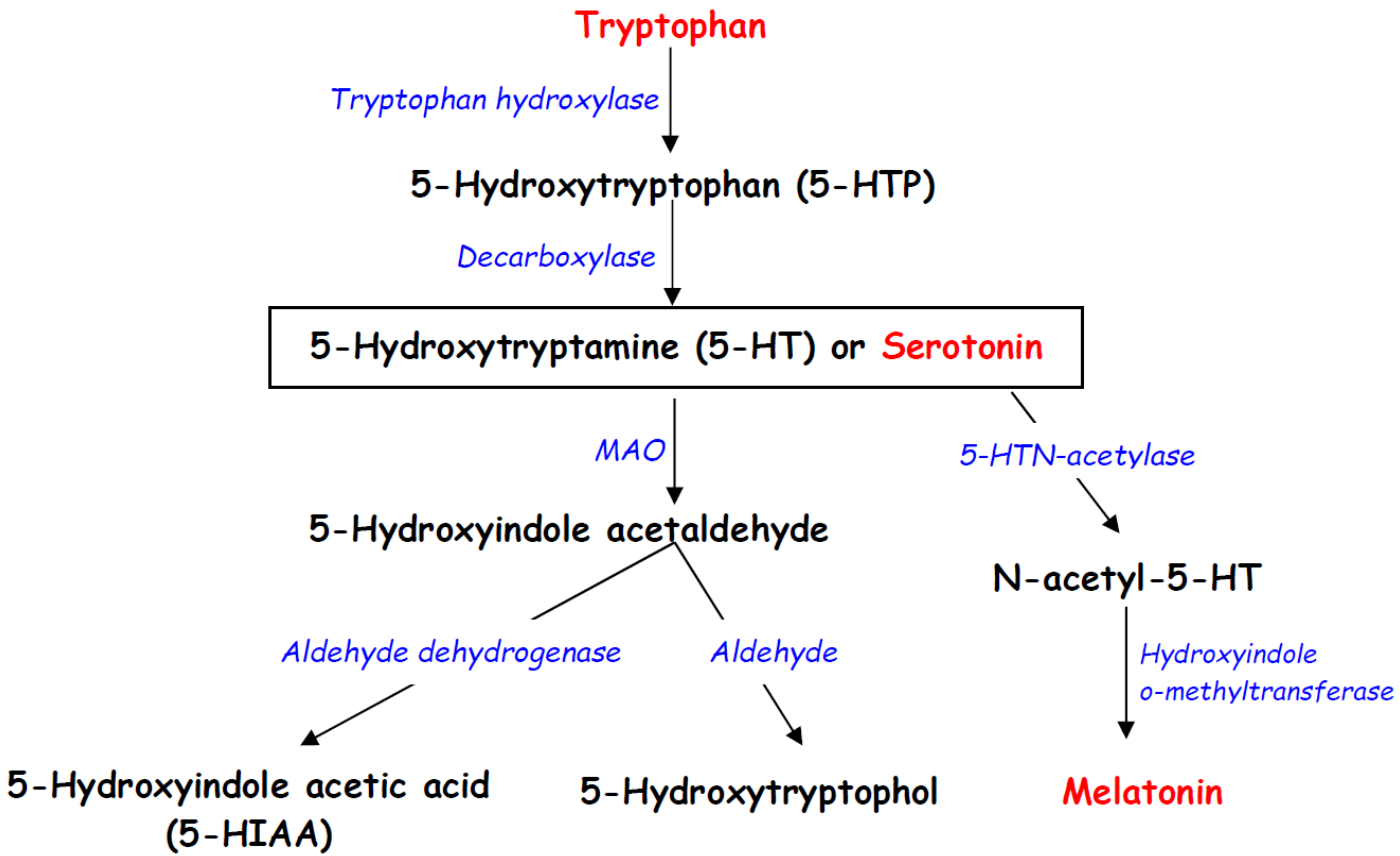

Fig.: Showing synthesis and degradation of 5-HT

5-HT Receptors

- Four families of 5-HT receptors comprising of total **14** receptor subtypes:-

(1) 5-HT_1 {Five subtypes i.e. 5-$HT_{1A, 1B, 1C, 1D, 1E}$}**:** Autoreceptors; inhibit serotonergic neural activity in brain. Functions are neural inhibition and vasoconstriction.

(2) 5-HT_2 {Three subtypes i.e. 5-$HT_{2A, 2B, 2C}$}**:** CNS and peripheral sites (esp. vascular and visceral smooth muscles, platelets and ANS neurons). Effects are vasoconstriction, intestinal, bronchial and uterine contraction and platelet aggregation.

(1) 5-HT_3 {No subtype}**:** Peripheral Nervous System – Emesis, gut peristalsis, bradycardia, transient hypotension, apnoea, pain, itching etc.

(2) 5-HT_{4-7}:

- (i) 5-HT_4: (No subtype) Enteric nervous system. Mediate intestinal secretion and augments peristalsis.
- (ii) 5-HT_5: Two subtypes i.e. 5-$HT_{5A, 5B}$
- (iii) 5-HT_6: No subtype.
- (iv) 5-HT_7: No subtype.

Pharmacological effects of 5-HT

- **[I]. C.V.S.:**

✓ Vasoconstriction on major arteries and veins.

✓ Activation of 5-HT receptors in endothelial cells and local release of EDRF and prostaglandins.

✓ **Triphasic Response** (produced by Rapid i.v. infusion of 5-HT):-

(a) An initial fall of systemic arterial B.P. accompanied by bradycardia caused mainly by reflex chemoreceptor stimulation (Bezod – Jarisch Effect).

(b) A short period of pressure effect; and

(c) A prolonged fall in systemic B.P. attributed to a vasodilator effect in the vascular bed of skeletal muscle.

- ✓LSD, Ergot alkaloids, Methysergide,
- ✓Ketanserin,
- ✓**Clozapine** (**effective in schizophrenia**),
- ✓Risperidone
- ✓The therapeutic value of 5-HT antagonists in veterinary medicine is not yet established.

5- HT Antagonist

- METOCLOPRAMIDE. It acts on dopamine as well as serotonin receptor. It acts as 5-HT_3-receptor antagonist and 5-HT_4-receptor agonist. It is used as prokinetic and antiemetic drug.
- 5-HT_3- antagonist – Ondansetron, granisetron, tropisetron, dolasetron - Used to prevent nausea and vomition associated cancer chemotherapy
- CYPROHEPTADINE: it is 5-HT_{2A} antagonist,weak anticholinergic and H_1-antihistaminic action.

✓ LSD, Ergot alkaloids, Methysergide,

✓ Ketanserin,

✓ **Clozapine** (**effective in schizophrenia**),

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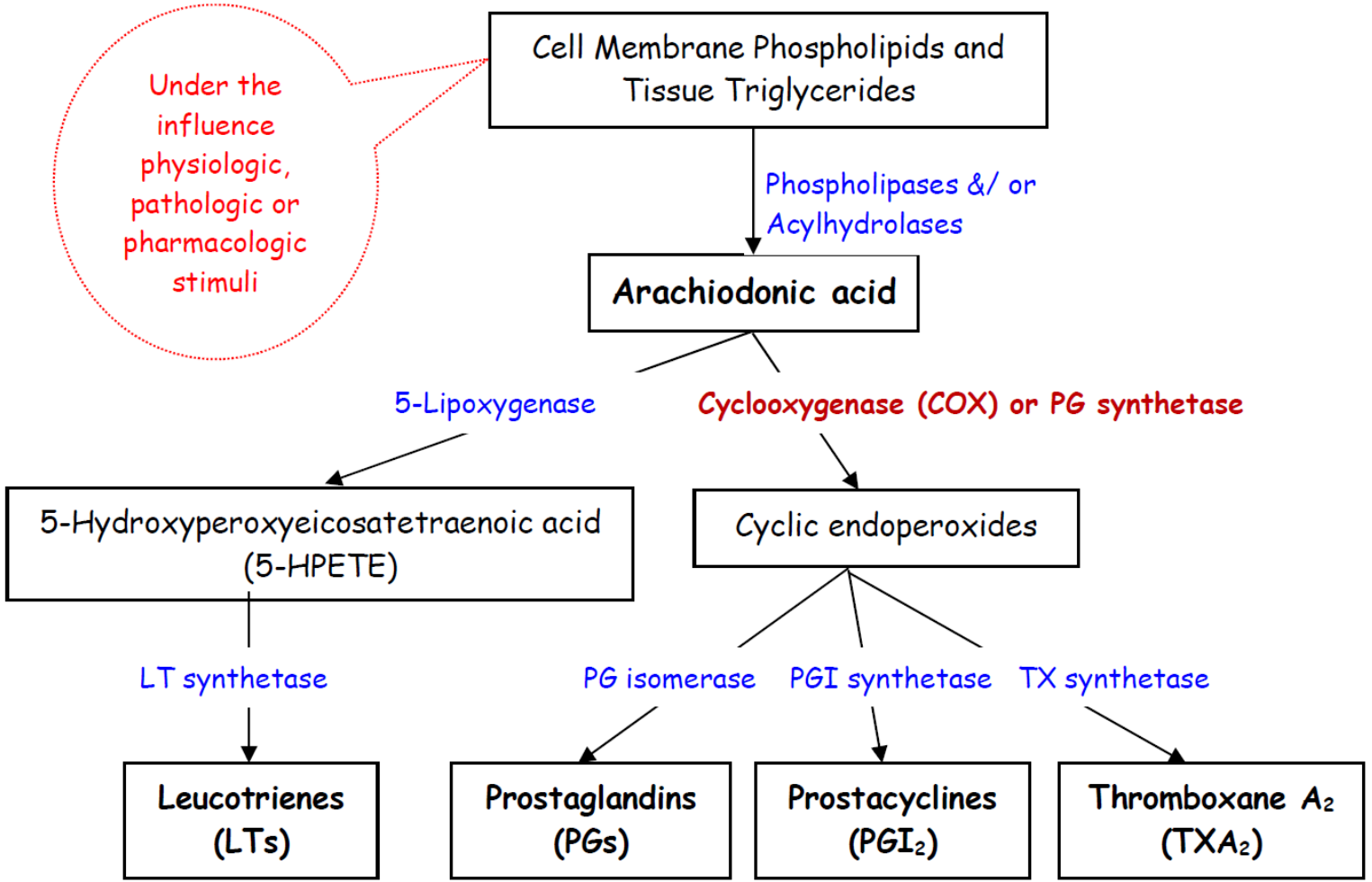
Eicosanoids (PG, PGI, TXA & LT)

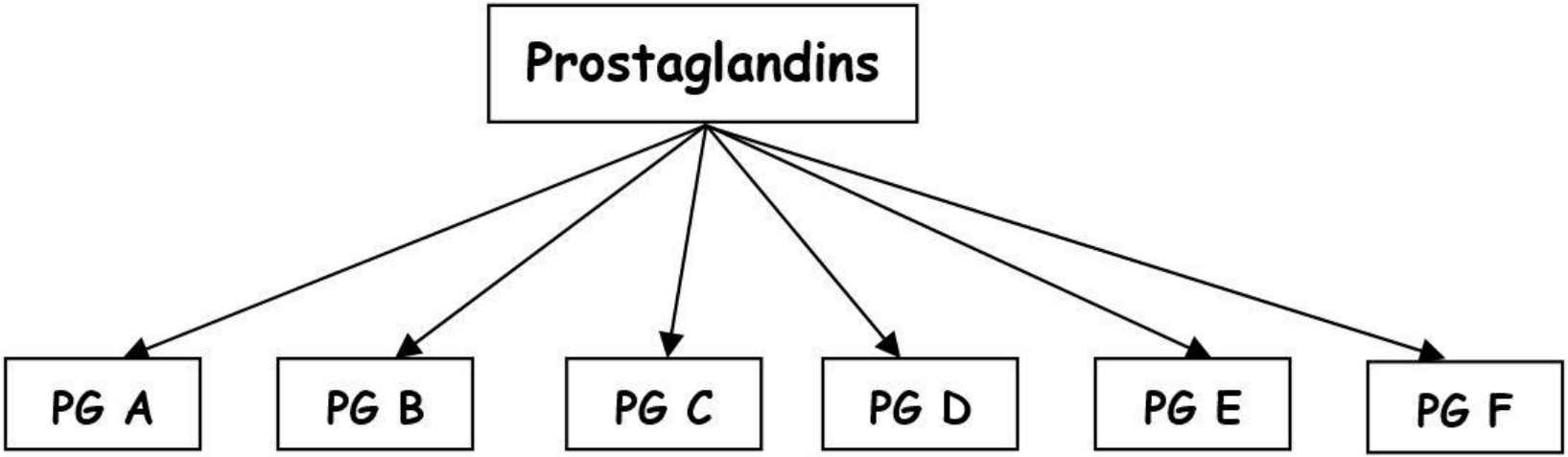
- ✓ The biologically active substances that are derived from **20 carbon polyunsaturated fatty acids** (mainly arachiodonic acid) which share a prefix **'eicosa' (means twenty)** are termed eicosanoids.

- ✓ These include **prostaglandins (PG), prostacyclins (PGI)**, **thromboxane (TXA)** and **leucotrienes (LT)**.

Synthesis of Eicosanoids



Classification of Prostaglandins (PGs)



Cyclooxygenase (COX)

- ✓ Metabolizes arachiodonic acid to its PG derivatives.
- ✓ Two major isoforms : COX-1 and COX-2.
- ✓ **COX-1:** Synthesizes the small amounts of PGs that participate in **normal physiologic functions**. Have **protective** actions on GI mucosa. Inhibition of COX-1 activity : Loss of GI protection of mucosal epithelial cells.
- ✓ **COX-2:**
  - Not constitutive; rather it is **inducible** in nature. Bacterial lipopolysachharide and certain inflammatory cytokines & growth factors induces synthesis of COX-2. Participate in **inflammatory reactions**.

Clinical Uses of Eicosanoids

- ✓ **PGF_2a analogues** (**Dinoprost, Tiaprost**) are used for:- **Oestrous synchronization** (cow, ewe, goat, buffalo etc.) **Induction of oestrous** in anoestrous animals. **Expulsion of mummified foetus**; and **Expulsion of pus** in pyometra.

- ✓ **Misoprostol** is a prostaglandin E1 analogue used to reduce the risk of NSAID-induced gastric ulcers and to terminate pregnancies.

Drugs Acting On CNS

- Anaesthetics – drugs that produce reversible loss of sensation eg. halothane.
- Dissociative anaesthetic – drug that produces a feeling of dissociation from one's own body and surroundings including profound analgesia, immobility, amnesia with light sleep.
- Preanaesthetic medication – use of drugs before anaesthesia to make it more pleasant and safe.
- Sedative – drug that subdues excitement and calms the subject without inducing sleep.
- Hypnotic – drug that induces or maintains sleep
- Narcotic – drug that induces sleep (refers to opioids – the term is not used now)

- Antiepileptic drug – drug that is used to control seizures
- Analeptics - CNS stimulants – drugs that induce CNS stimulation
- Analgesic – drug that selectively relieves pain without altering consciousness
- Anxiolytic drugs – group of mild CNS depressants that produce a restful state of mind, without interfering with normal mental or physical functions
- Antidepressants – drugs that can elevate the mood in depressive illness
- Antimanic drugs – drugs that stabilize the mood in manic conditions
- Hallucinogens –(psychotomimetics) drugs that alter mood, behaviour, thought and perception in a manner similar to that seen in psychosis.

Neurotransmitters

- substances stored in the presynaptic area in vesicles. On release lead to excitation or inhibition.
- Biogenic amines -- Histamine, 5-HT, Adrenaline, Noradrenaline, Dopamine, ACh
- Amino Acids – GABA, Glycine, Glutamate, Aspartate
- Peptides – Somatostatin, Substance P, enkephalin, Endorphin, Oxytocin, Vasopressin, Cholecystokinin, Thyrotrophic hormone, Angiotensin, Vasoactive intestinal peptide, Neuropeptide Y.
- Neurohormones: Hormone arising from a neuron. Eg: oxytocin, vasopressin.
- Neuromodulators: Originates from cellular and nonsynaptic sites, influence the general level of excitability without altering the membrane potential. Eg: ammonia, CO2, Prostaglandins, steroid hormones.
- Neuromediators: Those that participate in the elicitation of response to a transmitter. Eg: Second messengers cAMP, cGMP, IP3.

NEUROTRANSMITTERS IN THE CNS

- Neurotransmitters may be broadly divided into fast neurotransmitters and slow neurotransmitters.
- Fast neurotransmitters operate through ligand gated ion channels (eg. glutamate, GABA) while slow neurotransmitters and neuromodulators operate mainly through G-protein coupled receptors (eg. dopamine, neuropeptides, prostanoids).
- The same agent (eg. glutamate, 5HT and acetylcholine) may act through both ligand gated channels and G- protein coupled receptors.

- Acetylcholine: Muscarinic M1 –M5 subtypes and also nicotinic seen in CNS - Forebrain and striatum-inhibitory (muscarinic)
- Norpinephrine: α1 and α2 β1 and β2 -mainly in brain stem and reticular formation – control in sleep and wakefulness, mood and emotion, temperature etc.
- Epinephrine: seen in reticular formation. Role not well established.
- Dopamine: D2 subtypes – in basal ganglia and limbic system. Behaviour disturbances, control of movements (implicated in Parkinsonism) and in hypothalamic – pituitary system.
- 5-HT – multiple subtypes – sleep and wakefulness, mood and behaviour, appetite and neuroendocrine control.
- Aminoacids – Excitatory – Glutamate and Aspartate – 5 subtypes -- NMDA receptor – in dissociative anaesthesia, involved in epilepsy and anxiety states.
- GABA -Inhibitory - major inhibitory. Glycine – restricted to spinal cord and retina.
- Peptides – eg. Substance P – in pain perception, opioid peptides (endogenous opioids like endorphins and enkhepalins)– analgesia, behaviour and sedative actions.

- Depending upon the type of behavioural effects produced the drugs acting on CNS can be classified into two broad groups.

I CNS depressants

II CNS stimulants

CNS stimulants drugs

1. On the basis of part of CNS where drug act:

- **Spinal Stimulants or convulsants:** Strychnine, picrotoxin
- **Medullary Stimulants:** Doxapram, Bemegride, Picrotoxin, Nikethamide, Leptazol
- **Cortical Stimulants:** Cocaine, amphetamine, methylxanthines.

2. On the basis of action (Direct or Indirect):

- **Direct acting stimulants :** Strychnine, picrotoxin and xanthenes derivatives.
- **Indirect (Reflexly) acting stimulants:** lobeline, ammonia, Veratrum, nicotine.

3. On the basis of clinical uses:

- Analeptics: Nikethamide, bemegride, doxapram.
- **Psychostimulants:** Amphetamines, methylphenidate, cocaine, methylxanthines, caffeine, theophylline.
- **Cerebroactive drugs**: Piracetam, dihydroergotoxine, Pyritinol.

CNS depressant drugs

- Anaesthetics: The word anaesthesia mean ‘without sensation’. These agents produce reversible loss of consciousness i.e. causes unconsciousness and loss of whole body sensation, e.g. Ether, Halothane, Barbiturates.
- Narcotics: These agents produce profound sleep (Narcosis) from which the animal can be aroused with a great difficulty, e.g.

i) Morphine and related compounds

ii) Subanaesthetic dose of anesthetics e.g. Barbiturates, chloralhydrate.

- When narcotics are used before general anaesthetics these may be called as basal anaesthetics. It is a state of unconsciousness which is too light for surgical anaesthesia. Under basal anaesthesia – the patient is already asleep so it reduces anxiety and hastens the induction of anaesthesia

- Hypnotics: These agents produce CNS depression equivalent to the natural sleep. e.g. Barbiturates, benzodiazepines. Large doses of hypnotics may produce anaesthesia and small doses produce sedation.
- Sedatives: These agents lower down the cerebral perception and make the animal calm and quiet. These agents relieve the mental anxiety and tension without producing sleep and individual is able to carry out routine work.
- e.g. Small doses of hypnotics
- Tranquillizers – These drugs insulate the animal from external environment and calm down the disturbed and aggressive animal. e.g. CPZ, increase in dose of tranquillizers do not produce hypnosis.

- Analgesics: These agents relieve pain without affecting consciousness, e.g. pethidine, pentazocin, aspirin, phenylbutazone.
- Antiepileptics: These agents prevent the epileptic seizures or convulsions, e.g. dilantin, tridione.

- **Central muscle relaxants:** Guaiphenesin, Mephenesin.

- **Anticonvulsants** : Phenobarbitone, Phenytoin, Diazepam, Carbamazepine, (Antiepileptics)
  Ethosuximide

- **Neuroleptanalgesics**: Fentanyl + Droperidol

Anesthetics

- The word anaesthesia is derived from the Greek word meaning “insensible” or “without feeling”. The word does not necessarily imply loss of consciousness. Anaesthesia is defined as total but reversible loss of sensation in a particular
- I. General Anaesthetics II. Local Anaesthetics
- part of the body (local anaesthesia) or in the entire body (general anaesthesia) which results from administration of a drug (or drugs) that depress the activity of part or all of the nervous system.
- Depending upon route of administration further sub-classified into two groups.
- Inhalational anaesthetics –given by inhalation.
- Injectable anaesthetics –given by injection.

- 1846 - Oliver **Wendell Holmes** coined the term Anaesthesia
- **1776** - first anaesthetic, nitrous oxide gas (laughing gas) was discovered by **Priestly**
- **John Snow : 1st Anesthesiologist – used ether and Chloroform**
- **1872--Chloral hydrate was the first intravenous anaesthetic.**

CHARACTERISTICS OF AN IDEAL ANAESTHETIC AGENT

- Non irritant and free from disagreeable odours
- Adequate analgesia
- Rapid and smooth induction and recovery
- Adequate muscular relaxation
- No side-effects, e.g. excessive salivation, respiratory secretion, hypotension, bradycardia, respiratory depression.

Preanesthetic Drugs

- various ancillary drugs (subordinate drugs) with complimentary pharmacological actions are administered prior to anaesthetics to achieve perfect anaesthesia.
- Combination of two or more anaesthetics with or without ancillary drugs to achieve perfect anaesthesia is termed as Balanced Anaesthesia. These ancillary drugs are also called as preanaesthetics as these are given prior to anaesthetics.
- Objectives of Preanesthetic medication.
- To decrease anxiety and apprehension without producing excessive drowsiness
- To facilitate smooth and rapid induction and recovery
- To produce adequate muscular relaxation
- To produce adequate analgesia in order to relieve post operative pain.
- To minimize undesirable side-effects such as salivation, coughing, bradycardia, vomiting.
- To reduce the dose of anaesthetics so as to avoid toxic effects.

Preanesthetic drugs

- Tranquillizers/sedatives: These agents lower down cerebral perception and make animal calm and quiet, decrease motor activity and increase threshold to external stimuli. These agents produce
  - Sedation and relieves apprehension and anxiety.
  - Reduce the dose of anaesthetics.
  - Also prevent the anaesthetic induced side effects.
- Agents:
- Penothiazine derivatives produce sedation/tranquillization: Acepromazine: 0.05 – 0.01 mg/kg, i.m., all spp., Promazine: 2-5 mg/kg, i.m., all spp., Chlorpromazine: 1-2 mg/kg, i.m. all spp., Trifluopromazine: 0.1 – 0.3 mg/kg in large animals and 2-4 mg/kg in small animals
- Butyrophenones produce antiemetic action and tranquillization - Droperidol , Azaperone
- Benzodiazepines produce sedation and muscle relaxation: Diazepam, Midazolam, Lorazepam
- α_2 – adrenoceptor agonists produce sedation and analgesic action: Xylazine, Medetomidine

- Analgesics: These agents are used to reduce the amount of anaesthetics, provides adequate analgesia to relieve pain and decrease anxiety. Commonly used analgesics are opioid analgesics, which are used alone or in combination with tranquillizers, e.g.
- Morphine sulphate – 0.1 to 2.0 mg/kg, s.c.
- Meperidine/pethidine – 3-5 mg/kg, i.m.
- Fentanyl
- Pentazocin

- Hypnotics: used to:
  - Provide sedation and relieve anxiety and apprehension.
  - Produce basal anaesthesia to facilitate the smooth & rapid induction of anaesthesia following administration of inhalation anaesthetics.
- Agents:
- For small animals
  - Thiopentone (Intraval/Pentothal)
  - Pentobarbitone (Nembutal)
  - Secobarbitone (Seconal)
- For large animals: Chloralhydrate: 15-45 g total amount before general anaesthetics by oral route.

- Anticholinergics: These agents are used to
  - Prevent the excessive salivary and respiratory secretion.
  - Prevent reflex vagal action produced due to irritant action of anaesthesia on
    - Heart – Bradycardia, hypotension
    - Respiratory muscles – Bronchospasm, Laryngeal spasm.
- Commonly used drugs are:
- Scopolamine : 0.01-0.02 mg/kg, i.m.
- Atropine sulphate: 0.05 – 0.06 mg/kg, i.m.
- Scopolamine is preferred over atropine as it produces CNS depression.

- Muscle Relaxants:These agents are given to produce adequate muscular relaxation. These agents facilitate Endotracheal intubation and endoscopy.
- Skeletal muscle relaxation for easy surgical access particularly during abdominal surgery.
- e.g. Various neuromuscular blockers:
  - d-tubocurarine, gallamine.

General Anaesthetics

- General anaesthetics are drugs that produce reversible loss of all sensations and unconsciousness.
- Classification Based on route of administration

1. Inhalation Anaesthetics
2. Parenteral Anaesthetics or Injectable
3. Dissociative Anaesthetics

- The cardinal signs of general anaesthesia are: Loss of all sensation, especially pain, Sleep (unconsciousness) and amnesia, Immobility and muscle relaxation, Abolition of somatic and autonomic reflexes

Dosage and potency of general anaesthetics

- Potency of inhalational anaesthetics: expressed in terms of minimum alveolar concentration (MAC)
- MAC (at 1 atm pressure) of an anesthetic that prevents gross purposeful movement in 50% of subjects exposed to a supramaximal noxious stimulus. Thus, MAC corresponds to the effective dose-50, or ED50; half of the subjects are anesthetized and half are not.
- The anesthetic potency is inversely related to MAC (i.e., potency = 1/MAC).
- From information presented above it also follows that MAC is inversely related to the oil/gas PC.
- Thus, a very potent anesthetic (e.g., methoxyflurane) has a low MAC value and a high oil/gas PC; an agent of low anesthetic potency (e. g., N_2O) has a high MAC and a low oil/gas PC.

Classification of Inhalational Anesthetics

- ***Gaseous agents***: Nitrous oxide and Cyclopropane.
- ***Volatile liquids***: Methoxyflurane, Halothane, Ether, Chloroform, Enflurane, Isoflurane, Desflurane, Sevoflurane

Blood: Gas Partition Coefficient

- **The blood/ gas solubility is a measure of the speed of anaesthetic induction, recovery and change of anaesthetic levels.**
- **Lower the blood/ gas partition coefficient, the more rapid the anaesthetic induction or rate of change of anaesthetic level in response to a stepwise change in anaesthetic delivery**
- **Oil : Gas partition coefficient: higher the coefficient more potent the agent**

DRUGS ACTING ON CNS

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Theories of Mode of action of General Anaesthetics

- **Lipid solubility theory of Overton and Meyer (1901)**

➢ **Compounds with high lipid solubility easily penetrate the CNS, being rich in lipids, and alter the function of nerves.**

➢ **Theory: Potency of an anaesthetic is directly proportional to its affinity and solubility in lipid portion of the nerves.**

➢ **Higher the partition coefficient, higher the potency of anesthetics**

Surface Tension or Adsorption Theory of Traube (1904)

- Ability of the agent to reduce the surface tension of the neuronal membrane by adsorption.
- Alters the transmembrane ionic permeability across the neuronal membrane and interfere with nerve function (generation of AP), resulting into anesthesia.

Microcrystal Theory of Pauling and Miller (1961)

- **Anesthetics facilitate formation of microcrystals or iceberg/clathrates: (anesthetics hydrate crystals) ice crystals within the nerve cells and thus disrupt conductance of impulses.**

- **Impede ionic mobility, electrical charge, and chemical and enzymatic activity of the brain, (produce depression and unconsciousness).**

Protein Binding Theory of Frank and Lieb (1982)

- Anaesthetics act by reversibly binding to a hydrophobic domain of a protein or by concentrating at the lipid-protein interface in the nerve cell membrane.
- The binding causes expansion of the nerve membrane and thus interferes with the function of nerve membrane proteins.

Receptor Theory

- Anaesthetics act by interacting with the NT receptors (**as agonists of inhibitory transmitters,** GABA and glycine **or antagonist of excitatory transmitter,** glutamate, Ach and 5-HT,**)** in the CNS.
- Anaesthetic agents affect **synaptic transmission** rather than axonal conduction.
- **$GABA_A$ receptors - Halogenated anaesthetics (halothane, enflurane, isoflurane & sevoflurane) and some injectable anaesthetics like barbiturates, propofol, etomidate and neurosteroids.**
- **Glycine receptors - Propofol, Barbiturates.**
- **NMDA (N-methyl-D- aspartate) receptors -Ketamine, N_2O.**

Ion Channel Theory: Anaesthetic bind to voltage-gated ion channels and reduce excitability or promote inhibition of nerve membrane.

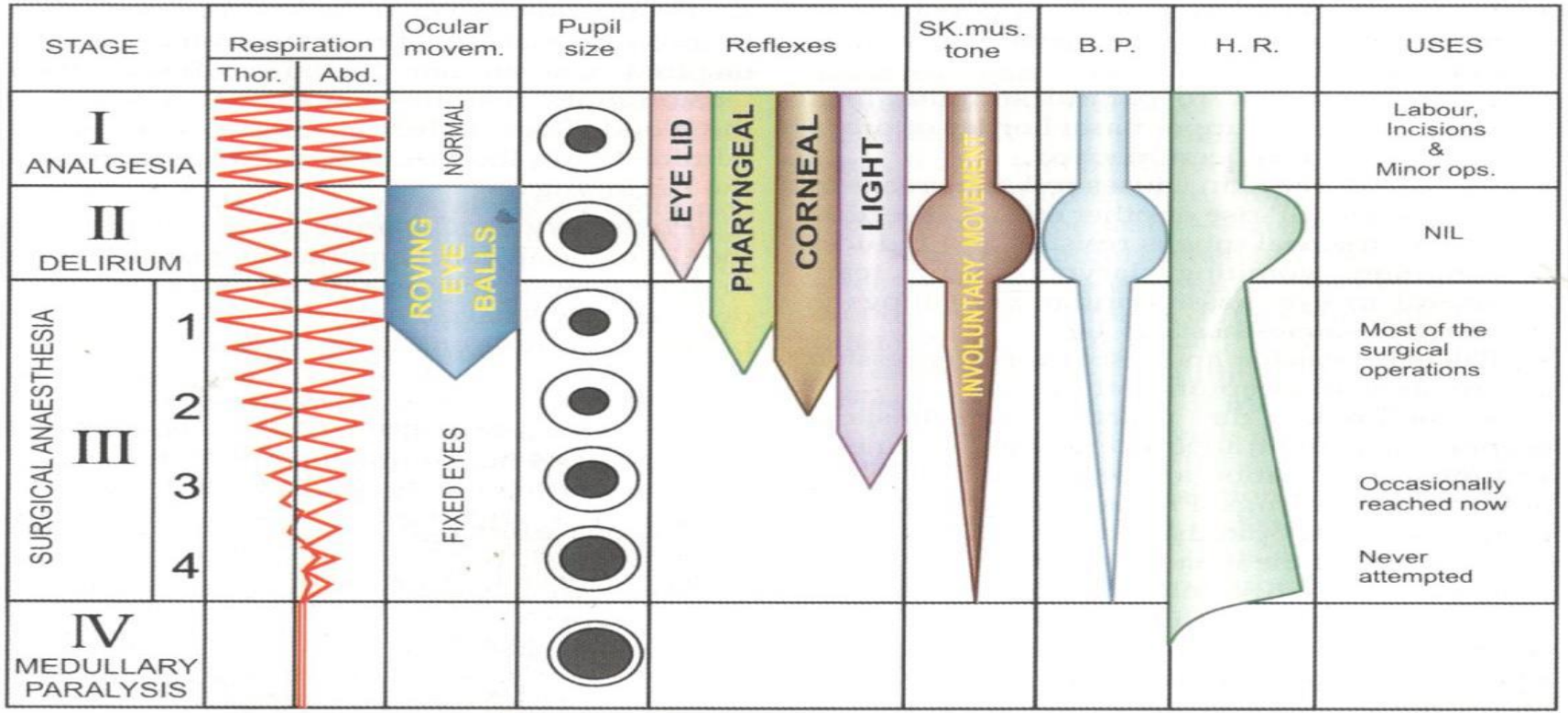
Stages of Anesthesia

classification was described by A.E. Guedel in 1920 for humans using diethyl ether

The depth of anesthesia may be classified into four stages:

- **Stage I or (stage of voluntary movement or Excitement) - stage of Analgesia**
- **Stage II or (stage of involuntary movement or Excitement) - stage of Delirium**
- **Stage III or surgical anaesthesia**
  Plane 1 & Plane 2 : Light surgical anaesthesia
  Plane 3 & Plane 4 : Deep surgical anaesthesia
- **Stage IV or medullary paralysis.**

Stages of general anesthesia



Stage I (stage of Analgesia)

- **This stage starts from the beginning of anaesthetic inhalation and lasts up to the loss of consciousness.**
- **The animal struggles to avoid inhaling strange and unpleasant anaesthetic vapours.**
- **There is release of adrenaline due to fear and excitement.**
- **Pupil is dilated.**
- **Sensory cortex is depressed.**
- **Respiration is rapid and deep, with rise in BP and rise in pulse rate.**
- **All sensory reflexes are present.**

Stage II (Stage of Delirium)

- **Starts from loss of consciousness.**
- **The animal lose its ability to stand, assumes lateral recumbency.**
- **Gradually loses consciousness and reacts to external stimuli with reflex struggling or movements of limbs (with pedal or galloping movements).**
- **Reflex vomition occurs in dogs unless feed is withheld.**
- **Nystagmus (slow rhythmic oscillation of the eye ball) in horses.**
- **Depression extends to motor cortex.**
- **Respiration is very irregular, with rise in BP and rise pulse rate.**
- **All sensory reflexes are present.**
- **The stages I and II are collectively comprise induction of Anaesthesia.**

Stage III (Stage of Surgical anaesthesia)

- This stage extends from onset of regular respiration to cessation of spontaneous breathing.
- Depression is extended from cortex and mid brain to spinal cord.
- It is divided into 4 planes.
- **Planes 1 and 2: Light surgical anaesthesia**
- **Planes 3 and 4: Deep surgical anaesthesia.**

- **Plane 1**

✓ Depression is extended to mid brain and spinal cord partly,

✓ with slow and regular respiration,

✓ normal BP and

✓ normal pulse rate and

✓ presence of all neuromuscular (NM) reflexes.

Plane 2

- The depression covers all spinal cord, with slow and regular respiration, normal BP and pulse rate.
- Absence of eye lid, skin, swallowing (pharyngeal) and photomotor reflexes.
- The corneal and cough reflexes are present.
- Presence of cough reflex prevents entry of tissue debris into respiratory tract during pharyngeal surgery.
- **Most of the surgical operations are done in Plane 2 of Stage III.**

- The animal is not generally allowed to pass into deep surgical anaesthesia, where there is marked depression of respiration and CV functions accompanied by hypothermia, (depression of hypothalamic thermoregulatory center).
- **Plane 3**
- In Plane 3 the depression covers whole of spinal cord, with thoracic or abdominal respiration, fall in BP and rapid and weak pulse absence of all the reflexes;
- pupil starts dilating.

Plane 4

- In Plane 4 the depression extends to part of medulla
- shallow abdominal respiration (intercostal paralysis),
- fall in BP and rapid and weak pulse,
- dilated pupil and
- absence of all NM reflexes.

Stage IV

- This stage starts from cessation of breathing and extends till cardiovascular failure and death.
- This stage is called stage of medullary paralysis
- where the vital medullary centers are paralyzed
- cessation of respiration,
- severe fall in BP,
- Weak pulse and absence of all NM reflexes.
- animals dies unless urgent revival measures are not readily available (artificial respiration, administration of analeptics and CV stimulants) to counter excess CNS depression are not instituted at once.

- **Totipotent anaesthetics:** Ether and chloroform induce all stages (i.e. I, II, III & IV) of anaesthesia and therefore called as Totipotent anaesthetics (i.e. 100% anaesthesia produced).

- **Incomplete anaesthetics** : whereas nitrous oxide and trichloroethylene do not produce stage 3 and 4 and therefore called as **Incomplete anaesthetics** (50% anaesthesia).

- Methoxyflurane, halothane and barbiturate (stage II absent, stage of involuntary Excitement) are considered as good agent for induction of anaesthesia.

Volatile Anaesthetics

Parameter	Ether	Halothane	Methoxyflurane
Properties	Characteristic odor and sweetish taste	Characteristic sweetish odor	Characteristic pungent odor
MAC (%)	3 Least potent. Slow induction	0.75-1.20. Induction 3-5 min	0.23 Slow induction (10 min)
CNS	All stages are seen	Stage II bypassed	Stage II bypassed
CVS	Induction- release of adrenaline: increase in heart rate & BP. Stage III: Fall in BP and COP (depression of VM centre). Does not sensitize heart to catecholamines.	Direct myocardial depression (reducing intracellutar Ca^{++}). Sensitizes heart to catcholamines (arrhythmia)	No change in heart rate or mild tachycardia. Adrenaline can induce cardiac arrhythmia.

Parameter	Ether	Halothane	Methoxyflurane
Respiration	**Initial stimulation followed by progressive depression. Increase bronchial secretion.**	**Depression with increase in duration of anaethesia, may develop acidosis.**	**Initial stimulation followed by progressive depression with increase in anaethesia.**
Liver	Prolonged anesthesia lowers liver glycogen. Not hepatotoxic	Hepatotoxic like chloroform	No significant effect
Body Temperature	Hypothermia	Malignant hyperthermia in pig and horse (persisten muscle contraction due release of Ca^{++} from sarcoplasmic reticulum) and hypothermia in others.	Hypothermia

- Malignant hyperthermia or hyperpyrexia (>45^{o} C), which is developed particularly in swines, may be due to increased muscular activity, rigidity of muscles, loss of control over i/c regulation of Ca^{+2} Paracetamol is generally avoided → hepatotoxicity.
- Dantrolene is the drug of choice.
- Dantrolene is classified as a direct-acting skeletal muscle relaxant. It is currently the only specific and effective treatment for malignant hyperthermia

- Enflurane:
  - The most frequently used potent anaesthetic in human surgery.
  - It is classified as a convulsive anaesthetic
  - MAC for horse is 2.12%.
  - CNS excitation in dogs
  - does not sensitize heart to catecholamine's
- **Isoflurane**
  - an isomer of enflurane does not cause CNS excitation.
  - **MAC 1.3%**

Chloroform

- During induction majority of deaths occur due to direct toxic effect on heart
- During stage I the animal tries to avoid inhaling chloroform vapours by temporary **breath-holding**, which is followed by reflex **deep breathing** taking a high concentration of chloroform vapours into lungs, from there through pulmonary veins into the heart, causing ventricular fibrillation and/or **cardiac arrest**
- Prolonged surgical anaesthesia may cause **respiratory failure** due depression of medullary respiratory centre
- exposure to **air and light** **chloroform** gets oxidized to **phosgene gas** (a marked lung irritant).

Nitrous Oxide (N_2O; Laughing gas)

- Joseph Priestly (1772)

- Has very low anaesthetic potency (MAC 188 (cat) 255 (dog)%) It has good analgesic, but poor muscle relaxant effects
- To avoid hypoxia, it is used in combination with oxygen (nitrous oxide 70% oxygen 25%) and other inhalation anaesthetic (0.2 – 2%).

AGENT	MAC	POTENCY
Methoxy-flurane	0.16%	Most potent
Halothane	0.74%	
Isoflurane	1.17%	
Enflurane	1.7%	
Sevoflurane	2.05%	
Desflurane	6.0%	
Nitrous oxide	104%	Least potent

The lower the MAC– the more potent the agent!

INTRAVENOUS ANESTHETICS

Barbiturates Anaesthetics- Thiopentone, Thiamylal, Thialbarbitone, Methohexitone and Pentobarbitone

Non – BarbituratesAnaesthetics -

1. Phenol derivatives- propofol
2. Imidazole derivatives- etomidate and metomidate
3. Steroidal anesthetics- saffan (alphaxalone-alphadolone)
4. Chloral derivatives- chloral hydrates.
5. Benzodiazepines- midazolam and diazepam.
6. Opioid and neurolept analgesics-fentanyl, fentanyl- droperidol combination.
7. Miscellaneous anesthetics- chloralose and urethane.

Dissociative anaesthetics- ketamine, tiletamine, Phencyclidine.

Barbiturates

- Derivatives of malonyl urea (condensation product of urea and malonic acid)
- Classification

(i) Long Acting Barbiturates (8 hrs or more) : e.g. Phenobarbitone, barbitone, methylphenobarbitone and aprobarbitone.

(ii) Intermediate Acting Barbiturates (4-8 hrs): e.g. Butobarbitone, mephobarbitone, cyclobarbitone and amylobarbitone.

(iii) Short Acting Barbiturates (< 4 hrs) : e.g. pentobarbitone, secobarbitone and quinalbarbitone.

iv) Ultrashort Acting Barbiturates (< 30 min) : e.g. thiopentone, thiamylal, hexobarbitone and methylhexitone.

Fig: GABA Receptor chloride channel complex

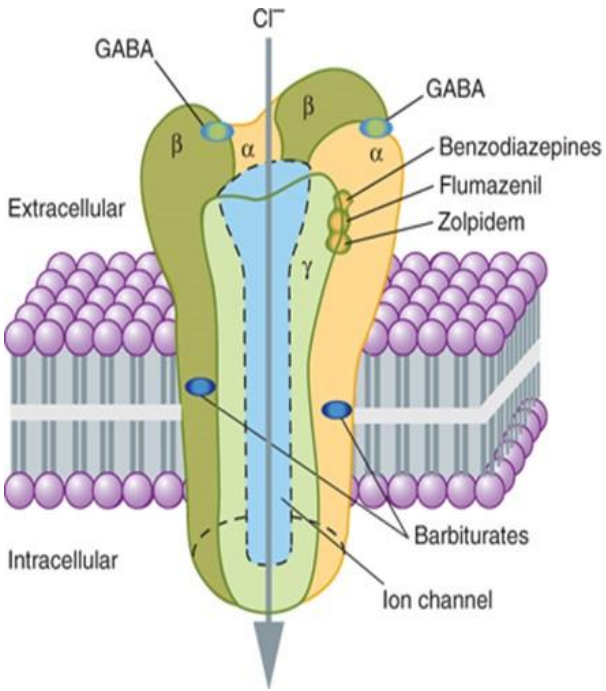


Fig: GABA Receptor chloride channel complex. (linear view)

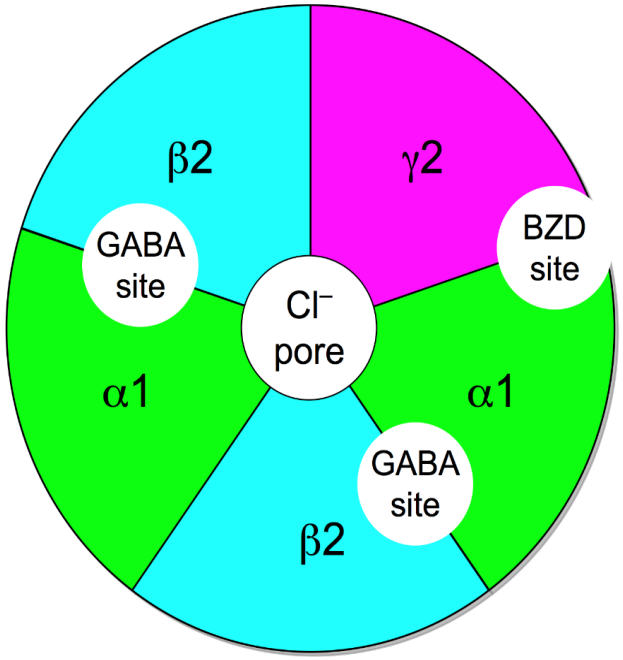


Fig: GABA Receptor (front view)

GABA receptors

- GABA- A receptors: Ligand gated chloride ion channels i.e. ionotropic receptors
- Muscimol: agonist at GABAA site
- Bicuculline: competitive antagonist at GABA- A receptor
- Picrotoxin: Blocks Cl- Channel noncompetitively
- GABA – B receptors : GPCRs
- Agonist: Baclofen
- Antagonist: Phaclofen
- GABA- C receptors: slow and sustained ionotropic receptors

- Barbiturates: **Agonist at an allosteric site**; prolong GABA action; open **Cl^- Channel**
- Alcohol, Inhalational anaesthetics, Propofol: open **Cl^- Channel** directly.
- Benzodiazepines: Agonist at an allosteric BZD site - facilitate GABA action.
- β – carboline : **inverse agonist** at BZD site- impede GABA action
- Flumazenil: **competitive antagonist** at BZD site

MOA of Barbiturates

- act at GABA:BZD receptor – Cl^- Channel complex and prolong the opening time of Cl^- Channel induced by GABA
- At high concentrations, barbiturates directly increase Cl^- conductance (GABA- mimetic action; contrast BZD which have only GABA facilitatory action) and inhibit Ca++ dependent release of neurotransmitter
- depress glutamate induced neuronal depolarization through AMPA receptors.
- At very high concentrations, barbiturates depress voltage sensitive of Na^+ and K^+ channels.

THERAPEUTIC USES

- As Hypnotic & Sedatives
- Antiepileptic
- Anticonvulsant
- As IV general Anesthesia
- For euthanasia
- * Stage II bypassed

Major pharmacological effects

- CNS: Dose dependent depression: mild sedation to deep hypnosis and surgical anaesthesia. Depress both sensory and motor cortex
- Respiratory system- slight depression at anaesthetic dose, but respiration failure at high dose.
- CVS- Rapid IV injection causes sharp, but transient fall in BP
- Uterus and foetus: depress parturient uterine contractions. Also cross placenta causes depression of foetal respiration and death of foetus in utero.

Pharmacokinetics

- Barbiturates are readily absorbed from GIT and widely distributed in the body.
- The rate of entry of barbiturates into CNS depends on their lipid solubility.
- Plasma protein binding varies with compound, thiopentone- 75% phenobarbitone-20%.
- Barbiturates readily cross placenta and enter foetus and also are secreted in milk
- **Glucose effect: glucose deceases microsomal metabolism of barbiturates ; so anaesthetizing action in seen in animals recovering from barbiturate anaesthesia when glucose administered**

- The action of barbiturates are terminated by three process:

✓ Redistribution (high lipid soluble thiopentone)

✓ Hepatic microsomal metabolism.

✓ Renal excretion (drugs with low lipid solubility : long acting)

Toxicity of barbiturates: death due to respiratory failure followed by cardiac arrest.

Treatment: Animals should be treated with oxygen support and analeptics like bemegride, leptazole etc. Bemegride is preferred as it has structural similarity with barbiturates.

Thiopentone (Pentothal/ Intraval)

- Dog &cat---20-25 mg/kg
- Pig-10-12mg/kg
- Calf/goat– 15-20 mg/kg
- Horse- 10mg/kg
- For euthanasia: 40-60 mg/kg
- administered as 2.5% solution in small animals and as 5-10% aqueous solution in large animals.
- ½ dose –fast IV then slow IV
- NOT SC or IM

- Phenobarbital: Dogs: 2–4 mg/kg, PO, bid
- Amobarbitone Sodium : Sedative and basal anaesthetic dose in all species animal is 4-11 mg/kg.
- Pentobarbitone sodium: most commonly used as anaesthetic agent and for control of convulsions.
  - Anaesthetic use: in dogs and cats. Dose range 24-33 mg/kg, i.v.
  - Dogs: Average i.v. dose 30mg/kg
  - Cats: Average i.v. dose 25 mg/kg
- Administered slowly in repeated small doses over a period of 2-4 min. with continuous monitoring of depth of anaesthesia. Lethal dose is 40-60 mg/kg, i.v.
- Large animals: 10-15 mg/kg, i.v.

Species variation

- **Grey hounds: deficient in oxidative enzymes and have low fat stores---------→ barbiturates contraindicated in grey hounds**
- **Cattle: Pink tooth – congenital condition due to porphyrin pigment**
- **pigs: redistribution due to more fat reserves**
- **horses : excitement & incoordination**

Chloral hydrate

- Low margin of safety, Poor analgesic effect, Satisfactory hypnotic effect
- 95% - trichloroethanol after administration (active form)
- Pre-anaesthetic, sedative and hypnotic in large animal.
- 10-20gm/adult as 7% solution IV
- As i.v. anaesthesia of large animal: Curariform effect (skeletal muscle relaxation) of $MgSO_4$ and hypnotic effect
- Horse and cattle : Chloralhydrate (12%) and $MgSO_4$ (6%) slow iv
- Camel : Chloralhydrate (12%) and $MgSO_4$ (12%)

Chlorpent anaesthesia

- **[Chloral hydrate + $MgSO_4$ + Pentobarbital Sodium]**
- Produces satisfactory anaesthesia without the toxic effect of individual drug.
- 3% Chloralhydrate + 1.5% mag.sul + 0.66% pentobarbitone

Dissociative anaesthetics

- agents that induce a state of altered CNS activity in which the anaesthetised patient feels totally dissociated from its surroundings during induction
- produce marked sensory loss, analgesia, amnesia and paralysis of movements without apparent loss of consciousness (patients appears to be awake but actually is unconsciousness)
- drugs disassociate thalamocortical and limbic systems

- Dissociative anaesthetics- ketamine, tiletamine, Phencyclidine

- - non competitive antagonist of NMDA (N-methyl-D-aspartate) receptors and prevent binding of excitatory amino acid glutamate

Ketamine

- In 1970, it was introduced for anaesthesia in the **cat**
- **It induces only stage I and II but not III & IV**
- It does not depress respiration, there is profound analgesia and amnesia, muscle relaxation is poor
- Can be used as sole anesthetic in **Cats and Birds**

Dosage of Ketamine

Dog : As anaesthetic – 5-10 mg/kg IV after diazepam (0.5mg/kg)

- **Horse**: 2 mg/kg IV in combination with diazepam (0.2mg/kg) and xylazine (0.1mg/kg)
- **Cattle**: induction- 2 mg/kg rapid IV or IV

  maintenance: 0.2 % ketamine in normal saline solution administered @ 10 ml/min.
- **Goat**: 10 mg/kg IV after xylazine (0.2mg/kg)
- Cats: 11, 22, 33 mg/kg
- 11 mg/kg – as minor restraint for induction of anaesthesia, which is maintained by inhalant anaesthetics.
- 22 mg/kg – minor surgery e.g. Castration.
- 33 mg/kg – major surgery – ovariohysteroectomy, cesarean section etc.

Steroidal anesthetics- saffan/ Althesin

- First injectable steroid anaesthetic - hydroxydione Na.
- Toxicity (thrombophlebitis) – so not used
- generally used for induction of anesthesia.
- It contains two pregnanedions, alphaxalone (steroid I)-alphadolone(steroid II).
- Produces rapid induction of short duration anaesthesia.

- Althesin is combination of two steroid drugs solubilized in an aqueous formulation containing polyethylated castor oil (Cremophor EL).
- Contraindicated –not used in dogs due to vehicle surfactant (Cremophor EL) in the preperation causes excessive histamine release from mast cells resulting in profound depression.

Propofol- phenol derivative

- It resembles thiopentone in being highly lipid soluble.
- Quick recovery - rapidly metabolized
- MOA: similar like barbiturates
- Should be given as constant rate infusion
- decreases intracranial pressure and cerebral perfusion pressure : useful in CNS diseases

Imidazole derivatives

Etomidate

- Has potent hypnotic effect but no analgesic effect.
- Has wide margin of safety.
- No hangover like thiopentone sodium
- GABA like effect
- contraindicated in patients with renal insuuficency: anticorticosteroid activity due to inhibition of 11-beta- hydoxylase

Metomidate

- It is recommonded for anesthesia in birds.
- Also in pig, dog & cats.
- Has wide margin of safety.
- No hangover like thiopentone sodium

Urethane

- Also called Ethyl carbamate.
- Chemically related to urea.
- Commonly used in **laboratory animals**

Chloralose

- It is the condensation product of glucose and chloralhydrate.
- it is transformed to chloraldehyde which is further metabolized to trichloroethanol.
- Produces dissociative anaesthesia like Ketamine
- Used in Lab animals

Hypnotic- Sedatives

- CNS depressants with some what differing **time-action** and **dose action** relationships.
- **quicker onset, shorter duration and steeper dose-response curves** - *hypnotics* while **slowly acting drugs with flatter dose-response curves** are employed as *sedatives*.
- do not possess analgesic property, but dull the perception of pain sensation
- Hypnotics given in high doses can produce general anesthesia.
- Hypnotics in higher doses cause deep sleep (narcosis) and hence are also called as narcotics.
- Tranquillized animals are usually easy to handle, but they may be aroused by and respond to stimuli in a normal way (biting, scratching and kicking)
- Sedatives are generally used to restrain, to facilitate handling and transport, and to modify behavior of animals
- Sedatives are commonly included in pre- anesthetic medication and are also used to facilitate minor surgery or diagnostic procedures

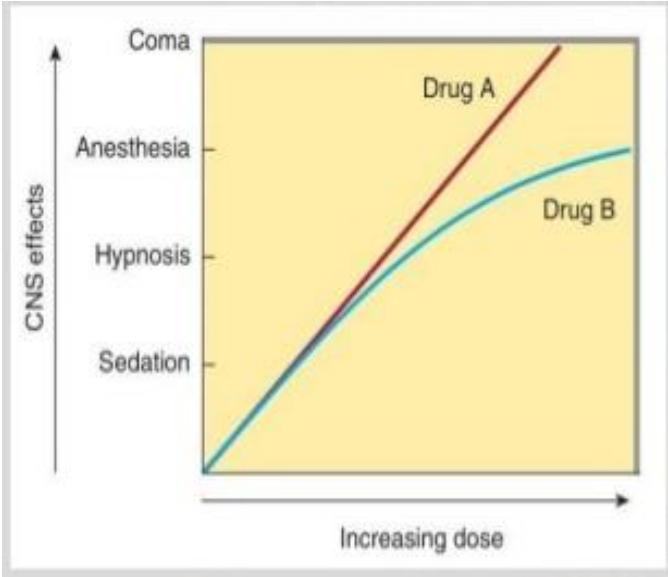
Dose response curve of sedative and hypnotics

- **Drug A**

  Barbiturates
  Steeper DRC
  Narrow margin of safety

- **Drug B**

  Benzodiazepines
  Flatter DRC
  Wide margin of safety



Classification of Hypnotic- Sedatives

Barbiturates

- Barbitone,
- Phenobarbione,
- Pentobarbitone,
- Amobarbitone,
- Secobarbitone.

Benzodiazepines

- Long acting Benzodiazepines: Diazepam, Flurazepam, nitrazipam and flunitrazepam.
  - Short acting Benzodiazepines: Midazolam, triazolam, timazepam, lorazepam, oxazepam.

Miscellaneous agents

- Cloralhydrates
  - Paraldehyde
  - Methaqualone
  - Glutithimide
  - Xylazine hydrochloride
  - Detomidine hydrochloride
  - Medetomidine hydrochloride

Benzodiazepines

- Benzodiazepines are commonly used as sedatives or hypnotics
- These compounds have several advantages over barbiturates as hypnotic and sedatives. ---

  - **Benzodiazepines have high therapeutic index. Ingestion of even 20 hypnotic doses does not usually endanger life—there is no loss of consciousness**
  - **do not affect respiration or cardiovascular function.**
  - **Their toxicity (due to higher dosage) can be overcome by giving specific benzodiazepine receptor antagonist flumazenil.**

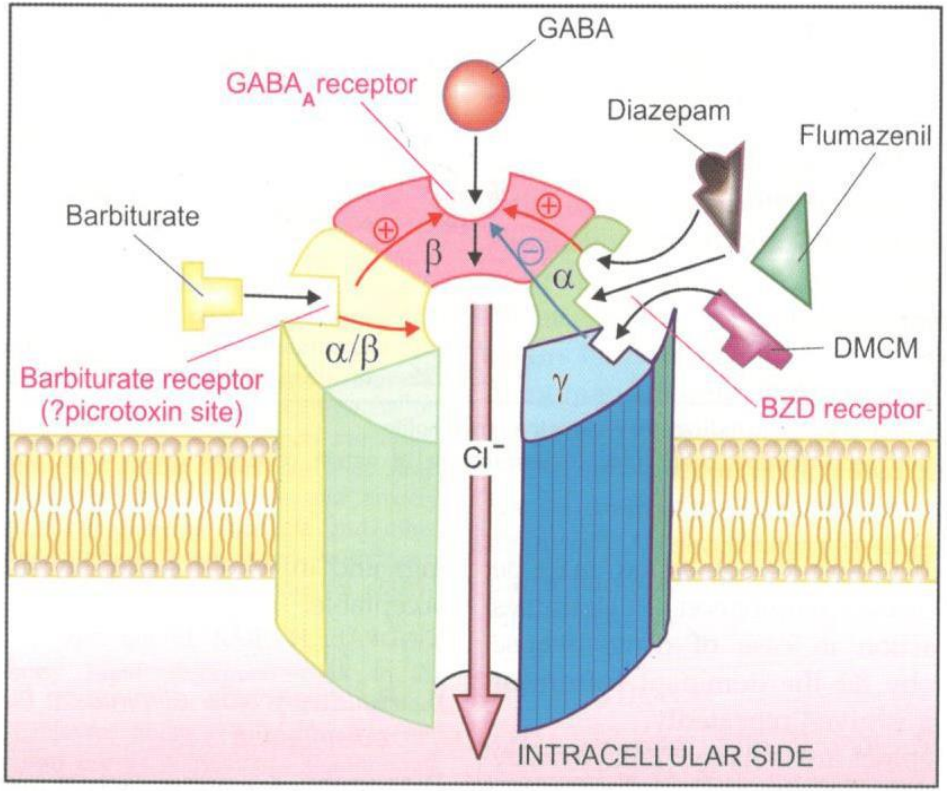
Classification of Benzodiazepines

Hypnotic- Diazepam,
Flurazepam,
nitrazipam
flunitrazepam

Anxiolytics:- Diazepam,
Chlordiazepoxide,
Oxazepam
Lorazepam.

Anticonvulsants-Diazepam, Clonazepam

Mechanism of Action of Benzodiazepines



- The modulatory BZD receptor **increases the frequency of Cl^- channel opening** induced by submaximal concentrations of GABA. The BZDs also enhance binding of GABA to $GABA_A$ receptor.
- The BZDs do not themselves increase CI^- conductance, these exert only GABA facilitation, but not GABA mimetic action.

- metabolized in liver
- Most of the benzodiazepine drugs have active metabolites (glucuronide conjugates) are excreted through urine.
- active metabolites (chlordiazepoxide, desmethyldiazepam, diazepam, flurazepam etc.) which undergo **enterohepatic recycling (have long half-lives).**
- Chlorazepine is metabolically activated to desmethyldiazepine, which is further metabolically activated to oxazepam.

- Diazepam
- Dogs: 1 mg/kg with a maximum of 20 mg by IV or oral route
- Cats : 1 mg/kg with a maximum of 5mg by the same routes.
- Goats:0.88 mg/kg by IM route.
- Cattle: 0.4 mg/kg by IV route.
- Swine: 8.5 mg/kg by IM route.

Xylazine hydrochloride

Xylazine is classified as an analgesic as well as a sedative and skeletal muscle relaxant.

- Xylazine is a potent a_2-adrenergic agonist.
- not a neuroleptic or tranquillizer nor an anesthetic agent
- **It is not effective in swine.**

Doses

- **Dog & cat : 1.1 mg/kg I.V. route ; 2.2 mg/kg I.M. or SC route.**
- **Horse: 1.1 mg/kg I.V. route; 2.2 mg/kg I.M. or route.**
- **Cattle: 0.1 – 0.35 mg/kg I.M. route.**
- **Goat: 0.1 mg/kg I.V. or route.**

Detomidine hdrochloride:

•It is selective a_2-adrenergic agonist, developed as sedative and analgesic for use in animals.

•Primarily used as sedative analgesic in horses

Medetomidine hydrochloride:

•It is also selective a_2-adrenergic agonist.

•It is a mixture of two optical isomers, the dextrorotatory isomer being the active components.

TRANQUILLIZER-SEDATIVES/TRANQUILIZERS

- Tranquillizers: is a drug which reduces mental tension and produces calmness without inducing sleep.
- Drugs that produces calmness in an agitated patients and reduces anxiety without producing sedation or affecting consciousness.
- Also termed as **peace pills.**
- **Ataractics, Psycholeptics or neuroleptics.**
- Tranquillizers:

  Antipsychotic drugs or Major Tranquillizers

  Anxiolytics or Minor Tranquillizers

Classification

- **Phenothiazines- chlorpromazine, promazine, Triflupromazine Acepromazine,**
- **Thioxanthins- choprothixene**
- **Benzodiazepines- Diazepam, lorazepam, oxazepzm, temazepam, nitrazepam, chlodiazepoxide, flurazepam, chlonazepam, midazolam,**
- **Butyrophenones- Azaperone, Droperidol**

- **Rauwolfia derivatives: Metoserpate hydrochloride**

Phenothiazine derivatives

- Phenothiazine derivatives are tranquillizers or neuroleptics, which have been used in humans to treat a variety of **psychotic disorders.**
- In veterinary medicine, they are used primarily for **chemical restraint.**
- These are widely used **to restrain refractory animals during examination or transportation, and to prevent animals from licking wounds or chewing bandages and splints.**
- Although phenothiazines may reduce an animal's response to conditioned stimuli.

- **potent action on dopamine receptor, especially D_2-dopamine receptor blocking action.**
- mainly block postsynaptic dopamine receptors in the CNS and may also inhibit synthesis and/or release of dopamine through D_2-receptors located pre-synaptically
- Dopaminergic receptors in the basal ganglia appear to cause the extrapyramidal symptoms, while those in the chemoreceptor trigger zone (CTZ) are responsible for antiemetic action
- exert a sedative action by depressing the brain stem and the connections to cerebral cortex.

Effects

- Chlorpromazine is effective in antagonizing apomorphine induced emesis in dogs, but not in cats
- The antiemetic effect is related to its selective depression of the emetic centre CTZ located in the brain stem.
- At high doses, chlorpromazine appears to block the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH).
- Ovulation is blocked and oestrous cycle is suppressed.
- Chlorpromazine increases plasma prolactin concentration through **inhibition of D_2 dopamine receptors**
- **Promazine: It is thought to have certain advantages over CPZ atleast in Horses as the latter produces excitation in horses while the former does not. Thus preferred over CPZ in horses as it seldom produces excitement or recumbency.**

- **Species Differences**
- *Horse:* Paraphimosis (penile prolapse) in the horse, particularly in stallions leading to swelling, trauma, and failure to retract normally. It is generally recommended to not administer phenothiazines to breeding animals.
- Therapeutic use of CPZ is contraindicated in horses because of violent incoordination, muscle weakness and excitement following CPZ administration.
- *Dog:* In boxer dogs, sedation and hypotension due to acepromazine are greater than expected, presum-ably due to the adrenergic blocking effects of the drug, and there have been reports of syncopal (temporary loss of consciousness) episodes presumably from hypotension.

Butyrophenon Derivatives

- Butyrophenon tranquillizers or neuroleptics are commonly used for sedation and **chemical restraint**
- action is through **antagonism of dopamine through blockade of D_1 (+) and D_2 (+++) receptors in CNS**
- Examples of butyrophenon derivatives -- Azaperone, Droperidol

Azaperone

- It is extensively **used in pigs,** for pigs it is considered as sedatives of choice

Droperidol:

- Droperidol as a tranquillizer-sedative is about 400 and 3000 times more potent than chlorpromazine and promazine
- 1000 times more active than chlorpromazine and chlorprothixene as an **antiemetic.**
- Its cataleptic immobility potential also is **several times higher** than chlorpromazine and chlorprothixene.

Rauwolfia Derivatives

- Reserpine is the alkaloid obtained from the roots of an Indian medicinal plant ***Rauwolfia serpentina.***
- It is used as a tranquilizer and as an **antihypertensive drug in man.**

- **Metoserpate HCI**

  Synthetic analog of reserpine.

  It is used as tranquilizer for flock treatment of **birds**

neuroleptanalgesia

- Combination of opioid with tranquilizer
- neuroleptic (tranquilizer) + opioid (analgesic)
- most popular practice for sedating or chemically restraining animals
- combinations provide heavy sedation and analgesia for minor surgical procedures
- allow endotracheal intubation (airway support or anesthetic induction)

- morphine + acepromazine
- morphine + medetomidine
- morphine + diazepam
- butorphanol + medetomidine

- butorphanol + diazepam
- hydromorphone + acepromazine
- hydromorphone + diazepam
- hydromorphone + medetomidine
- oxymorphone + acepromazine
- oxymorphone + diazepam
- oxymorphone + medetomidine
- fentanyl + droperidol

Local anaesthetics

- Esters: Procaine, Chloroprocaine, Tetracaine
- Amides: lidocaine, Bupivacine
- MOA: Block nerve conduction by inhibiting influx of Na+ ions through ion gated sodium channels in nerve membrane leading to impairment of generation of Action potential
- Efficacy increased when used with Epinephrine

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- morphine + medetomidine
- morphine + diazepam
- butorphanol + medetomidine

- butorphanol + diazepam
- hydromorphone + acepromazine
- hydromorphone + diazepam
- hydromorphone + medetomidine
- oxymorphone + acepromazine
- oxymorphone + diazepam
- oxymorphone + medetomidine
- fentanyl + droperidol

Local anaesthetics

- ***Local anaesthetics*** are drugs which cause reversible loss of sensation of a particular area or region of the body.

Mechanism of action:

- The local anaesthetics ***prevent depolarization of the neurons*** by interfering with Na^+ ion permeability resulting in blockade of impulse conduction.
- This effect is due to ***reversible binding to the Na^+ ion channels*** in the neuronal membrane.

Classification of local anaesthetics

Categories	Duration of action	Examples
1. Ultra-short acting	Less than or equal to 15 min.	Proparacaine, Benoxinate
2. Short acting	Approx. 1 hour	Procaine, Chlorprocaine, Cocaine
3. Intermediate acting	1 – 4 hour	Lidocaine (Xylocaine), Mepivacaine, Prilocaine
4. Long acting	4 – 10 hours or longer	Bupivacaine, Ropivacaine, Tetracaine,Etidocaine, Hexylcaine, Cinchocaine

ANTICONVULSANTS

- Anticonvulsants are drugs that depress the CNS and control convulsions.
- These drugs are intended for the treatment of various convulsive/ seizure disorders in man and animals.
- The primary use of anticonvulsants is in epilepsy hence they are also called anti epileptics.

Status epilepticus:

- **epileptic seizures that are so frequently repeated** or **so prolonged as to create a fixed and lasting epileptic condition.**

- In this type, patient has a **subsequent generalized seizure before recovering from the initial seizure.**

- In status epilepticus, there may be extreme exhaustion, hyperpyrexia or even death.

General Mechanism of anticonvulsant Action

- Altered neuronal membrane function which can lead to excessive depolarization
- Decreased inhibitory N.T. such as GABA
- Increased excitatory N.T. such as Glutamate
- Increase in extracellular potassium and decrease Ca^{+2} concentration facilitate the initiation and spread of seizures.

Classification of Anticonvulsant drugs

1. **BARBITURATES**: e.g. PHENOBARBITONE, MEPHOBARBITONE.

- *MOA*: Decreases seizure activity by enhancing responsiveness to inhibitory postsynaptic effects of GABA. Also inhibit glutamate activity and Ca^{+2} fluxes in presynaptic neurons leading to decreased release of excitatory neurotransmitter.

- **PHENOBARBITONE**: Phenobarbital is considered the first drug of choice for long-term treatment of seizure disorders in dogs and cats

- Dogs are usually started on *2.5-3* mg/kg ql2h and adjusted up to 6-8 mg/kg q12h, gradually—if necessary.

2.DEOXYBARBITURATES:PRIMIDONE(2-deoxyanalogue of phenobarbitone):

- *MOA*: Primidone is a GABA receptor agonist.

- Metabolised into phenobarbitone and phenylethylmalonamide (PEMA) readily in dogs and not in cats. It is not used in cats as metabolism of primidone to phenobarbitone is negligible in cats.

3. HYDANTOINS:PHENYTOIN, MEPHENYTOIN, ETHOTOIN

- MOA: Phenytoin acts on sodium channels on the neuronal cell membrane and blocks inward movement of Na, stabilises excitable neurons. Also decreases Ca inward flow during depo-larization, thus, inhibiting Ca-dependent release of neurotransmitters
- *Horses*. Phenytoin has been used in horses for 'tying-up syndrome'

BENZODIAZEPINES:

- **DIAZEPAM**: **drug of choice for treating status epilepticus** because it is distributed rapidly to the CNS after IV administration.
- Unusitable for longer treatment because of short half life.
- Hepatic Toxicosis in Cats
- Treatment of Anxiety, Aggression, Anorexia and Behavioral Disorders
- E.g. Clonazepam (no hepatotoxicity in cats), Clorazepate

- **FELBAMATE:** antagonist at the N-methyl-D-aspartate (NMDA) receptor-ionophore complex Which block effects of excitatory amino acids and suppress seizure activity

- **ALIPHATIC CARBOXYLIC ACIDS: Valproic acid/ Valproate sodium.**

Valproic acid can stimulate the activity of the GABA synthetic enzyme, glutamic acid decarboxylase, and inhibit GABA degradative enzymes, GABA transaminase and succinic semialdehyde dehydrogenase.

- **POTASSIUM BROMIDES: replaces Cl^- ions and causes hyperpolarization → Anticonvulsant action.**

- **ZONISAMIDE:** sulfonamide anticonvulsant
- inhibits the T-type Ca^{2+} currents and prolong the inactivated state of voltage-gated Na^{+} channels

- **LEVETIRACETAM**: stimulate synaptic vesicle protein 2A (SV2A), inhibiting neurotransmitter release.

- **GABAPENTIN:** structural analog of gamma-aminobu-tyric acid (GABA).
- Blocks- calcium-dependent channels i.e. the alpha-2-delta ($\alpha_2\delta$) subunit and prevent release of neurotransmitters-specifically excitatory amino acids

- **VIGABATRIN (gamma-Vinyl GABA):** prevents the catabolism of GABA by irreversibly inhibiting the enzyme GABA transaminase which metabolises GABA

- **LAMOTRIGINE**: inhibits voltage-sensitive sodium channels and/or calcium channels, modulating presynaptic transmitter release of excitatory amino acids (e.g., glutamate and aspartate).

- **CARBAMAZEPINE**: Prolong Na^+ channels in inactivated state

- **TIAGABINE** : derivative of nipecotic acid and inhibits the GABA transporter, GAT-1

- **TOPIRAMATE**
  Topiramate (TOPAMAX) is a sulfamate-substituted monosaccharide which reduces voltage-gated Na^+ currents in cerebellar granule

Analgesics

- Drugs that relieve pain
- analgesics are divided into 2 main groups:
  Opioid analgesics (narcotic or morphine like analgesics)

  Non- Opioid analgesics (non-narcotic or aspirin like analgesics)

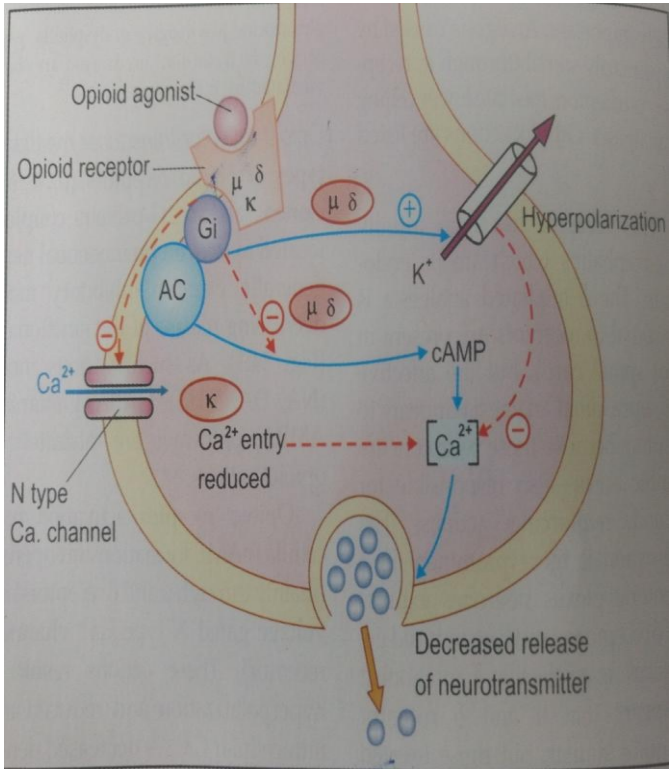
- OPIOIDS: refer to all compounds which act through opioid receptors, drugs derived from juice of opium poppy, *Papaver somniferum*
- Opium contains over 20 different alkaloids and belongs to two distinct chemical classes. Phenanthrenes & benzylisoquinolines.
- PHENANTHRENES: Morphine - Analgesic, CNS depressant.
- Codeine – analgesic, antitussive
- Thebaine- CNS stimulant
- BENZYLISOQUINOLINES: Papaverine → Vasodilator, Spasmolytic.
- Noscapine → Antitussive .
- **Morphine is principal alkaloid of opium.**

Opioid receptors

Receptor type	Physiological role
μ	Analgesia, indifference, cough suppression, respiratory depression, cardiovascular depression, physical dependence, hypothermia.
δ	Probably analgesia and indifference.
κ	Analgesia, sedation and ataxia.

Mechanism of Analgesic Effect of Opioids

- The analgesic effect - is through their action on opioid receptors (G-protein coupled receptors)
- inhibition of adenylate cyclase causing decrease in intracellular second messenger cAMP.
- They are also linked to ion channels (G-protein coupled ion channels), interaction with which results in opening of K channels and inhibition of opening of Ca^{++} channels causing hyper polarization and non release of pain inducers.
- Thus the opioid analgesics block nociception neuronal pathway.



Pharmacological effect of morphine

On CNS: Depression or Excitement depending on species.

- ✓ Depression in man, monkey and dog.
- ✓ Restlessness in cattle, sheep, got and horse.
- ✓ **Excitement in cat**

- ✓ Has analgesic effect due to central (supraspinal) and peripheral actions, blocks the nociception transmission i.e. antinociception).

On GIT (severe constipation):

- ✓ suppresses the defecation reflex and causes constriction of anal sphincter causing severe constipation.

On Respiration:

- ✓ Depression, accompanied by reduced sensitivity of respiratory centre to PCO_2,
- ✓ Higher doses causes direct depression of medullary respiratory centre.
- ✓ Bronchoconstriction due to histamine release by morphine.

- **On CV system:**

- ✓ No significant effect
- ✓ Hypotension due to histamine release.
- ✓ At higher doses causes fall in BP and bradycardia due to depression of vasomotor centre.

- **On Cough Centre:** Potent antitussive (cough suppressant) by depression of cough centre. (Medulla oblongata)

- **On Emetic Centre:**

✓ Nausea and vomition through stimulation of CTZ at analgesic doses.

- **On Pupil (Eye):**

✓ Marked dilatation in horse, monkey, sheep, cattle etc.

✓ Pin point constriction in man (diagnostic), dog, rat and rabbit.

- **On Kidney:**

✓ In dog morphine initially causes urination and later oligouria or anuria (decrease release of ADH)

✓ increase in tone of urinary bladder and constriction of bladder sphincter.

- Thermoregulatory Centre:
- Hypothermia – dogs, rabbit and humans
- Hyperthermia – cattle, horse, goats and cats

- Treatment of toxicity: Naloxone alongwith respiratory support.

Opioid receptor agonist and antagonist

- **Opioid agonists -** Morphine, Codeine, Hydromorphone, Oxymorphone, Meperidine, Methadone
- **Opioid antagonists –** Naloxone, Diprenorphine, Naltrexone, Nalmefene
- **Partial opioid agonists-** Buprenorphine, Tramadol
- **Opioid agonist – antagonist (Mixed)-** Nalbuphine, Pentazocine, Butorphanol, Nalorphine

CODEINE:

- It is used as the phosphate salt to relieve coughing , and as analgesic and cough suppressant in the man.

DIAMORPHINE (Diacetylmorphine or Heroin):

- It is about 5 times as potent as morphine as an analgesic, narcotic and respiratory depressant.
- It has addictive properties.

METHADONE:

- It is a synthetic compound, approx. equipotent with morphine as an analgesic.
- It is a powerful antitussives agent and used in horses & dog for cough suppression.

PETHIDINE (Meperidine):

- It is about 1/10th as active as morphine as an analgesic.
- It is less likely than morphine to produce narcosis, vasodepression, emesis and depression of the medullary cough and respiratory centers.
- Thus, it is more suitable for use in dog and pregnant animals than morphine.

APOMORPHINE:

- It is particularly potent as a centrally acting emetic acting as a stimulant on the CTZ of the medulla. used as an emetic in the dog in cases of poisoning.

DEXTROMETHORPHAN:

- It lacks most of the properties of morphine including the analgesic, addictive, narcotic and spasmogenic actions.
- It does however, depresses the cough centre in the medulla and is used clinically as an antitussive in dogs when control of the dry productive cough is required.
- Centrally acting antitussive

FENTANYL:

- It is approximately 50-100 times more potent than morphine as an analgesic.
- The main use of fentanyl is in neuroleptanalgesia.

- **Thebaine Derivatives:**

Etorphine :

✓ These drugs cause neuroleptanalgesia (analgesia + neurolepsia i.e. tranquility).

✓ Etorphine is 1000 times more potent than morphine and is used to immobilize wild animals for trapping.

Buprenorphine:

✓ Buprenorphine is a partial agonist on mu receptors.

- Used in drug dependence cases

Non-steroidal anti-inflammatory drugs (NSAIDs)

- Steroidal anti-inflammatory agents/ Corticosteroids/ Glucocorticoids: Inhibit release or synthesis of many endogenous mediators, which play role in inflammation.
- Non steroidal Anti inflammatory drugs: drugs generally having four types of actions.

1. Analgesic action: relieve pain without inducing central depressant or sedative activity.
2. Anti-inflammatory action: Reduce or block process of inflammation.
3. Antipyretic action: used in pyrexia or fever.
4. Antigout: causes increased excretion of uric acid and help in treating gout

Nonselective COX inhibitors (traditional NSAIDs)					
Salicylates	Propionic acid derivatives	Fenamate	Enolic acid derivatives	Acetic acid derivatives	Pyrazolone derivatives
Aspirin	Ibuprofen, Naproxen, Ketoprofen, Flurbiprof- en	Mephena- mic acid.	Piroxicam, Tenoxicam	Ketorolac, Indometha- cin, Nabumeto- ne	Phenylbut- azone, Oxyphenb- utazone

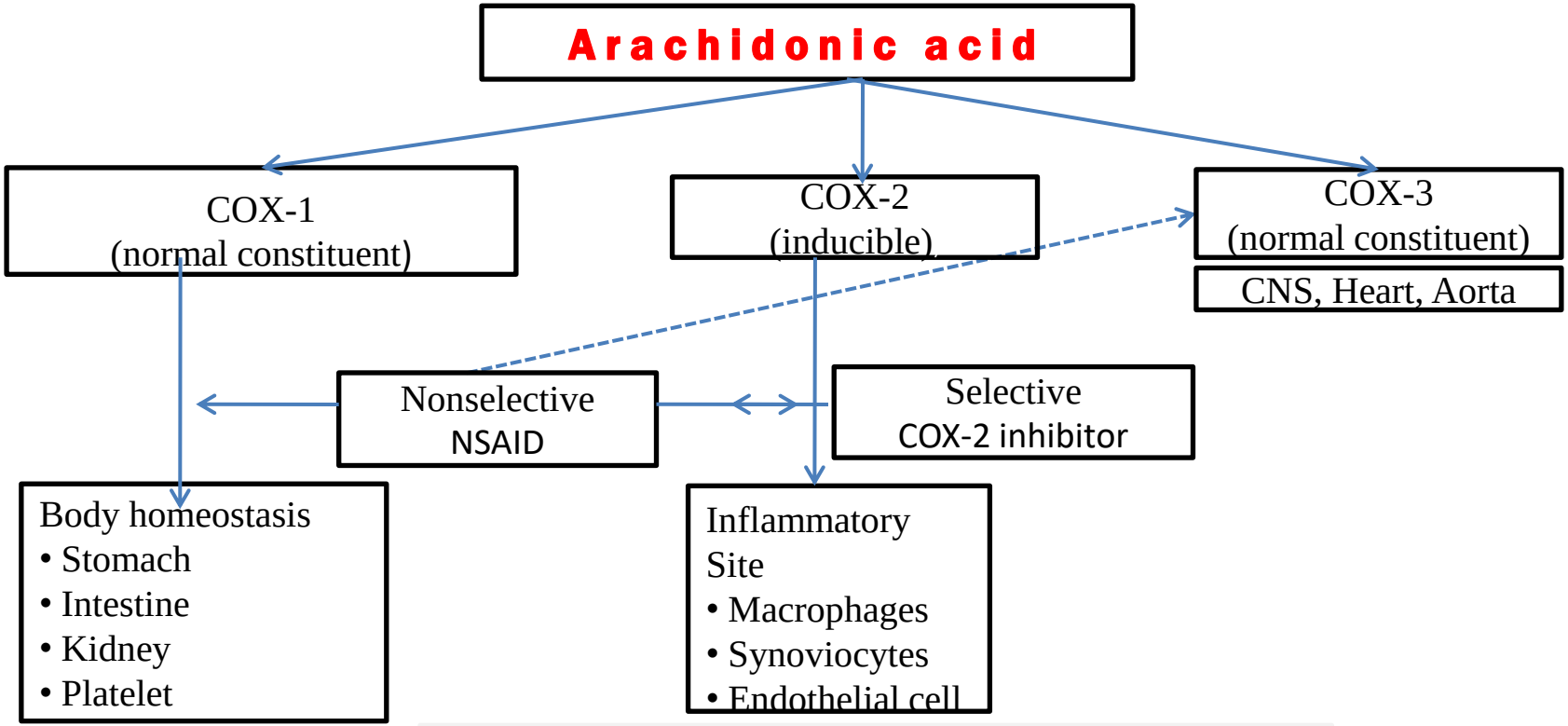
Preferential COX-2 inhibitors	Selective COX-2 inhibitors	Analgesic-antipyretics with poor Antiinflammatory action
Nimesulide, Diclofenac, Aceclofenac, Meloxicam, Etodolac	Celecoxib, Etoricoxib, Parecoxib.	1.Paraaminophenol derivative: Paracetamol(Acetaminophen). 2.Pyrazolone derivatives: Metamizol (Dipyrone), Propiphenazone. 3. Benzoxazocine derivative: Nefopam.

MOA

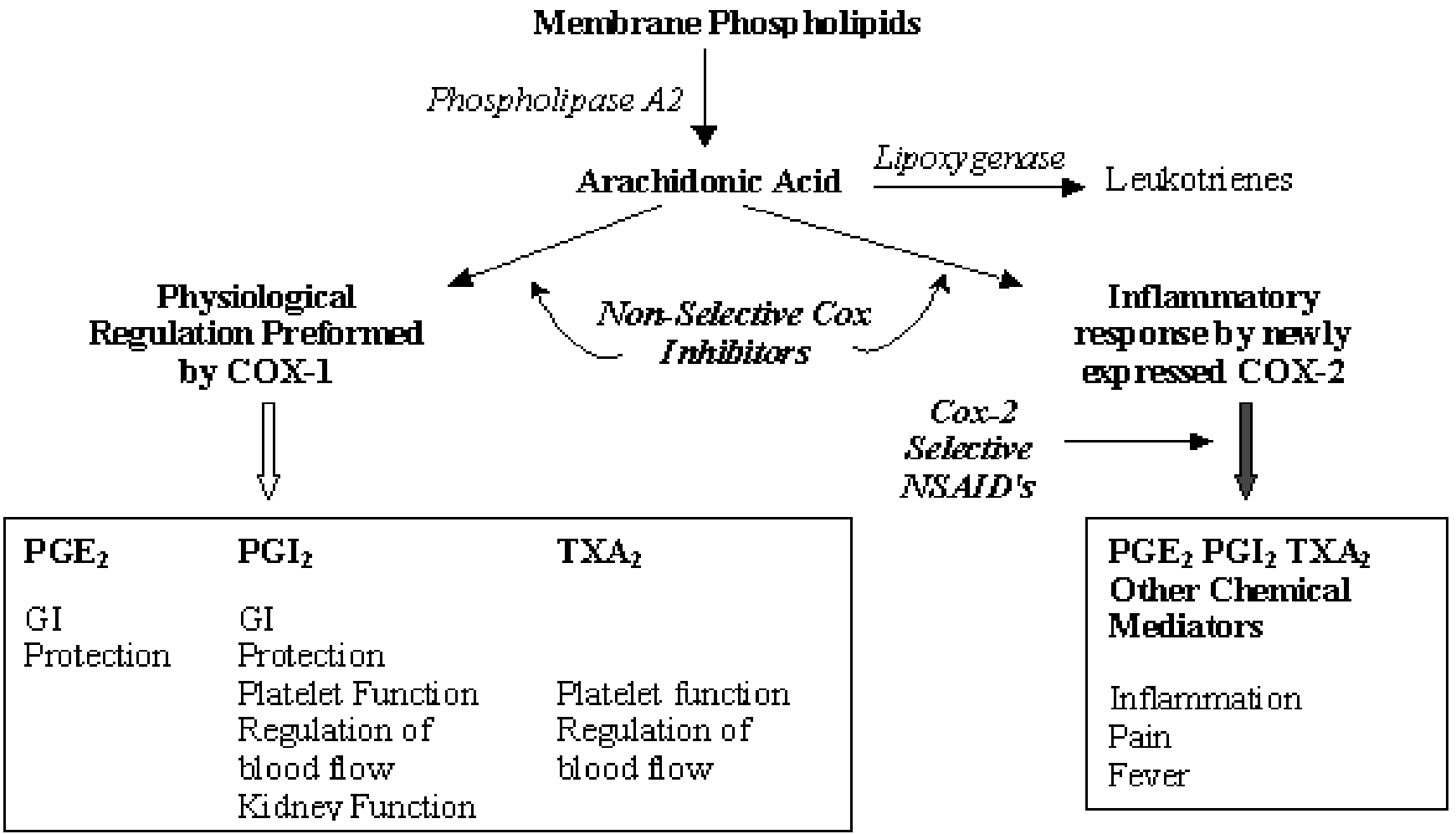
- MOA: These drugs block cyclo-oxygenase enzyme (COX-enzyme) either reversibly or irreversibly (Aspirin) causing inhibition of synthesis of PGs, prostacyclin (PGI_2) and thromboxane A_2 (TXA_2)
- Block of Cox-1 and Cox-2 are Non specific/Non-selective COX Inhibitors
- Blockers of COX-2 are called selective COX-2 Inhibitors or Coxibs.

Classification of NSAIDs based on selectivity of COX Inhibition:

- ***Non-selective COX Inhibitors (Conventional NSAIDs):***
  - ***Salicylates:*** Aspirin, Diflunisal.
  - ***Pyrazolone derivatives:*** Phenylbutazone, Oxyphenbutazone.
  - ***Indole derivatives:*** Indomethacin.
  - ***Propionic acid derivatives:*** Ibuprofen, Naproxen, Ketoprofen, Flurbiprofen.
  - ***Anthranilic acid derivatives:*** Mefenamic acid.
  - ***Aryl acetic acid derivatives:*** Diclofenac.
  - ***Oxicam derivatives:*** Piroxicam, Tenoxicam.
  - **Pyrrolo-pyrrole derivatives:** Ketorolac.
  - **Carboxylic acid derivatives:** Flunixin meglumine
- ***Preferential COX-2 Inhibitors:*** Nimesulide, Meloxicam, Nabumetone.
- ***Selective COX-2 Inhibitors:*** Celecoxib, Rofecoxib, Valdecoxib



Mechanism: COX-1, COX-2 & COX-3 inhibition


Membrane Phospholipids
Phospholipase A2
Arachidonic Acid
Lipoxygenase
Leukotrienes
Physiological Regulation Preformed by COX-1
Non-Selective Cox Inhibitors
Inflammatory response by newly expressed COX-2
Cox-2 Selective NSAID's
PGE2
GI Protection
PGI2
GI Protection
Platelet Function
Regulation of blood flow
Kidney Function
TXA2
Platelet function
Regulation of blood flow
PGE2 PGI2 TXA2 Other Chemical Mediators
Inflammation
Pain
Fever

Effects due to inhibition of PG synthesis

- Analgesia
- Antipyresis
- Anti-inflammatory
- Antithrombotic
- Closure of ductus arteriosus in newborn

Antipyresis

- Thermoregulatory Centre in Hypothalamus

- pathogenic microbial endotoxins cause release of pyrogen interleukin-I from macrophages, which stimulates the generation of prostaglandins (E series) in hypothalamus, resulting in pyrexia or lever.

- The NSAIDs exert antipyretic effect by irreversibly inhibiting the enzyme cyclo-oxygenase 1 or cyclo-oxygenase 2 or both

- COX-1 is a responsible for physiological synthesis of prostaglandins for tissue homeostasis (including protection on gastric mucosa; PGI_2 and PGE_2). Whereas, COX-2 is an inducible enzyme responsible for synthesis of prostaglandins which have a role in fever, pain and inflammation.

Anti inflammatory and analgesic effect

- The inflammatory stimuli in the inflammatory cells induce synthesis of prostaglandins through COX2.
- The NSAIDS exert anti-inflammatory effect by inhibition of prostaglandin synthesis by inhibition of this enzyme.
- The prostaglandins sensitize nociceptors to pain
- NSAIDs act by inhibiting prostaglandin synthesis through irreversible inactivation of COX-1 or COX-2 or both.

Antiplatelet aggregator

- TXA2 is pro-aggregator (COX-1)
- Most NSAIDs - effects on TXA2 predominates and inhibits aggregation – prolonged bleeding time
- Aspirin is highly active and acetylates COX in circulation – before hepatic 1st pass metabolism

Piroxicam

- anti-tumor medication used in dogs primarily to treat bladder transitional cell carcinoma
- as well as other cancers, such as squamous cell carcinoma, mammary adenocarcinoma, inflammatory mammary carcinoma, and transmissible venereal tumors
- It can also be used to treat degenerative joint disease

- DICLOFENAC: Renal failure occurs in vultures

- PARACETAMOL (ACETAMINOPHEN): Toxic to cats deficient in glucuronyl transferase and therefore have limited capacity to glucuronidate this drug
- causing Liver and kidney damage, cyanosis (due to conversion of Hb to methaemoglobin), haemolysis of R.B.C. due to formation of sulphaemoglobin leading to anaemia and jaundice.

- Antidote: N- **Acetylcysteine**

Relative Potency of NSAIDs

- **Antipyretic Effect:** Aspirin = Paracetamol > Phenacetin > Phenylbutazone
- **Analgesic Effect:** Aspirin > Phenacetin & Paracetamol > Phenylbutazone
- **Anti-inflammatory Effect:** Phenylbutazone > Aspirin

Uricosuric agents

- Increase the rate of excretion of uric acid
- Indomethacin
- PROBENECID: developed for the purpose of delaying the excretion of penicillin.
- SULFINPYRAZONE: developed from phenylbutazone, but lacks anti-inflammatory and analgesic activity, potent uricosuric effects.
- BENZBROMARONE: potent uricosuric agent, excreted primarily in bile

Other Drugs for Gout Rx: Colchine

- Allopurinol: Allopurinol inhibits xanthine oxidase and prevents the synthesis of urate from hypoxanthine and xanthine.

SIDE EFFECTS OF NSAIDS/ TOXICITY OF NSAIDS

- GASTROINTESTINAL TOXICITY/ HYPERACIDITY AND GASTRIC ULCERS: There is increased gastric acid secretion (blockade of PGI_2) and decreased secretion of mucus (blockade of PGE_2).
- misoprostol, a stable derivative of PGE_1, has been used in combination with diclofenac in man.
- Increased blood clothing time:- Reversibly or irreversibly inhibit the Tx synthetase enz & the syn. of thromboxane A_2 and delays platelet aggregation
- Delayed parturition

Drugs acting on Digestive System

- **Sialagogues (sialics):** increase flow of saliva

e.g. Gentian, Nuxvomica, Quassia, Ipecac (Bitters)

- **Antisialagogues (antisialics):** decrease the volume of salivary secretions.

- Antimuscarinic agents – atropine, hyoscine, glycopyrronium
- Atropine or glycopyrrolate are commonly used to reduce secretions as a premedicant during surgery to reduce salivary and bronchial secretions.

- **STOMACHICS:** increase the tone and function of stomach by increasing the gastric secretion and motility.

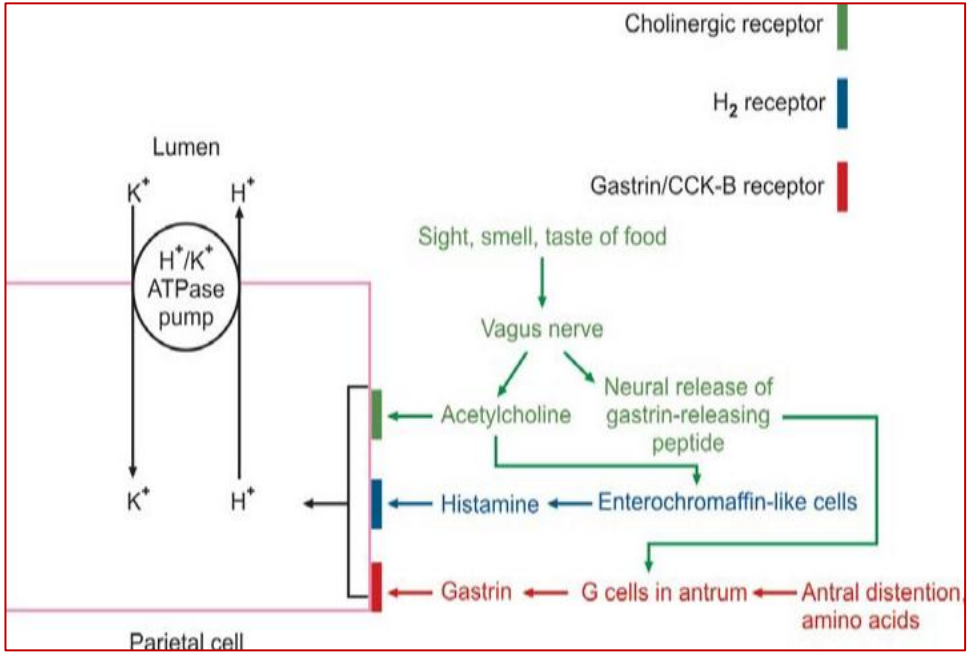
- Eg : Ginger, Nuxvomica.

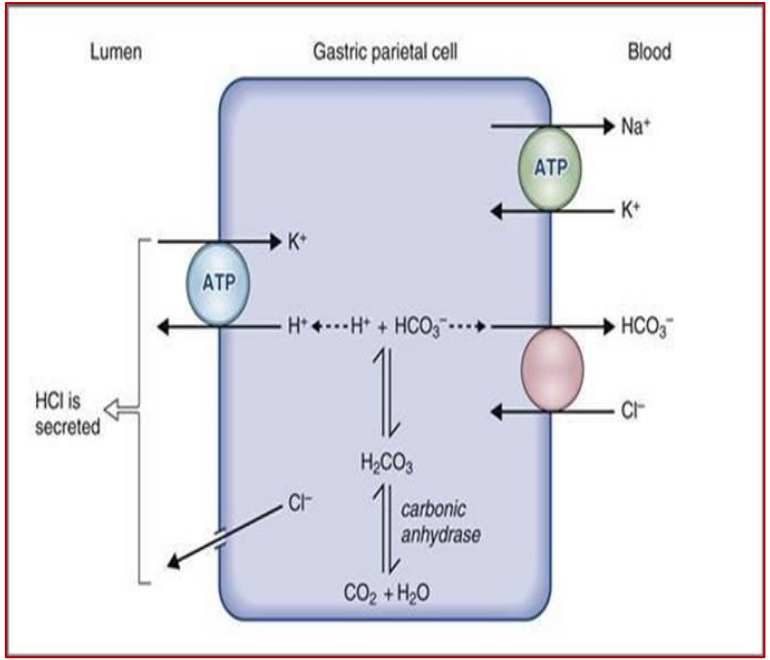
Gastric Acid

- Secreted by **Parietal Cells:** H^+-K^+-ATPase (the proton pump), which exchanges hydrogen and potassium ions across the parietal cell membrane.
- Naturally secreted by action of

- Acetylcholine through M3 receptors
- Histamine through H2 receptors
- Gastrin through CCK3 receptors

* Prostaglandins E_2 and I_2, directly inhibit gastric acid secretion by parietal cells. Mucus production is stimulated by PGs.


Cholinergic receptor
H2 receptor
Gastrin/CCK-B receptor
Lumen
K+
H+
H+/K+ ATPase pump
K+
H+
Sight, smell, taste of food
Vagus nerve
Acetylcholine
Neural release of gastrin-releasing peptide
Histamine
Enterochromaffin-like cells
Gastrin
G cells in antrum
Antral distention, amino acids
Parietal cell


Lumen
Gastric parietal cell
Blood
Na+
ATP
K+
K+
ATP
H+ ← H+ + HCO3− → HCO3−
HCl is secreted
Cl−
H2CO3
Cl−
carbonic anhydrase
CO2 + H2O

I Drugs stimulating gastric secretions

A) Gastrin analogues (PentaGastrin)

B) Histamine and analogues (Betazol)

C) Stomachics-cholinergic agents and bitters.

II Drugs inhibiting gastric secretions

A) H_2 – receptor antagonists

B) Proton-pump inhibitors

C) Muscarinic receptor antagonist

D) Prostaglandin analogues.

Drugs inhibiting gastric secretions

- Used in conditions like – hyperacidity, peptic ulcers, reflex oesophagitis, Zollinger-Ellision syndrome (gastrin producing tumors), abomasal ulceration in cattle
- H_2–receptor antagonists – Cimetidine, ranitidine, nizatidine, famotidine, zimatidine, roxatidine, loxatidine **(Famotidine – most potent)**
- Proton pump inhibitors: Omeprazole, lansoprazol, pantoprazol, rabeprazole
- Muscarinic receptor antagonists:

i) Non selective inhibitors: Atropine, glycopyrronium

ii) Selective M_1 muscarinic receptor antagonists *pirenzepine* and *telenzepine*

iii) Selective M_3 muscarinic receptor antagonists: Darifenacin

- Prostaglandin analogues:
- i) PGE_2 and I_2 act as cytoprotective agents by enhancing production of mucus.
- ii) Misoprostol (Methyl ester analogue of PGE_1) generally indicated alongwith NSAIDS

Antacids

- Neutralizes preformed HCl in stomach

1. Fast acting antacids/systemic antacids – sodium bicarbonate. Onset of action fast and can be absorbed systemically.

2. Modest to slow acting antacids/Non-systemic antacids: - Salts of Aluminum, magnesium and calcium

- Aluminum hydroxide, Alum. hydrate , Mag. Hydroxide, Magnesium trisilicate, Magnesium and Calcium carbonate

* Cytoprotective agents:

- Sucralfate –polymerises to a viscous, sticky substance which protects the ulcerated site

- Colloidal bismuth subcitrate: Effective against *Helicobacter pylori*

Prokinetics - increase motility of a segment of the GIT

- D_2-dopamine receptor antagonists: Metoclopramide, domperidone.
- 5-HT_4-receptor agonists: Cisapride, tegaserod, prucalopride.
- Motilin like drugs e.g. erythromycin.
- Histamine (H_2) receptor antagonist: Ranitidine, nizatidine.
- Prostanoids – Misoprostol
- Lidocaine – In horses
- Miscellaneous agents – Mosapride, alvimopan, methylnaltrexone.

* **Metoclopramide: Prokinetic + Antiemetic**

Laxatives and Purgatives

- Laxatives (Aperients): Drugs which promote elimination of soft-formed stool from rectum
- Purgatives (Cathartics): Are stronger in action and tend to produce the evacuation of unformed, usually watery fecal material from the entire colon
- All purgatives can work as laxatives in smaller doses but all laxatives cannot work as purgatives in higher doses like liquid paraffin

Classification

1. Lubricant laxatives: liquid parrafin, glycerol
2. Surfactant Laxatives (Stool softeners): Docusates, Poloxamers, bile acids
3. Bulk forming laxatives: carboxymethyl cellulose, wheat bran and ispaghula husk
4. Hyperosmotic purgatives :-

a. Saline Osmotic purgatives: Sodium sulfate, Magnesium oxide, Magnesium Sulfate

b. Carbohydrate osmolic purgatives : Lactulose, Lacitol, Sorbitol, Polyethylene glycol (PEG) & Mannitol

- Lactulose : Syn. derivative of lactose

5. Irritant purgatives:

(a) Direct irritant purgatives :- Mercury compounds, Phenolphthalein and Vegetable oils, **Bisacodyl**

(b) Indirect irritant purgatives :- Aloes, Senna, Cascara, Rhubarb, Danthrone **(Anthraquinone),** Castor oil, linseed oil

(c) Drastic irritant purgatives :- Jalap, podophyllum, corotonil, barium chloride and colocynth

6. Neuromuscular purgatives: Pilocarpine, Arecholine, Physostigmine

7. Enema: Soapy water, Sod. citrate, sorbitol, glycerin, hypertonic Nacl, Minerals and vegetable oils

Antidiarroheals

GI mucosa protectactants – Kaolin, Pectin, Activated charcoal & Bismuth subsalicylate

GI motility inhibitors –

* Anticholinergic – Propantheline, Aminopentamide

*Opiates – Atropine, Hyoscine, Diphenoxylate, Loperamide

* α_2-agonists - clonidine reduces GIT muscle tone and secretions.

* Calcium - calmodulin Antagonists: e.g. CPZ, trifluperazine, octreotide

* Specific chemotherapeutic agents

Emetics

- Vomition is usually considered a protective reflex that occurs in certain species like cat, dogs but not in horses, ruminants, rodents, Guinea pigs and rabbits.
- **The chemoreceptor trigger zone- The chemoreceptor trigger zone** is a bilateral set of centers in the brainstem lying under the floor of the fourth ventricle (Medulla oblongata)
- Neurotransmitters in vomition: dopamine (D_2), histamine (H_1), serotonin (5-HT_3), acetylcholine (M_1), substance P/ neurokinin (NK-1) receptors.
- Dopamine receptor mediated vomition is more stronger in dogs
- Alpha-2 adrenergic mediated vomition is more stronger in cats

Emetics

- Emetics are administered in animals capable of vomiting e.g. Dogs & Cats. Not employed in horses and cattle.
- **Classification:**

Reflex emetics/ Irritant emetics : These agents cause vomition by irritating the epithelium of pharynx, oesophagus, stomach & duodenum and reflexly stimulate the emetic centre.

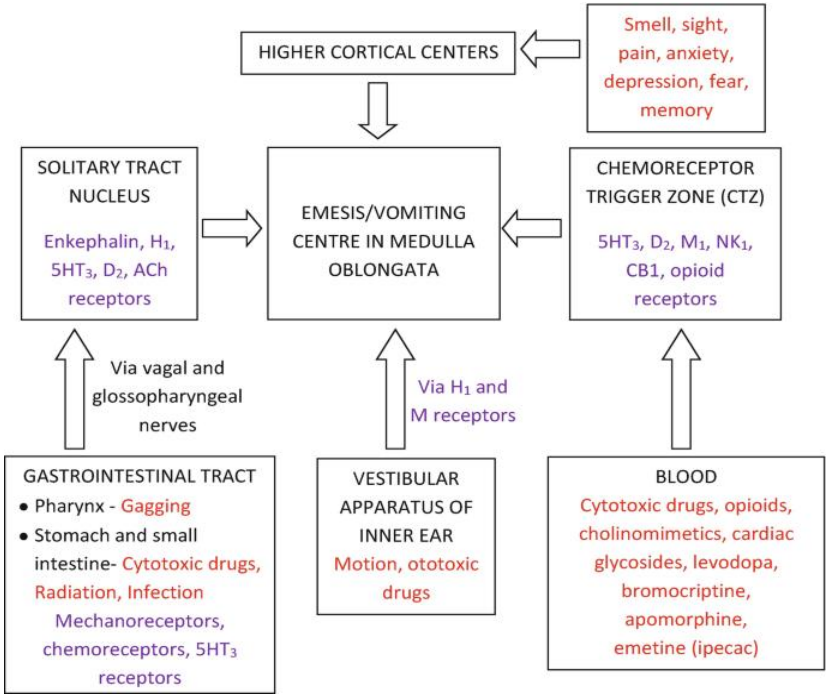
Eg : sodium chloride, sodium carbonate, Hydrogen peroxide etc.

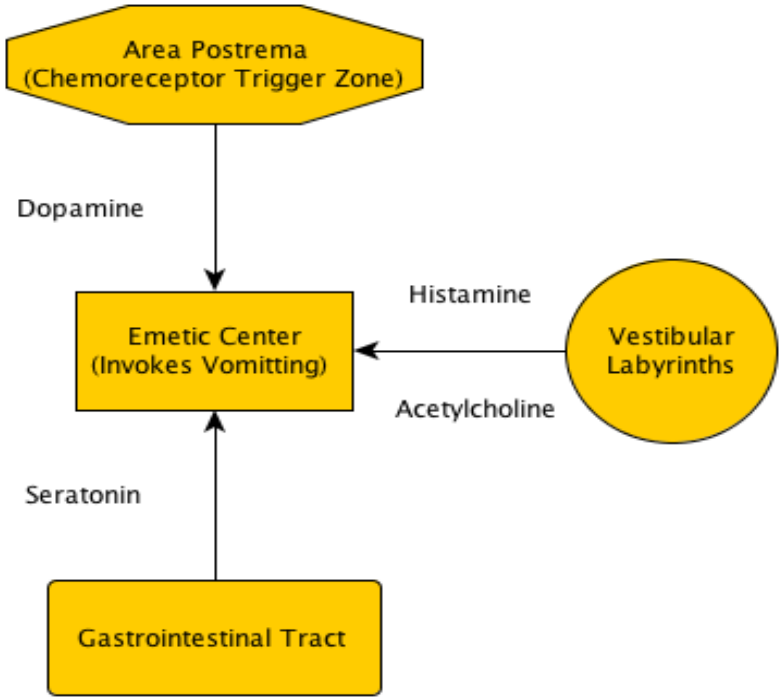
Central emetics : These agent cause vomition by stimulating the medullary emetic centre directly or through CTZ

Eg - Apomorphine hydrochloride

Xylazine

Vomiting reflex





Anti Emetics

- **Locally acting Antiemetics:**

1. Demulcents & protectants: kaolin, pectin, bismuth salts

2. Gastric antacids and Local Anaesthetics: Mag. hydroxide, Aluminium hydroxide, Benzocaine

3. Anticholinergics: Glycopyrronium, Scopolamine, propantheline, Atropine

4. Prokinetics: Domperidone, Cisapride, Metaclopramide

- H_1 receptor antagonists, e.g. diphenhydramine, dimenhydrinate, promethazine, meclizine
- D_2-dopamine receptor antagonists, e.g. Droperidol, Haloperidol, *Prochlorperazine*
- 5-HT_3 – receptor antagonists: Ondansetron, Granisetron

- Used in antineoplastic therapy to control vomition

- Muscarinic receptor antagonists: Atropine, Hyoscine/Scopolamine
- NeuroKinin-1 (NK-1) receptor antagonists: Maropitant

*Motion sickness: H1 antagonist like promethazine, meclizine

Carminatives

- Carminatives are the agents which helps in the expulsion of gas from stomach, they have effect of mild irritation with vasodilation and relaxation of oesophageal sphincter and therefore assist in eructation process.

- Eg : Turpentine oil, ginger powder, anise, *Asafoetida* etc.

Antizymotics

- Antizymotics are the drugs which prevents or decreases excess microbial fermentation in rumen or intestine, used in bloat, tympanitic colic in horse or cattle.
- Turpentine oil, linseed oil , Formalin – suppress fermentation

- **ANTIFOAMING AGENTS**: These agents are usually surfactant, which decrease the stability of foam in rumen and release trapped gas.
- Agents

i.) Organic silicones – i) Polymerised Methyl Silicones e.g. Dimethyl polysilicone, Dimethicone, simethicone.

ii) Poloxalone: Allow escape of gas from foam by dispersing foam.

CHOLAGOGUE: Substances that cause contraction of the gall bladder and increase the bile flow into the duodenum

- Concentrated Magnesium sulphate, Ceruletide

- **Cholerectics:** Agents that stimulate the liver to increase the output of bile

Ursodeoxycholic acid, Chenodeoxycholic acid , Natural bile salts like Glycocholate, Taurocholate

- **Oesophageal groove closures**: muscles of oesophageal groove contracts and forms a complete tube from the cardia to the omasal canal allowing ingested fluid to pass directly from oesophagus to abomasum bypassing the rumen, reticulum and omasum.
- Sodium bicarbonate, $CuSO_4$, $ZnSO_4$

- **Ruminotorics**- stimulate rumino-reticular contractions and cause improvement in general functioning of rumen
- Neostigmine, nuxvomica, Metoclopramide

Drugs acting on Digestive System

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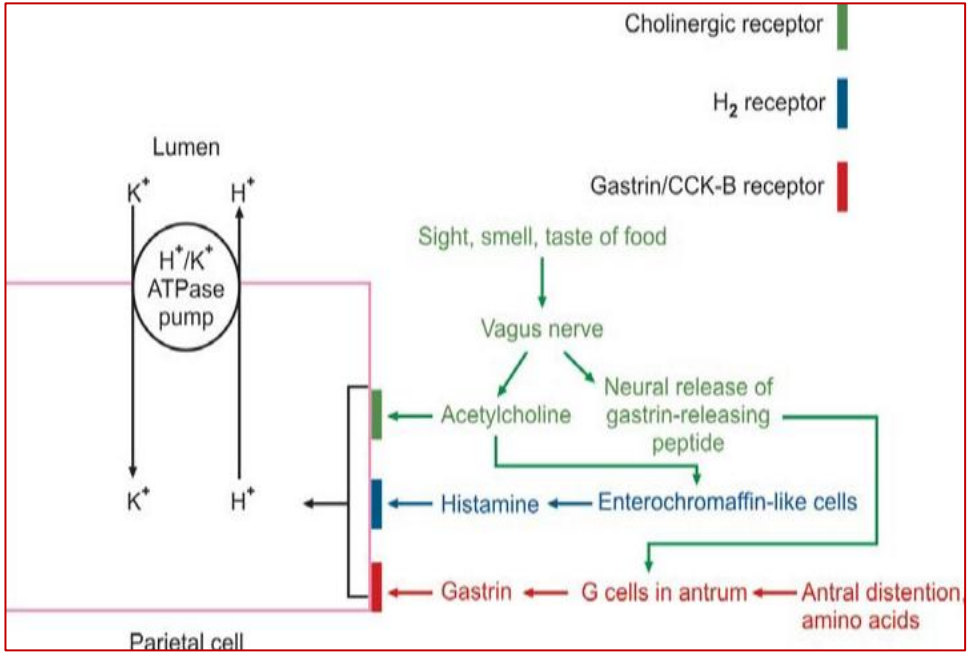
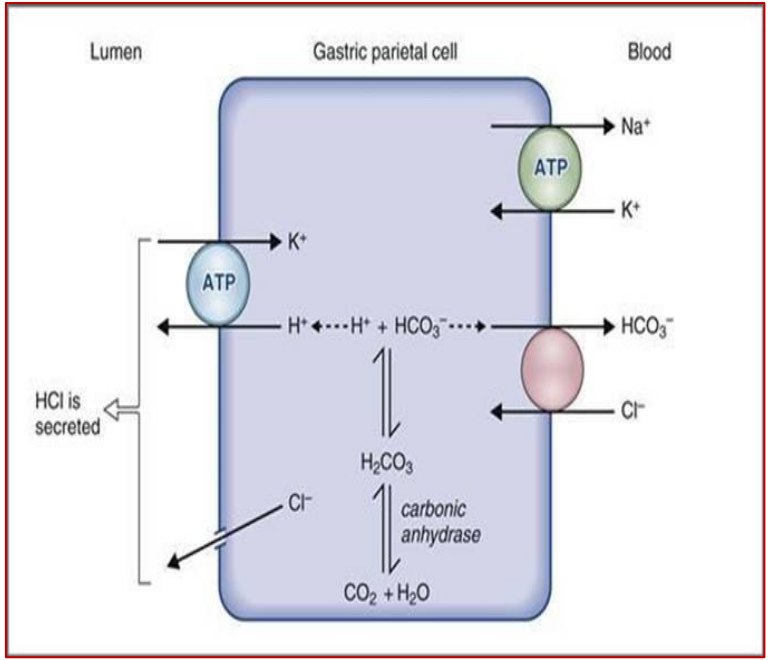
* Prostaglandins E_2 and I_2, directly inhibit gastric acid secretion by parietal cells. Mucus production is stimulated by PGs.


Cholinergic receptor
H2 receptor
Gastrin/CCK-B receptor
Lumen
K+
H+
H+/K+ ATPase pump
K+
H+
Sight, smell, taste of food
Vagus nerve
Acetylcholine
Neural release of gastrin-releasing peptide
Histamine
Enterochromaffin-like cells
Gastrin
G cells in antrum
Antral distention, amino acids
Parietal cell


Lumen
Gastric parietal cell
Blood
Na+
ATP
K+
K+
ATP
H+ ← H+ + HCO3− → HCO3−
HCl is secreted
Cl−
H2CO3
Cl−
carbonic anhydrase
CO2 + H2O

I Drugs stimulating gastric secretions

A) Gastrin analogues (PentaGastrin)

B) Histamine and analogues (Betazol)

C) Stomachics-cholinergic agents and bitters.

II Drugs inhibiting gastric secretions

A) H_2 – receptor antagonists

B) Proton-pump inhibitors

C) Muscarinic receptor antagonist

D) Prostaglandin analogues.

Drugs inhibiting gastric secretions

- Used in conditions like – hyperacidity, peptic ulcers, reflex oesophagitis, Zollinger-Ellision syndrome (gastrin producing tumors), abomasal ulceration in cattle
- H_2–receptor antagonists – Cimetidine, ranitidine, nizatidine, famotidine, zimatidine, roxatidine, loxatidine **(Famotidine – most potent)**
- Proton pump inhibitors: Omeprazole, lansoprazol, pantoprazol, rabeprazole
- Muscarinic receptor antagonists:

i) Non selective inhibitors: Atropine, glycopyrronium

ii) Selective M_1 muscarinic receptor antagonists *pirenzepine* and *telenzepine*

iii) Selective M_3 muscarinic receptor antagonists: Darifenacin

- Prostaglandin analogues:
- i) PGE_2 and I_2 act as cytoprotective agents by enhancing production of mucus.
- ii) Misoprostol (Methyl ester analogue of PGE_1) generally indicated alongwith NSAIDS

Antacids

- Neutralizes preformed HCl in stomach

1. Fast acting antacids/systemic antacids – sodium bicarbonate. Onset of action fast and can be absorbed systemically.

2. Modest to slow acting antacids/Non-systemic antacids: - Salts of Aluminum, magnesium and calcium

- Aluminum hydroxide, Alum. hydrate , Mag. Hydroxide, Magnesium trisilicate, Magnesium and Calcium carbonate

* Cytoprotective agents:

- Sucralfate –polymerises to a viscous, sticky substance which protects the ulcerated site

- Colloidal bismuth subcitrate: Effective against *Helicobacter pylori*

Prokinetics - increase motility of a segment of the GIT

- D_2-dopamine receptor antagonists: Metoclopramide, domperidone.
- 5-HT_4-receptor agonists: Cisapride, tegaserod, prucalopride.
- Motilin like drugs e.g. erythromycin.
- Histamine (H_2) receptor antagonist: Ranitidine, nizatidine.
- Prostanoids – Misoprostol
- Lidocaine – In horses
- Miscellaneous agents – Mosapride, alvimopan, methylnaltrexone.

* **Metoclopramide: Prokinetic + Antiemetic**

Laxatives and Purgatives

- Laxatives (Aperients): Drugs which promote elimination of soft-formed stool from rectum
- Purgatives (Cathartics): Are stronger in action and tend to produce the evacuation of unformed, usually watery fecal material from the entire colon
- All purgatives can work as laxatives in smaller doses but all laxatives cannot work as purgatives in higher doses like liquid paraffin

Classification

1. Lubricant laxatives: liquid parrafin, glycerol
2. Surfactant Laxatives (Stool softeners): Docusates, Poloxamers, bile acids
3. Bulk forming laxatives: carboxymethyl cellulose, wheat bran and ispaghula husk
4. Hyperosmotic purgatives :-

a. Saline Osmotic purgatives: Sodium sulfate, Magnesium oxide, Magnesium Sulfate

b. Carbohydrate osmolic purgatives : Lactulose, Lacitol, Sorbitol, Polyethylene glycol (PEG) & Mannitol

- Lactulose : Syn. derivative of lactose

5. Irritant purgatives:

(a) Direct irritant purgatives :- Mercury compounds, Phenolphthalein and Vegetable oils, **Bisacodyl**

(b) Indirect irritant purgatives :- Aloes, Senna, Cascara, Rhubarb, Danthrone **(Anthraquinone),** Castor oil, linseed oil

(c) Drastic irritant purgatives :- Jalap, podophyllum, corotonil, barium chloride and colocynth

6. Neuromuscular purgatives: Pilocarpine, Arecholine, Physostigmine

7. Enema: Soapy water, Sod. citrate, sorbitol, glycerin, hypertonic Nacl, Minerals and vegetable oils

Antidiarroheals

GI mucosa protectactants – Kaolin, Pectin, Activated charcoal & Bismuth subsalicylate

GI motility inhibitors –

* Anticholinergic – Propantheline, Aminopentamide

*Opiates – Atropine, Hyoscine, Diphenoxylate, Loperamide

* α_2-agonists - clonidine reduces GIT muscle tone and secretions.

* Calcium - calmodulin Antagonists: e.g. CPZ, trifluperazine, octreotide

* Specific chemotherapeutic agents

Emetics

- Vomition is usually considered a protective reflex that occurs in certain species like cat, dogs but not in horses, ruminants, rodents, Guinea pigs and rabbits.
- **The chemoreceptor trigger zone- The chemoreceptor trigger zone** is a bilateral set of centers in the brainstem lying under the floor of the fourth ventricle (Medulla oblongata)
- Neurotransmitters in vomition: dopamine (D_2), histamine (H_1), serotonin (5-HT_3), acetylcholine (M_1), substance P/ neurokinin (NK-1) receptors.
- Dopamine receptor mediated vomition is more stronger in dogs
- Alpha-2 adrenergic mediated vomition is more stronger in cats

Emetics

- Emetics are administered in animals capable of vomiting e.g. Dogs & Cats. Not employed in horses and cattle.
- **Classification:**

Reflex emetics/ Irritant emetics : These agents cause vomition by irritating the epithelium of pharynx, oesophagus, stomach & duodenum and reflexly stimulate the emetic centre.

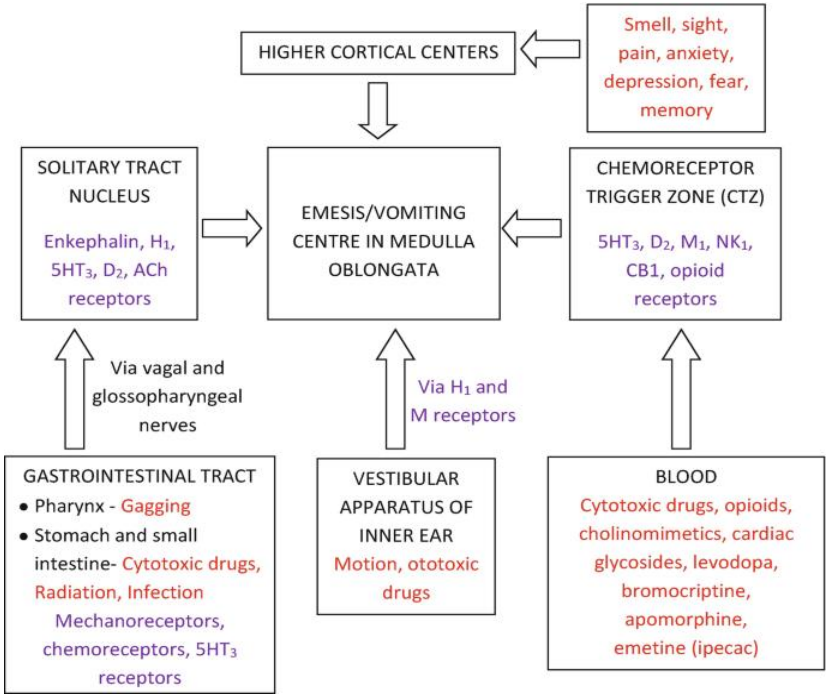
Eg : sodium chloride, sodium carbonate, Hydrogen peroxide etc.

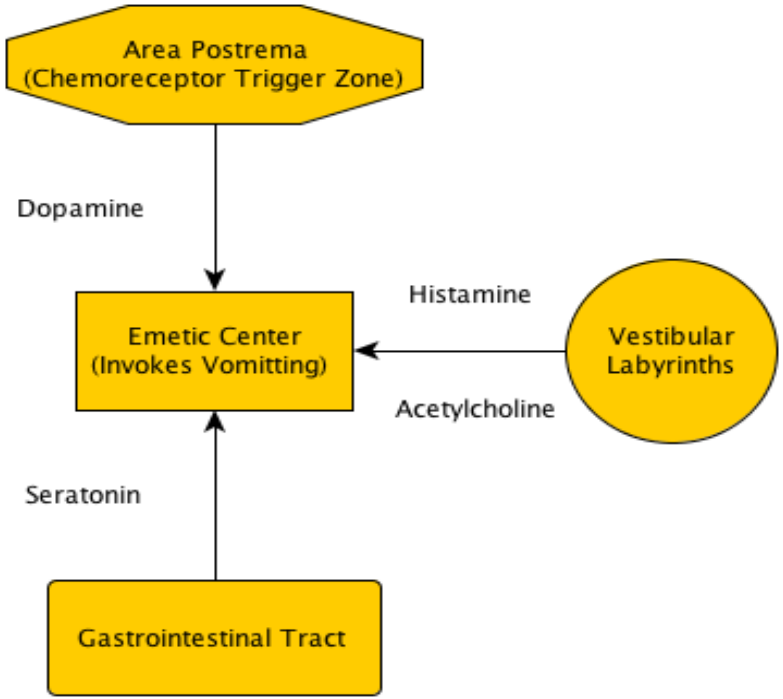
Central emetics : These agent cause vomition by stimulating the medullary emetic centre directly or through CTZ

Eg - Apomorphine hydrochloride

Xylazine

Vomiting reflex





Anti Emetics

- **Locally acting Antiemetics:**

1. Demulcents & protectants: kaolin, pectin, bismuth salts

2. Gastric antacids and Local Anaesthetics: Mag. hydroxide, Aluminium hydroxide, Benzocaine

3. Anticholinergics: Glycopyrronium, Scopolamine, propantheline, Atropine

4. Prokinetics: Domperidone, Cisapride, Metaclopramide

- H_1 receptor antagonists, e.g. diphenhydramine, dimenhydrinate, promethazine, meclizine
- D_2-dopamine receptor antagonists, e.g. Droperidol, Haloperidol, *Prochlorperazine*
- 5-HT_3 – receptor antagonists: Ondansetron, Granisetron

- Used in antineoplastic therapy to control vomition

- Muscarinic receptor antagonists: Atropine, Hyoscine/Scopolamine
- NeuroKinin-1 (NK-1) receptor antagonists: Maropitant

*Motion sickness: H1 antagonist like promethazine, meclizine

Carminatives

- Carminatives are the agents which helps in the expulsion of gas from stomach, they have effect of mild irritation with vasodilation and relaxation of oesophageal sphincter and therefore assist in eructation process.

- Eg : Turpentine oil, ginger powder, anise, *Asafoetida* etc.

Antizymotics

- Antizymotics are the drugs which prevents or decreases excess microbial fermentation in rumen or intestine, used in bloat, tympanitic colic in horse or cattle.
- Turpentine oil, linseed oil , Formalin – suppress fermentation

- **ANTIFOAMING AGENTS**: These agents are usually surfactant, which decrease the stability of foam in rumen and release trapped gas.
- Agents

i.) Organic silicones – i) Polymerised Methyl Silicones e.g. Dimethyl polysilicone, Dimethicone, simethicone.

ii) Poloxalone: Allow escape of gas from foam by dispersing foam.

CHOLAGOGUE: Substances that cause contraction of the gall bladder and increase the bile flow into the duodenum

- Concentrated Magnesium sulphate, Ceruletide

- **Cholerectics:** Agents that stimulate the liver to increase the output of bile

Ursodeoxycholic acid, Chenodeoxycholic acid , Natural bile salts like Glycocholate, Taurocholate

- **Oesophageal groove closures**: muscles of oesophageal groove contracts and forms a complete tube from the cardia to the omasal canal allowing ingested fluid to pass directly from oesophagus to abomasum bypassing the rumen, reticulum and omasum.
- Sodium bicarbonate, $CuSO_4$, $ZnSO_4$

- **Ruminotorics**- stimulate rumino-reticular contractions and cause improvement in general functioning of rumen
- Neostigmine, nuxvomica, Metoclopramide

DRUGS ACTING ON RESPIRATORY SYSTEM

I Cough sedatives/Cough Depressants/Antitussives

i) Peripherally acting/Locally acting

- A. Demulcents
- B. Expectorants
  - a) Direct /local expectorants
  - b) Reflex expectorants
  - c) Mixed action expectorants
- C. Mucolytics
- D. Bronchodilators and anti-inflammatory agents
  - a) β-receptor agonists
  - b) Muscarinic receptor antagonist
- c) Mast cell stabilizers
  - d) Miscellaneous agents
- E. Mucosal anaesthetic

ii) Centrally acting antitussives

-Narcotics

-Non narcotics

II. Respiratory stimulants

-Local Irritants

-Analeptics

-Natural/Physiological stimulants

III. Mucokinetics

-Drugs improving ciliary activity

-Drugs improving mobility of bronchial secretions (Mucolytics)

IV. Decongestants

Antitussive

- Antitussive are drugs that suppress coughing, by reducing activity of cough center in brain (Medulla oblongata)

- Anti tussives are indicated when coughing is painful, exhaustive & distressing and unproductive

- These are of 2 types :

1. Peripherally acting
2. Centrally acting

1. **Peripherally acting –** It depress tracheal & bronchial afferent sensory nerves and pulmonary stretch receptors, thus prevents activation of medullary cough center.

•**Demulcents:** coat, protect and soothe the m.m. of respiratory tract. e.g. gum acacia, licorice, glycerin, honey

Expectorants

- Drugs which increases fluidity & volume of bronchial secretions
- Helps in easy expulsion through coughing
- Also helps in promoting pulmonary drainage during inflammation

❑ there are 4 types –

1. Inhalation Expectorants
2. Sedative Expectorants
3. Stimulant Expectorants
4. Anodyne Expectorants

1. **Inhalation Expectorants** – Increase bronchial secretion by local action.
   Eg.- Steam, terebene, eucalyptus oil, turpentine oil, benzoin
2. **Sedative Expectorants** – stimulate mucus secretion in bronchi, protects & reduce acute inflammation in Respiratory passage.

a. Saline Expectorants – increase mucus from GIT (Route oral, small amount excreted by mucosal cells of respiratory tract)

Eg. Ammonium Chloride, Potassium Iodide

b. Nauseant Expectorants – increase respiratory secretions by nausea, Eg. Ipecac

Stimulant & Anodyne Expectorants

3. Stimulant Expectorants – stimulate & promote repair of chronic inflammatory process.

Eg. Guaiacol, **Guaifensin**, Eucalyptus Oil, Turpentine Oil

4. Anodyne Expectorants – Extensively increase respiratory secretion through GIT.

Eg. Camphorated tincture of opium(Paregoric).

Bronchodilators & Anti inflammatory

- Drugs that relax Bronchial smooth muscles, dilate respiratory passage & relive bronchial spasm.
- Classification based on mode of action –

A. β2-adrenoceptor agonists — salbutamol, terbutaline, clenbuterol.

B. Xanthines/Methylxanthines – Direct relaxant action on bronchial smooth muscles – caffeine, aminophylline & theophylline.

C. Anticholinergic – act by blocking cholinergic muscarinic receptors – Ipratropium, Atropine, glycopyrolate

Mast cell stabilizers

D. **Antihistamines (H1 Antagonists) –**

– Promethazine, Diphenhydramine.

E. **Cromolyn/ Cromoglicate** – inhibit histamine & leukoriene release

F. **Cysteinyl-Leukotriene Receptor antagonists** – act by preventing Leukotriene induced bronchoconstriction – Zafirlukast, Monteleucast

G. **Anti-inflammatory agents** – Act by reducing formation of cytokines, Eg. – Prednisolone, NSAIDs

*** Mucosal Anaesthetics -** BENZONATATE

2. Centrally acting –

Suppress cough by direct depression of medullary cough center.

Examples-

Narcotic: Codeine, hydrocodone, Morphine

Non Narcotic: Pholcodeine , Dextromethorphan, Butorphanol, Noscapine, levopropoxyphene

Respiratory Stimulant (Analeptics)

- Drugs which cause stimulation of depressed respiration

a. **Doxapram** – drug of choice in emergency cases, act by stimulation of respiration.

b. **Nikethamide** – First respiratory stimulant.

c. **Picrotoxin, Bemegride, Leptazol**

d. **Methyl Xanthines** – Caffeine, Aminophylline

e. **Natural or physiological stimulants** : carbogen (O_2 95% + CO_2 5%), (O2 40-60% CO2)

Ammmonia gas – local irritant

Mucolytics/ Mucokinetics

These are the drugs which loosen or break viscous or inspissated pulmonary secretion to facilitate expectorations.

Eg- Bromhexine

Acetylcysteine

Ambroxol

Decongestants

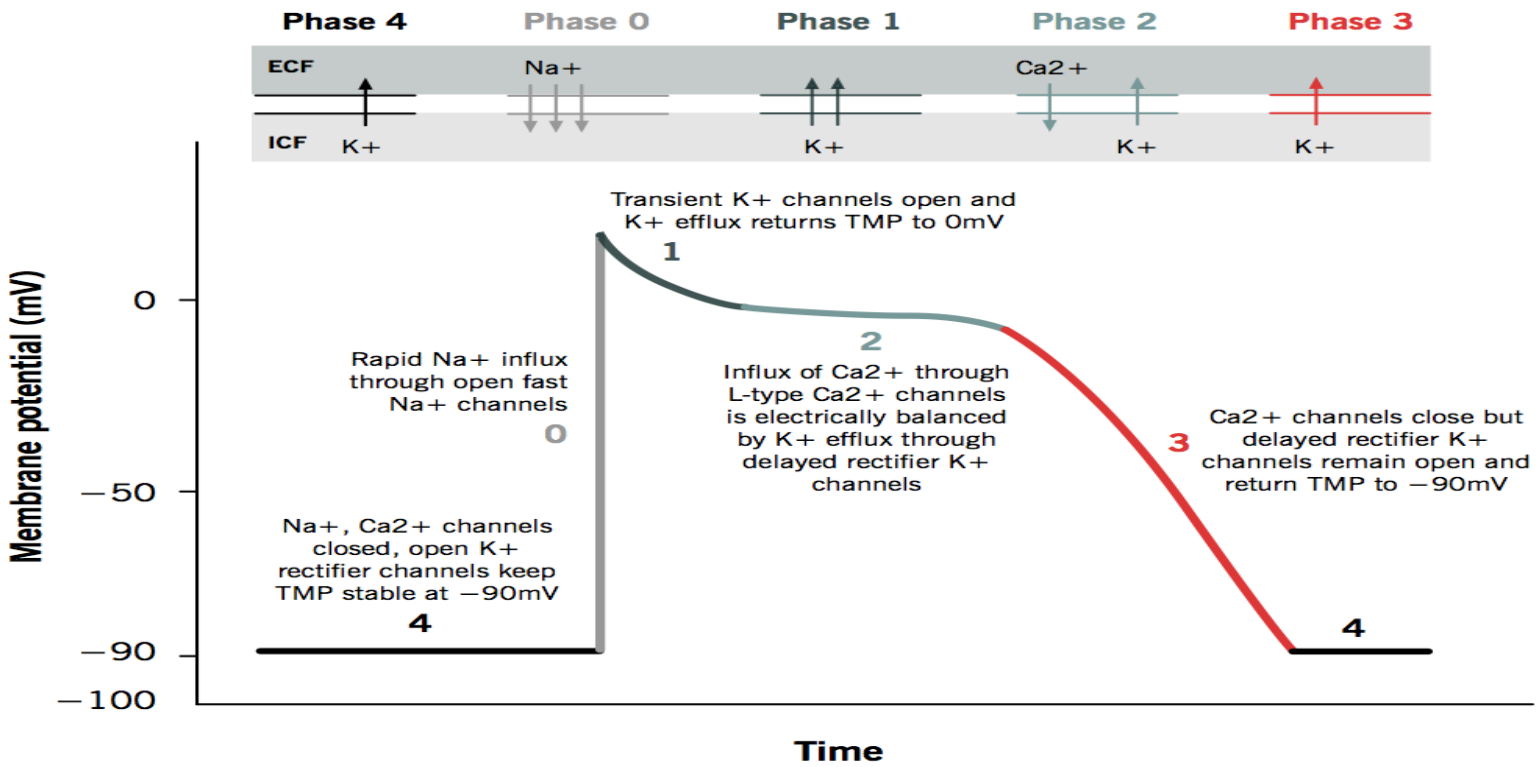
- Used in sinusitis (allergic or viral).
- Histamine receptor (H_1) antagonists e.g. *dimenhydrinate*, *diphenhydramine*, *chlorpheniramine*, *hydroxyzine*, Cetrizine
- Sympathomimetic drugs: α-adrenergic agonists e.g. *ephedrine*, *pseudoephedrine*, *phenylephrine*, *oxymetazoline*, *tramazoline*, *xylometazoline*.
- H_1-antagonists are generally given by oral route while α-adrnergic agonists are preferred by topical route to avoid systemic effects associated with oral therapy.

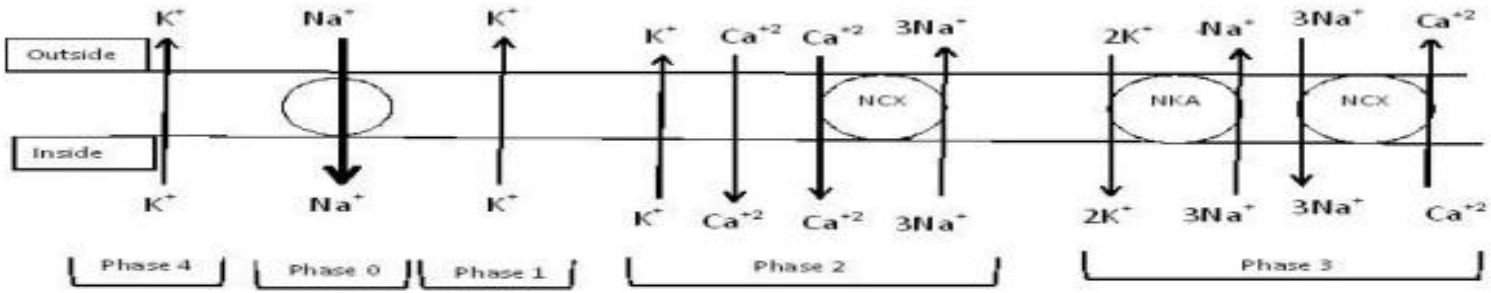
DRUGS ACTING ON CARDIO VASCULAR SYSTEM

* Cardiac glycosides
* Antiarrhythmic drugs
* Vasodilators
* Haematinics
* Anticoagulants
* Antihypertensive agents
* Coagulant

Action potential of cardiac muscles

Grigoriy Ikonnikov and Eric Wong





Working cardiac muscle cell potential.

NCX- Sodium calcium exchanger, NKA-sodium potassium ATPase

Myocardial stimulants

- positive inotropic drugs mainly used in condition likes Congestive heart failure
- **Classification**

1. Cardiac glycosides – Diagoxin, Digitoxin and Ouabain
2. Phosphodiestrase inhibitors:-

(i) Methylxanthines – aminophylline, theophylline
(ii) Bipyridine derivatives – amrinone and milrinone.
(iii) Pyridazone derivatives - pimobendan

3. Beta – receptor agonists : Epinephrine, isoprenaline, dobutamine, dopamine.
4. Miscellaneous agents:- Calcium & Glucagon

- inotropic (affect contractility)
- chronotropic (affect heart rate)
- dromotropic (affect rate of conduction through AV node)
- Bathmotropic if it affects the excitability
- Tonotropic if it affects the tonicity.

CARDIAC GLYCOSIDES

* obtained from plant *Digitalis purpurea*

- combination of a sugar portion and aglycone (genin)
- aglycone (genin) - pharmacologically active portion of the glycosides
- Sugar - affect its potency and duration of action

Cardiac glycosides are of plant origin :

Source	Part	Glycosides
Digitalis lanata	Leaves	Digitoxin,Gitoxin & Digoxin
Digitalis purpurea	Leaves	Digitoxin,Gitoxin & Gitalin
Strophanthus gratus	Seed	Strophanthin G (Ouabain)
Strophanthus kombe	Seed	Strophanthin K
Urgenia maritima	Bulb	Proscillaridin A
Bufo vulgaris	Toad skin	Bufotoxin

Mechanism of Action

- block membrane associated Na^{+}-K^{+} ATPase pump
- results in progressive accumulation of Na^{+} intracellularly
- This favours the exchange of Na^{+} with Ca^{+2} through Na^{+}-Ca^{+2} exchange mechanism.
- This causes intracellular calcium levels to raise that in turn leads to increased release of Ca^{+2} from the sarcoplasmic reticulum and hence increased contractility of cardiac muscle.
- Cardiac glycosides have the positive ionotropic effect on heart. They increase the force of contraction of myocardium & Decrease in heart rate (-ve Chronotropic effect due to vagal stimulation & slowing rate of conduction)
- Its main action in congestive heart failure

Cardiac glycosides

- a positive inotropic effect (an increase in the force of systole, an increase in the myocardial tone)
- a negative chronotropic effect (the prolongation of diastole, slowing of heart rate)
- a negative dromotropic effect (deceleration of conductivity)
- a positive bathmotropic effect (an increase in myocardium excitation)

Digitalisation

- **Digitalisation-** It is a basic procedure followed to quickly achieve the desired therapeutic effect by administering digitals initially in several divided doses over a relatively short period of time (24-48 hours).
- The dose required for this purpose is called as loading lose or digitalization dose. The dose needed daily to maintain the effect is called as maintenance dose.
- Oubain is the most potent therefore used in emergency therapy

Digitalisation

- Loading dose in dogs
- Slow method- 5 equal parts for 48hrs
- Rapid method- 3 equal parts @ 6hr interval.
- Intensive method- half dose initially, one fourth after 6hrs and one eighth each after 4 hr intervals
- Digitoxin- 0.11 – 0.22mg/kg total loading dose
- Maintenance dose-0.011mg/kg @12hr intervals in dogs

Treatment of Digitalis intoxication:

- abolishing of cardiac glycoside
- drugs containing potassium (potassium chloride; panangin)
- SH-group donator (Dimercaprol, or Unithiol)
- anti-arrhythmic agents (phenytoin, lidocaine, propranolol, atropine for AV block)
- — digoxin antibodies (digibind)
- — glucose, vitamin preparations, oxygen inhalation.

Phosphodiestrase Inhibitors

- phosphodiestrase enzyme that metabolises cAMP → More production of cAMP in cardiac muscle in turn cause increase myocardial contractility

1. Methylxanthines: Theophylline is the most cardiopotent in this class
2. Bipyridine derivatives- selectively inhibit phosphodiestrase III
   e.g. Amrinone & Milrinone
3. Pyridazone Derivatives – e.g. Pimobendan & Levosimendan

- MOA –positive inotropic action - increase the binding efficiency of cardiac myoflibril to calcium ions
- inhibits function of PDE III thereby increasing intracellular cAMP concentrations. They are potent inodilators.

- β–adrenorecepter Agonists
- E.g. - Epinephrine, Isoprenaline, Dobutamine.
- Epinephrine – is a non-selective adrenergic against that acts on both α and β - adrenoreceptors. It decreases both heart rate and the contractility through β_1- receptors.
- Isoprenaline – acts on both β_1&β_2 adrenoreceptors.
- Dobutamine – is selective β1 agonist

IV Miscellaneous agents

- Calcium salts – gluconate and chloride
- Glucagon –produced by the α- cells of islets of Langerhans has a patent inotropic activity in addition to its hyperglycaemic action.

ANTIARRYTHMIC DRUGS

- **Antiarrhythmic agents**, also known as **cardiac dysrhythmia medications**, are a group of drugs that are used to suppress abnormal rhythms of the heart.

Classification of Antiarrhythmic Drugs

Class I: Sodium channel blockers (membrane-stabilizing agents)

1 a: Block Na^+ channel and prolong action potential

1 b: Block Na^+ channel and shorten action potential

1 c: Block Na + channel with no effect on action potential

Class II: β- blockers

Class III: Potassium channel blockers (main effect is to prolong the action potential)

Class IV: Slow (L-type) calcium channel blockers

Class	Actions	Drugs
I	Sodium channel blockade	
IA	prolong repolarization	quinidine, procainamide, disopyramide
IB	shorten repolarization	lidocaine, mexiletine, tocainide, phenytoin
IC	little effect on repolarization	flecainide, encainide, propafenone
II	Beta-adrenergic blockade	propanolol, esmolol
III	Prolong repolarization potassium channel blockade	sotalol, amiodarone
IV	Calcium channel blockade	verapamil, diltiazem

Vasodilators & Antihypertensive drugs

- Vasodilators are a group of medicines that dilate blood vessels, which allows blood to flow more easily.
- The drugs which causes B.P to fall is known as hypotensive or antihypertensive drugs.
- Use – hypertension, Heart failure, Angina

Drug Classes Used to Treat Hypertension

- **Diuretics-**
  - **Thiazides:** Hydrochlorothiazide,
  - **High ceiling:** Furosemide
  - **K+ sparing:** Spironolactone, triamterene

- **Sympatholytic drugs**
  - **Centrally acting:** Clonidine, methyldopa
  - **ß-adrenergic blockers** Propranolol, metoprolol
  - **α – adrenergic blockers** Prazosin, phentolamine
  - **ß and α – adrenergic blockers** Labetolol and carvedilol

- **Direct acting vasodilator drugs-** Hydralazine and minoxidil, Diazoxide & nitroprusside

- **Calcium antagonist drugs-** Verapamil & diltiazem , amlodipine, nifedipine

- **Angiotensin-converting enzyme inhibitor and angiotensin :** Captopril, lisinopril., enalapril

- **Angiotensin receptor II blocking drugs** Losartan, candesartan

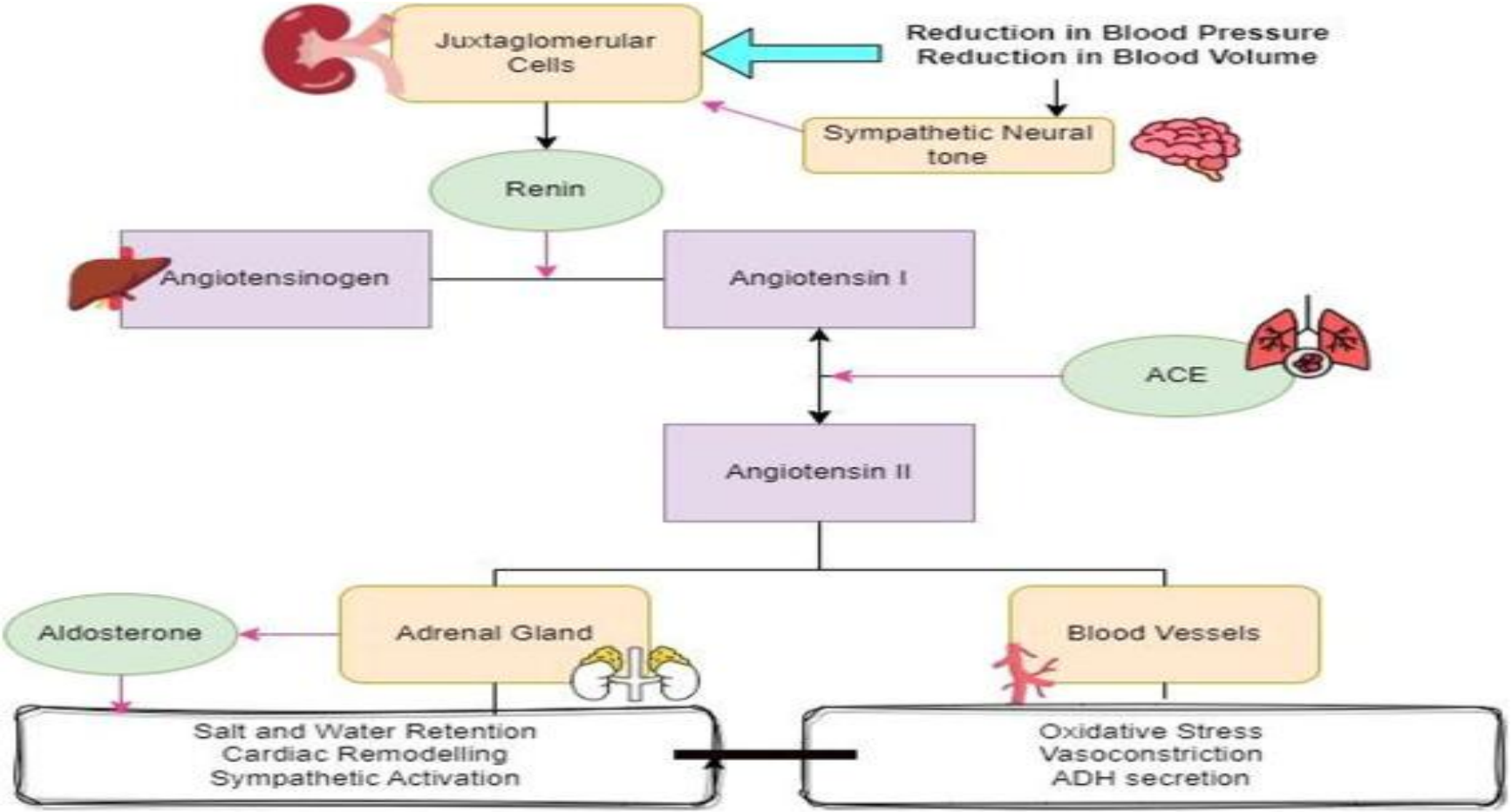
ACE inhibitors

Prodrugs

- Enalpril
- Ramipril
- Benzapril
- Quinapril
- Perinopril

Active drugs (no bioactivation required)

- Captopril
- Lisinopril
- Enalaprilat


Juxtaglomerular Cells
Reduction in Blood Pressure
Reduction in Blood Volume
Sympathetic Neural tone
Renin
Angiotensinogen
Angiotensin I
ACE
Angiotensin II
Aldosterone
Adrenal Gland
Blood Vessels
Salt and Water Retention
Cardiac Remodelling
Sympathetic Activation
Oxidative Stress
Vasoconstriction
ADH secretion

Ionodilators

- Ionotropic + vasodilators
- Pimobendan & Levosimendan

Haematinics

A **hematinic** are the drugs that required for the formation of blood cells in the process of hematopoiesis, and are used in he treatment of anaemia.

Substances required for formation of blood

- Iron
- Folic Acid
- Copper
- Vitamin B12
- Cobalt

- Mucosal block: Iron absorption stops when body reserves full

Erythropoietin- It is a glycoprotein hormone produced by the renal peritubular cells.

HAEMOSTATICS

- **Topical haemostatics**

i) Coagulant or clotting factors: E.g. Thromboplastin (Thrombokinase), Thrombin and Fibrinogen

ii) Occlusive or Artificial matrices: E.g. Fibrin foam, oxidized cellulose, gelatin sponge, calcium alginate

iii) Vasoconstrictors: E.g. adrenaline and noradrenaline

iv) Styptics / Astringents: cause precipitation of proteins

E.g. ferric sulphate, silver nitrate, alum, tannic acid, zincs chloride

- Vitamin K: Vit. K_3 (Menadione) – synthetic form
- Used only when there is deficiency of Vit. K like in poisoning of sweet clover, commercial rodenticides like coumarin and warfarin.
- **Fibrinolytic Inhibitors:** Aminocaproic acid , Tranexamic Acid
- **Protamine Sulphate** : Obtained from sperm or mature testes of fish. MOA- acts as antagonist of heparin
- Ethamsylate: by correcting abnormal platelet adhesion leading to repair of capillary wall integrity

Anticoagulants

i) Used for lab purpose- E.g. oxalates, sodium fluoride (for blood glucose studies), Ethylene diamine tetra acetic acid

ii) Used for blood transfusion- Sodium citrate, heparin

- *In vivo* anticoagulants:

i) Parenteral /systemic anticoagulants: Heparins &Heparinoids

ii) Oral anticoagulants/ slow acting anticoagulants: Coumarin derivatives – warfarin, dicoumarol, acenocoumarol

- Thrombolytic/Fibrinolytic agents: cause accelerated conversion of plasminogen to plasmin. E.g. Streptokinase, urokinase
- Antithrombotic / Antiplatelet drugs: Inhibitors of Thromboxane – aspirin, Dipyridamole

DRUGS ACTING ON CARDIO VASCULAR SYSTEM

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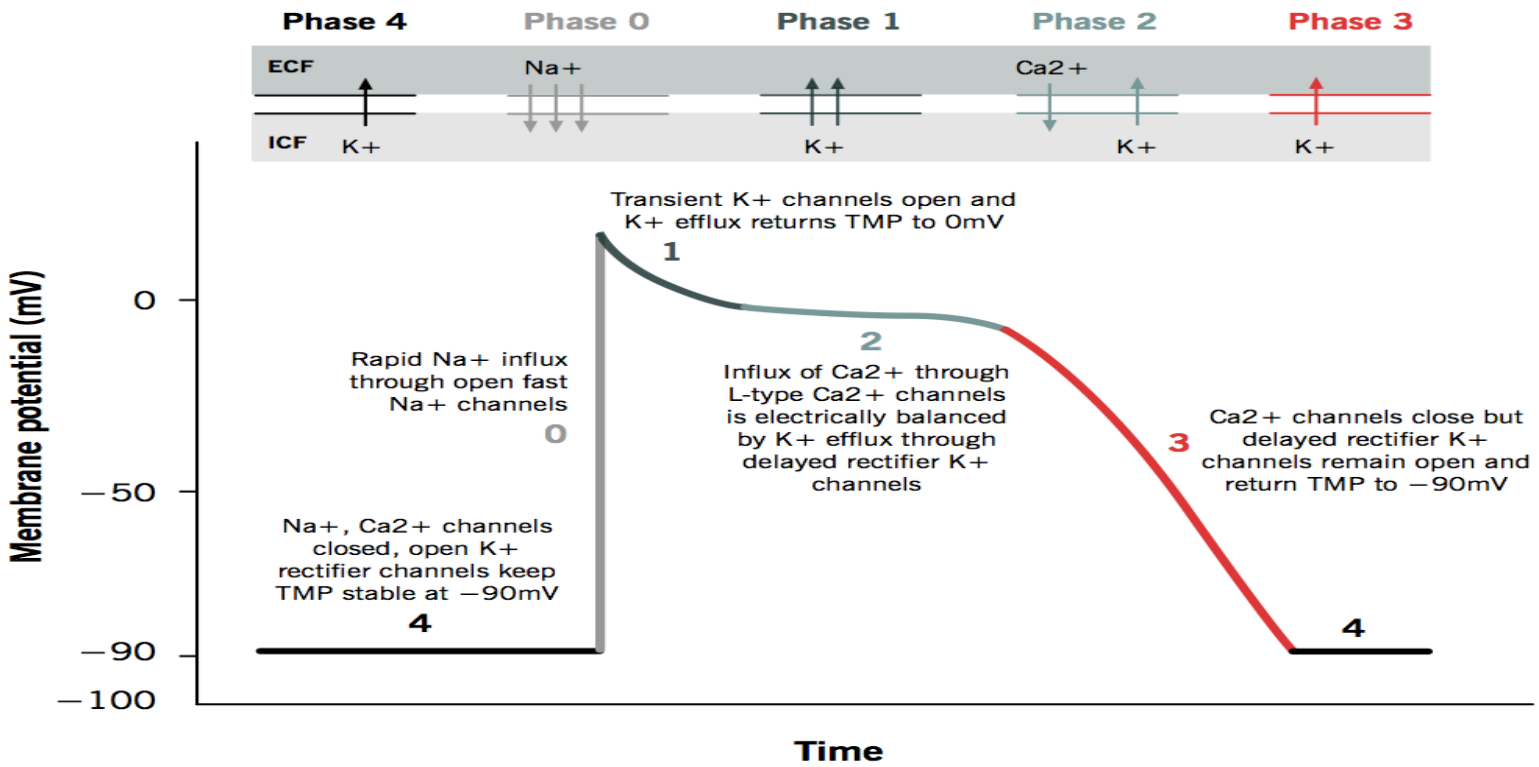
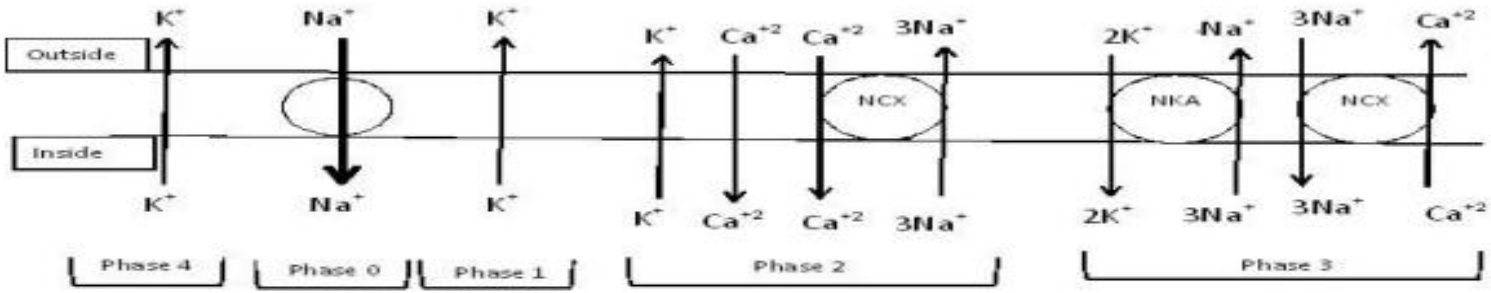
- Coagulant
- Anticoagulants

Action potential of cardiac muscles

Grigoriy Ikonnikov and Eric Wong





Working cardiac muscle cell potential.

NCX- Sodium calcium exchanger, NKA-sodium potassium ATPase

Myocardial stimulants

- positive inotropic drugs mainly used in condition likes Congestive heart failure
- **Classification**

1. Cardiac glycosides – Diagoxin, Digitoxin and Ouabain
2. Phosphodiestrase inhibitors:-

(i) Methylxanthines – aminophylline, theophylline
(ii) Bipyridine derivatives – amrinone and milrinone.
(iii) Pyridazone derivatives - pimobendan

3. Beta – receptor agonists : Epinephrine, isoprenaline, dobutamine, dopamine.
4. Miscellaneous agents:- Calcium & Glucagon

- inotropic (affect contractility)
- chronotropic (affect heart rate)
- dromotropic (affect rate of conduction through AV node)
- Bathmotropic if it affects the excitability
- Tonotropic if it affects the tonicity.

CARDIAC GLYCOSIDES

* obtained from plant *Digitalis purpurea*

- combination of a sugar portion and aglycone (genin)
- aglycone (genin) - pharmacologically active portion of the glycosides
- Sugar - affect its potency and duration of action

Cardiac glycosides are of plant origin :

Source	Part	Glycosides
Digitalis lanata	Leaves	Digitoxin,Gitoxin & Digoxin
Digitalis purpurea	Leaves	Digitoxin,Gitoxin & Gitalin
Strophanthus gratus	Seed	Strophanthin G (Ouabain)
Strophanthus kombe	Seed	Strophanthin K
Urgenia maritima	Bulb	Proscillaridin A
Bufo vulgaris	Toad skin	Bufotoxin

Mechanism of Action

- block membrane associated Na^{+}-K^{+} ATPase pump
- results in progressive accumulation of Na^{+} intracellularly
- This favours the exchange of Na^{+} with Ca^{+2} through Na^{+}-Ca^{+2} exchange mechanism.
- This causes intracellular calcium levels to raise that in turn leads to increased release of Ca^{+2} from the sarcoplasmic reticulum and hence increased contractility of cardiac muscle.
- Cardiac glycosides have the positive ionotropic effect on heart. They increase the force of contraction of myocardium & Decrease in heart rate (-ve Chronotropic effect due to vagal stimulation & slowing rate of conduction)
- Its main action in congestive heart failure

Cardiac glycosides

- a positive inotropic effect (an increase in the force of systole, an increase in the myocardial tone)
- a negative chronotropic effect (the prolongation of diastole, slowing of heart rate)
- a negative dromotropic effect (deceleration of conductivity)
- a positive bathmotropic effect (an increase in myocardium excitation)

Digitalisation

- **Digitalisation-** It is a basic procedure followed to quickly achieve the desired therapeutic effect by administering digitals initially in several divided doses over a relatively short period of time (24-48 hours).
- The dose required for this purpose is called as loading lose or digitalization dose. The dose needed daily to maintain the effect is called as maintenance dose.
- Oubain is the most potent therefore used in emergency therapy

Treatment of Digitalis intoxication:

- abolishing of cardiac glycoside
- drugs containing potassium (potassium chloride; panangin)
- SH-group donator (Dimercaprol, or Unithiol)
- anti-arrhythmic agents (phenytoin, lidocaine, propranolol, atropine for AV block)
- — digoxin antibodies (digibind)
- — glucose, vitamin preparations, oxygen inhalation.

Phosphodiestrase Inhibitors

- phosphodiestrase enzyme that metabolises cAMP → More production of cAMP in cardiac muscle in turn cause increase myocardial contractility

1. Methylxanthines: Theophylline is the most cardiopotent in this class
2. Bipyridine derivatives- selectively inhibit phosphodiestrase III
   e.g. Amrinone & Milrinone
3. Pyridazone Derivatives – e.g. Pimobendan & Levosimendan

- MOA –positive inotropic action - increase the binding efficiency of cardiac myoflibril to calcium ions
- inhibits function of PDE III thereby increasing intracellular cAMP concentrations. They are potent inodilators.

- β–adrenorecepter Agonists
- E.g. - Epinephrine, Isoprenaline, Dobutamine.
- Epinephrine – is a non-selective adrenergic against that acts on both α and β - adrenoreceptors. It decreases both heart rate and the contractility through β_1- receptors.
- Isoprenaline – acts on both β_1&β_2 adrenoreceptors.
- Dobutamine – is selective β1 agonist

IV Miscellaneous agents

- Calcium salts – gluconate and chloride
- Glucagon –produced by the α- cells of islets of Langerhans has a patent inotropic activity in addition to its hyperglycaemic action.

ANTIARRYTHMIC DRUGS

- **Antiarrhythmic agents**, also known as **cardiac dysrhythmia medications**, are a group of drugs that are used to suppress abnormal rhythms of the heart.

Classification of Antiarrhythmic Drugs

Class I: Sodium channel blockers (membrane-stabilizing agents)

1 a: Block Na^+ channel and prolong action potential

1 b: Block Na^+ channel and shorten action potential

1 c: Block Na + channel with no effect on action potential

Class II: β- blockers

Class III: Potassium channel blockers (main effect is to prolong the action potential)

Class IV: Slow (L-type) calcium channel blockers

Class	Actions	Drugs
I	Sodium channel blockade	
IA	prolong repolarization	quinidine, procainamide, disopyramide
IB	shorten repolarization	lidocaine, mexiletine, tocainide, phenytoin
IC	little effect on repolarization	flecainide, encainide, propafenone
II	Beta-adrenergic blockade	propanolol, esmolol
III	Prolong repolarization potassium channel blockade	sotalol, amiodarone
IV	Calcium channel blockade	verapamil, diltiazem

Vasodilators & Antihypertensive drugs

- Vasodilators are a group of medicines that dilate blood vessels, which allows blood to flow more easily.
- The drugs which causes B.P to fall is known as hypotensive or antihypertensive drugs.
- Use – hypertension, Heart failure, Angina

Drug Classes Used to Treat Hypertension

- **Diuretics-**
  - **Thiazides:** Hydrochlorothiazide,
  - **High ceiling:** Furosemide
  - **K+ sparing:** Spironolactone, triamterene

- **Sympatholytic drugs**
  - **Centrally acting:** Clonidine, methyldopa
  - **ß-adrenergic blockers** Propranolol, metoprolol
  - **α – adrenergic blockers** Prazosin, phentolamine
  - **ß and α – adrenergic blockers** Labetolol and carvedilol

- **Direct acting vasodilator drugs-** Hydralazine and minoxidil, Diazoxide & nitroprusside

- **Calcium antagonist drugs-** Verapamil & diltiazem , amlodipine, nifedipine

- **Angiotensin-converting enzyme inhibitor and angiotensin :** Captopril, lisinopril., enalapril

- **Angiotensin receptor II blocking drugs** Losartan, candesartan

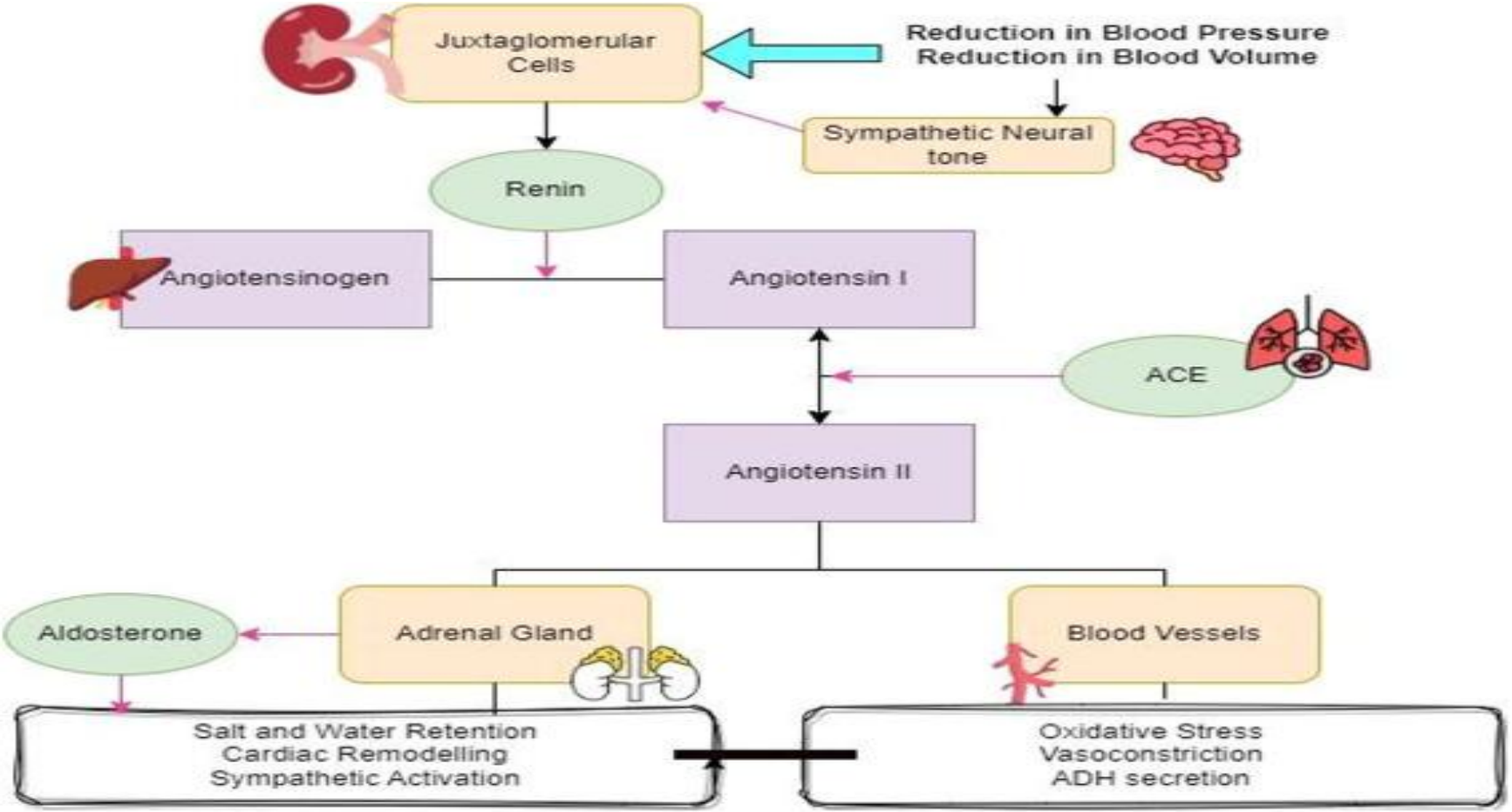
ACE inhibitors

Prodrugs

- Enalpril
- Ramipril
- Benzapril
- Quinapril
- Perinopril

Active drugs (no bioactivation required)

- Captopril
- Lisinopril
- Enalaprilat


Juxtaglomerular Cells
Reduction in Blood Pressure
Reduction in Blood Volume
Sympathetic Neural tone
Renin
Angiotensinogen
Angiotensin I
ACE
Angiotensin II
Aldosterone
Adrenal Gland
Blood Vessels
Salt and Water Retention
Cardiac Remodelling
Sympathetic Activation
Oxidative Stress
Vasoconstriction
ADH secretion

Ionodilators

- Ionotropic + vasodilators
- Pimobendan & Levosimendan

Haematinics

A **hematinic** are the drugs that required for the formation of blood cells in the process of hematopoiesis, and are used in he treatment of anaemia.

Substances required for formation of blood

- Iron
- Folic Acid
- Copper
- Vitamin B12
- Cobalt

- Mucosal block: Iron absorption stops when body reserves full

Erythropoietin- It is a glycoprotein hormone produced by the renal peritubular cells.

HAEMOSTATICS

- **Topical haemostatics**

i) Coagulant or clotting factors: E.g. Thromboplastin (Thrombokinase), Thrombin and Fibrinogen

ii) Occlusive or Artificial matrices: E.g. Fibrin foam, oxidized cellulose, gelatin sponge, calcium alginate

iii) Vasoconstrictors: E.g. adrenaline and noradrenaline

iv) Styptics / Astringents: cause precipitation of proteins

E.g. ferric sulphate, silver nitrate, alum, tannic acid, zincs chloride

- Vitamin K: Vit. K_3 (Menadione) – synthetic form
- Used only when there is deficiency of Vit. K like in poisoning of sweet clover, commercial rodenticides like coumarin and warfarin.
- **Fibrinolytic Inhibitors:** Aminocaproic acid , Tranexamic Acid
- **Protamine Sulphate** : Obtained from sperm or mature testes of fish. MOA- acts as antagonist of heparin
- Ethamsylate: by correcting abnormal platelet adhesion leading to repair of capillary wall integrity

Anticoagulants

i) Used for lab purpose- E.g. oxalates, sodium fluoride (for blood glucose studies), Ethylene diamine tetra acetic acid

ii) Used for blood transfusion- Sodium citrate, heparin

- *In vivo* anticoagulants:

i) Parenteral /systemic anticoagulants: Heparins &Heparinoids

ii) Oral anticoagulants/ slow acting anticoagulants: Coumarin derivatives – warfarin, dicoumarol, acenocoumarol

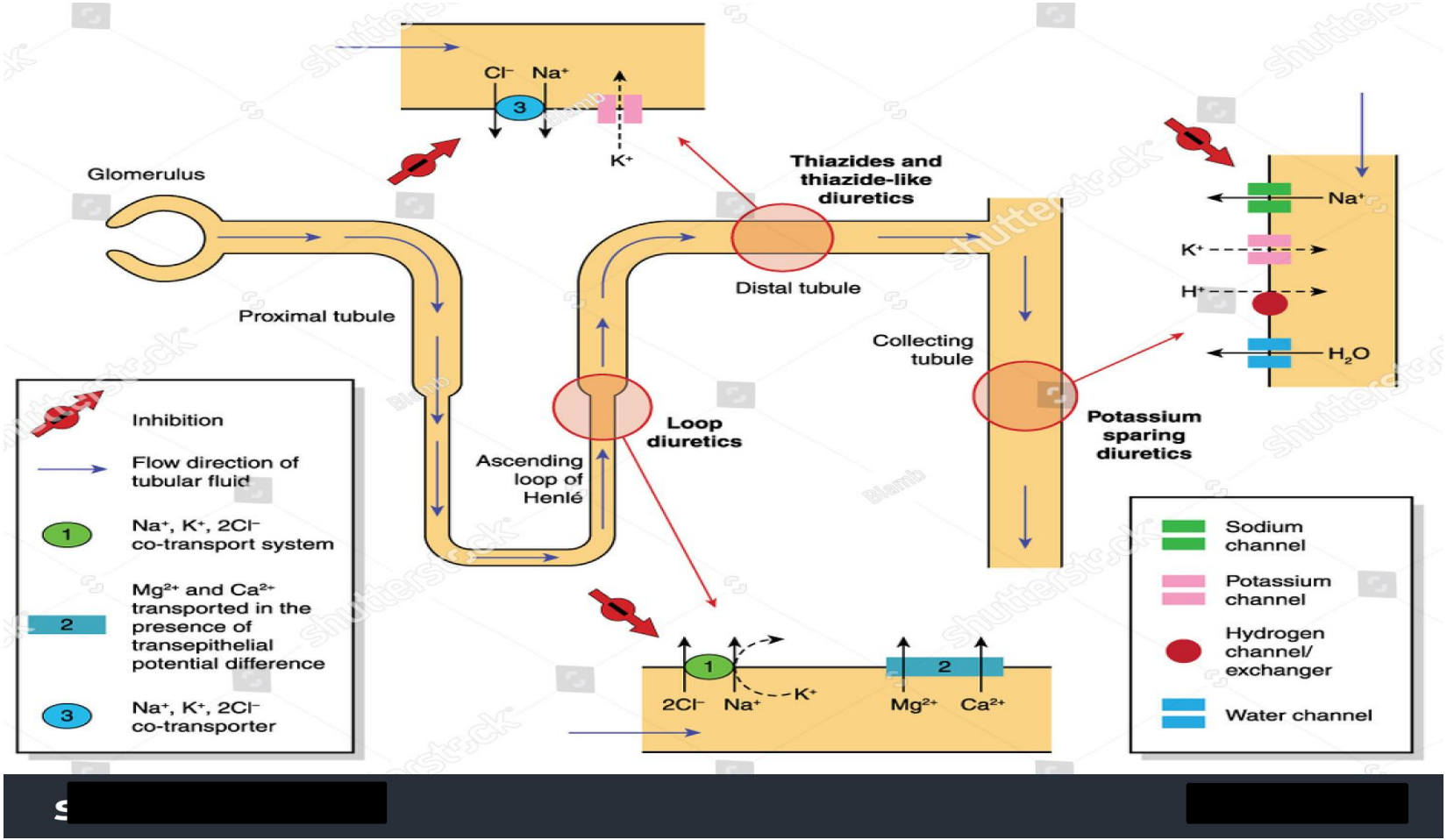
- Thrombolytic/Fibrinolytic agents: cause accelerated conversion of plasminogen to plasmin. E.g. Streptokinase, urokinase
- Antithrombotic / Antiplatelet drugs: Inhibitors of Thromboxane – aspirin, Dipyridamole

Drugs acting on Urinary System

- **Diuretics**
- **Classification of Diuretics**
- **Urinary Acidifiers**
- **Urinary Alkalizes**
- **Urinary Antiseptics**

Classification of diuretics :-

- **Osmotic Diuretics : Mannitol, Glycerol**
- **Carbonic Anhydrase Inhibitors : acetazolamide, Methazolamide**
- **Thiazide Diuretics : Hydrochlorthiazide, Metolazone, Chlorthalidon**
- **Potassium Sparing Diuretics : Amiloride, Triamterene**
- **Aldosterone antagonist : Spironolactone, Canrenone**
- **Mercurial Diuretic : Calomel, Mersalyl**
- **Loop Diuretic (High Ceiling): Furosemide Bumetanide, Ethacrynic Acid**
- **Xanthine derivatives : Theophylline, Aminophylline, Caffeine**


Cl⁻ Na⁺
3
K⁺
Glomerulus
Thiazides and thiazide-like diuretics
Distal tubule
Proximal tubule
Collecting tubule
Na⁺
K⁺
H⁺
H₂O
Loop diuretics
Ascending loop of Henlé
Potassium sparing diuretics
Inhibition
Flow direction of tubular fluid
1
Na⁺, K⁺, 2Cl⁻ co-transport system
2
Mg²⁺ and Ca²⁺ transported in the presence of transepithelial potential difference
3
Na⁺, K⁺, 2Cl⁻ co-transporter
1
2Cl⁻ Na⁺ K⁺
2
Mg²⁺ Ca²⁺
Sodium channel
Potassium channel
Hydrogen channel/ exchanger
Water channel

Continue….

Diuretic	Site of Action	Adverse Effects	Special points
Carbonic anhydrase inhibitors	PTC (inhibition of CAE)	Metabolic Acidosis	Weak, Used in Glaucoma, Petit mal epilepsy, Acute mountain sickness, to alkaline the urine
Osmotic Diuretics	PTC, LOH, DCT (Osmotic retention of water, Dilates Afferent arterioles, Increased hydrostatic pressure in glomerulus	Shifting of fluid from intracellular to extracellular, Hyponatremia, Pulmonary edema	Potent Used in Glaucoma, Poisoning, Increased ICT, impending ARF
Loop Diuretics	Thick Ascending Limb of Henle (NaK2Cl inhibition) Weak CAI action	Hyponatremia Hypomagnesaemia Hypocalcaemia Hyperuricemia Hyperglycemia Hyperlipidemia Hyperuricemia Ototoxic (ECA)	Most potent, Most Potent is Bumetanide, Effective even in low GFR, All except Ethacrynic acid are sulphonamide related, Venodilatation, Decrease Left Ventricle Pressure, Used in Acute LVF, Pulmonary Edema, Nephrotic syndrome, ARF, NSAIDS blunt effect, Cerebral edema, short term tt of Hypertension, to reduce volume overload during transfusion,
Thiazide Diuretics	DCT (NaCl)	Hypokalemic metabolic alkalosis (Gitelman's Syndrome) Hypercalcemia	Moderate, Chlorthalidone is Longest acting, Paradoxical effect in Diabetes Insipidus First line in Hypertension,
Potassium Sparing Diuretics	CD	HyperKalemia Antiandrogenic effect	Weak, As supplement to other to counter the hypokalemia, Canrenone is active metabolite, used in Conn's syndrome (Primary Hyperaldosteronism) cirrhotic edema, polycystic ovary

Based on their mode of action

- Osmotic diuretics – Glycerine, mannitol, urea, isosorbide
- Inhibitors of carbonic anhydrase – Acetazolamide, dichlorphenamidine
- Inhibitors of Na+-K+-2Cl- symport (High ceiling loop diuretics) – Frusemide, Ethacrynic acid, Bumetanide
- Inhibitors of Na+-Cl- symport – Thiazide and thiazide like drugs
- Potassium sparing diuretics
- Inhibitors of epithelial sodium channels – Triamterene, amiloride

- Antagonists of aldosterone – Spironolactone

- Xanthine diuretics – Theophylline

On basis of efficacy

- High ceiling diuretics: Loop diuretics

- Medium efficacy diuretics: Thiazides and Thiazide like drugs

- Weak or adjunct diuretics:
- Carbonic anhydrase inhibitors
- Potassium sparing diuretics
- Osmotic diuretics

- Based on their action on the kidneys diuretics are classified as
- Diuretics acting directly on the cells of the nephron
- Agents acting on the ascending loop of Henle – Ethacrynic acid, fursemide
- Agents acting on the early distal tubules – Thiazides like chlorthiazide
- Agents acting on the Collecting tubules and ducts – Triamterene, amiloride

URINARY ACIDIFIERS

Urinary acidifiers are drugs which cause acidification of urine.

* They help in increased excretion of basic drugs

* They enhance the antibacterial action of urinary antiseptics like hexamine and certain antibiotics (Penicillins and Tetracyclines).

- **Eg- Sodium acid phosphate, Ascorbic acid, Methionine**

URINARY ALKALIZERS

- **Urinary Alkilizers are basic agents for alkalinization of urine.**

*** Alkalinization of urine promotes antibacterial action of certain antibiotics (Aminoglycosides).**

*** It helps in excretion of acidic drugs.**

*** It increasing the solubility and reducing the risk of sulfonamide renal toxicity (crystalluria) especially in carnivores.**

- **Eg – Sodium bicarbonate, Potassium citrate**

Urinary antiseptics

Urinary antiseptics are oral agents that exert antibacterial activity in the urinary tract.

*** It has little or no systemic antibacterial effects.**
*** It's usefulness is limited to lower urinary tract infections**

- **Eg – Nitrofurantoin, Methenamine , Nalidixic acid, calcium Mandelate**

ECBOLICS

- These are agents that bring about increase in uterine contractions
- Oxytocin: It is hormone of the posterior pituitary received from the hypothalamus. It has amajor physiological role in milk let down and labor initiation.
- Ergot alkaloids: Alkaloids from the fungus Claviveps purpurea viz. ergometrine, ergonovine
- PGF2 alpha

TOCOLYTICS

- These are agents that inhibit uterine contractions. They relax uterine smmoth muscle and may be used to delay labor and to stop threatened abortion.
- Beta2 agonists: Salbutamol, terbutaline, isoxsuprine, clenbutrol
- Calcium channel blockers: Nifedipine, diltiazem
- Oxytocin antagonist: Atosiban

EMOLLIENTS

These are bland (mild, gentle) fatty materials often used to soften or moisten the skin. These are primarily useful for treating the skin conditions resulting from water soluble irritants and air borne bacteria.

eg:-

- Vegetable Oils: Olive oil, Corn oil, Almond oil,
- Animal fats: Lanolin, Lard, Whale oil.
- Hydrocarbons: Paraffin, Mineral oil, Vaseline

DEMULCENTS

Demulcents are inert substances which sooth and relieve irritation, primarily involving the inflamed/ injured mucous membranes, these are generally high molecular weight compounds that are water soluble and function by alleviating irritation. They form a protective layer over the irritated surfaces.

e.g. Glycerine, Propylene glycol, Gum acaia

Counter irritants & Rubefacient

- **counterirritant** is a substance which creates irritation or mild inflammation in one location with the goal of lessening discomfort and/or inflammation in another location. e.g. camphor, methyl salicylate

- Rubefacient is a topical substance that causes the skin to redden and become irritated due to increased blood flow

Chemotherapy

Chemotherapy

the treatment of systemic infection (caused by bacteria, viruses, fungi, protozoa,helminths etc.) or malignancy with specific chemicals that have *selective toxicity* for infecting organism /malignant cell with no or minimal effect on the host cell

Father of chemotherapy:- Paul Ehrlich

Anti microbial agents

synthetic as well as **naturally obtained** (microbial origin) drug that are used to inhibit or kill micro-organisms.

- **Classification**
- a) **Based on antibacterial action:-**
  - **Bacteriostatic** :- Suppression of bacterial growth and multiplication. E. g.- Sulphonamides, tetracyclines, erythromycin, chloramphenicol.
  - **Bactericidal** :- Cause death of bacteria. Eg.- Penicillin ,cephalosporins, streptomycin, kanamycin, colistin, bacitracin

Based on Antibacterial spectrum

- Broad spectrum :- Effective against both Gram positive & Gram negative bacteria E.g.:- Tetracyclines, chloramphenicol, fluoroquinolones, Sulfonamide
- Narrow Spectrum: - Effective against a limited group of bacteria.

  i) Gram positive :- Penicillin G, erythromycin, lincomycin, bacitracin etc.

  ii) Gram negative:- Streptomycin, gentamycin, polymyxinB etc.

Based on Source

a. **Fungal Origin:-** Penicillin, Cephalosporin and Griseofulvin.

b. **Bacterial Origin**:- Bacitracin , Polymyxin B,Colistin ,tyrothricin.

c. **Actinomycetes Origin:-** Streptomycin, tetracyclines, chloramphenicol, Macrolides

Principle of chemotherapy

- basic principle of chemotherapy is the selective toxicity i,e the drug should selectively inhibit or kill the disease causing pathogenic organism

a. Chemotherapy must be rational and needs to be supported by either a clinical or microbiological diagnosis to identify the pathogenic organisms.
b. Characterization of the pathogens including its sensitivity to an AMAs is essential.

Problems associated with Antibiotics

- **Local irritancy**: Practically all antimicrobial agents, especially erythromycin, tetracyclines and certain cephalosporins and chloramphenicol are irritants
- **Systemic toxicity**
- Drugs having Very Low Therapeutic Index (LD50/ ED50): Used in condition where no suitable alternative is available

Drugs with low TI

Drugs	Toxicity
Aminoglycosides	8th cranial nerve, Ear and kidney toxicity
Tetracyclines	Liver and kidney damage
chloramphenicol	Bone marrow depression

Hypersensitivity

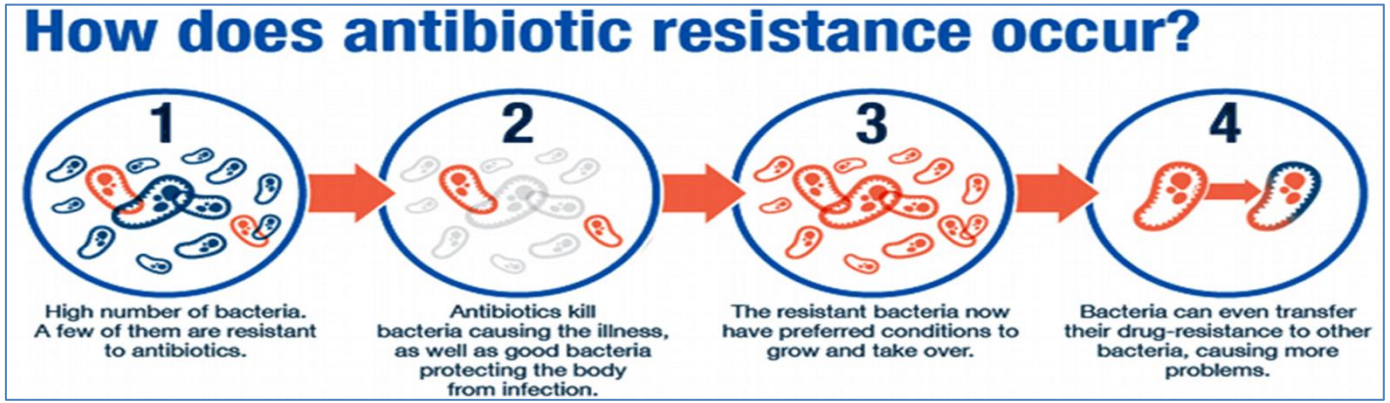
- These are **unpredictable and unrelated to dose**
- The whole range of reaction from harmless rashes to severe reaction (anaphylactic shock, haemolysis, allergic liver damage and bone marrow depression) can be produced.
- The most commonly involved AMAs are-penicillins, cephalosporins, sulphonamides and fluoroquinolones
- Penicillin, the commonest cause of drug induced anaphylaxis, produce this response in an estimated 1 in 50,000 patient exposed
- **Some example of haemolytic reaction**s are: haemolytic anaemia(sulphonamide), agranulocytosis(sulphonamide, **chloramphenicol)**

Drug Resistance

- **It refers to unresponsiveness of a microorganism towards an AMA**.
- Natural Resistance: Some microorganism have always been resistant to certain AMA. Example: Gram –ve bacilli are generally unaffected by Penicillin G. Anaerobic bacteria are resistant to gentamicin.
- Acquired Resistance: It is development of resistance by microorganism (which was sensitive before) due to use of an AMA over a period of time

Development of resistance

- **Resistance may be developed by mutation or gene transfer**
- **Mutation**: Stable and heritable genetic change that occur that occurs spontaneously and randomly among microorganism.



Resistant organism can be of three type

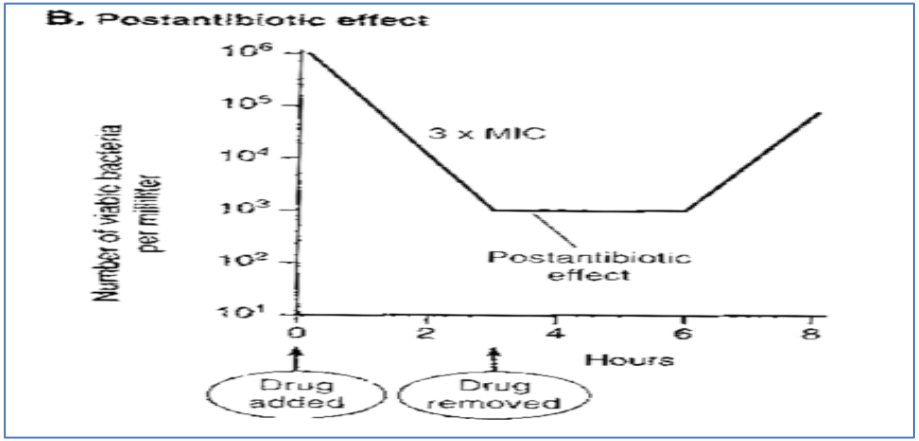
- Drug tolerant: Loss of affinity of target biomolecule of the microorganism for a particular AMA. e.g., certain penicillin resistant pneumococcal strains have altered penicillin binding proteins.
- Drug destroying: Resistant microorganism elaborate an enzyme which inactivate the drug. Beta lactamase for β lactam antibiotics, Acetyl transferase which inactivate chloramphenicol, Kinases inactivates Aminoglycosides.
- Drug impermeable: Many hydrophilic antibiotics gain access into the bacterial cell through specific channel formed by protein called porins or need specific transport mechanism. These may be lost by the resistant strain. Bacteria may acquire plasmid directed efflux protein in their cell membrane.

SuperInfection

- A new infection that arises during or after the treatment of a primary infection.
- The treatment for the initial infection can disrupt the balance of the body's microbial flora, allowing a different, often more resistant, pathogen to take hold and cause a new infection.
- Bacterial infection might be treated with antibiotics.
- However, the antibiotics can also kill off beneficial gut bacteria, creating an environment where a resistant fungal infection, like Candida, can thrive.

- MIC (Minimum Inhibitory Concentration) refers to the lowest concentration of an antimicrobial agent that inhibits visible bacterial growth
- MBC (Minimum Bactericidal Concentration) is the lowest concentration that kills a specific percentage (typically 99.9%) of the initial bacterial population

- After a brief exposure if the organism is placed in antibiotic free medium, it starts multiplying again, but after a lag period which depends on the antibiotic as well as the organism. This lag period in growth resumption is called Post Antibiotic effect.
- Long PAE is noted with fluoroquinolones and Aminoglycosides

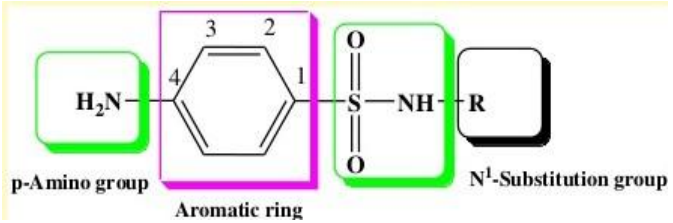


Sulphonamides

- first antimicrobial agent effective against pyogenic bacterial infections
- Sulphonamide is a class of organic compounds that are amides of sulphonic acids.
- Sulfonamido-chrysoidine (Prontosil-Red) - dye included by **Domagk** to treat experimental streptococcal infection in mice
- By 1937, it became clear that prontosil was broken down in the body release sulphanilamide (early example of prodrug)

Chemistry and SAR

- All sulfonamides are derivatives of sulfanilamide (para-aminobenzene sulfonamide), the antibacterial component of an azo dye (prontosil).
- sulfanilamide nitrogen designated as N1 and an amino nitrogen called N4.
- Most antibacterial sulfonamides have been synthesized by chemical substitution at N1 position
- A free amino group in N4 position is essential for antibacterial activity



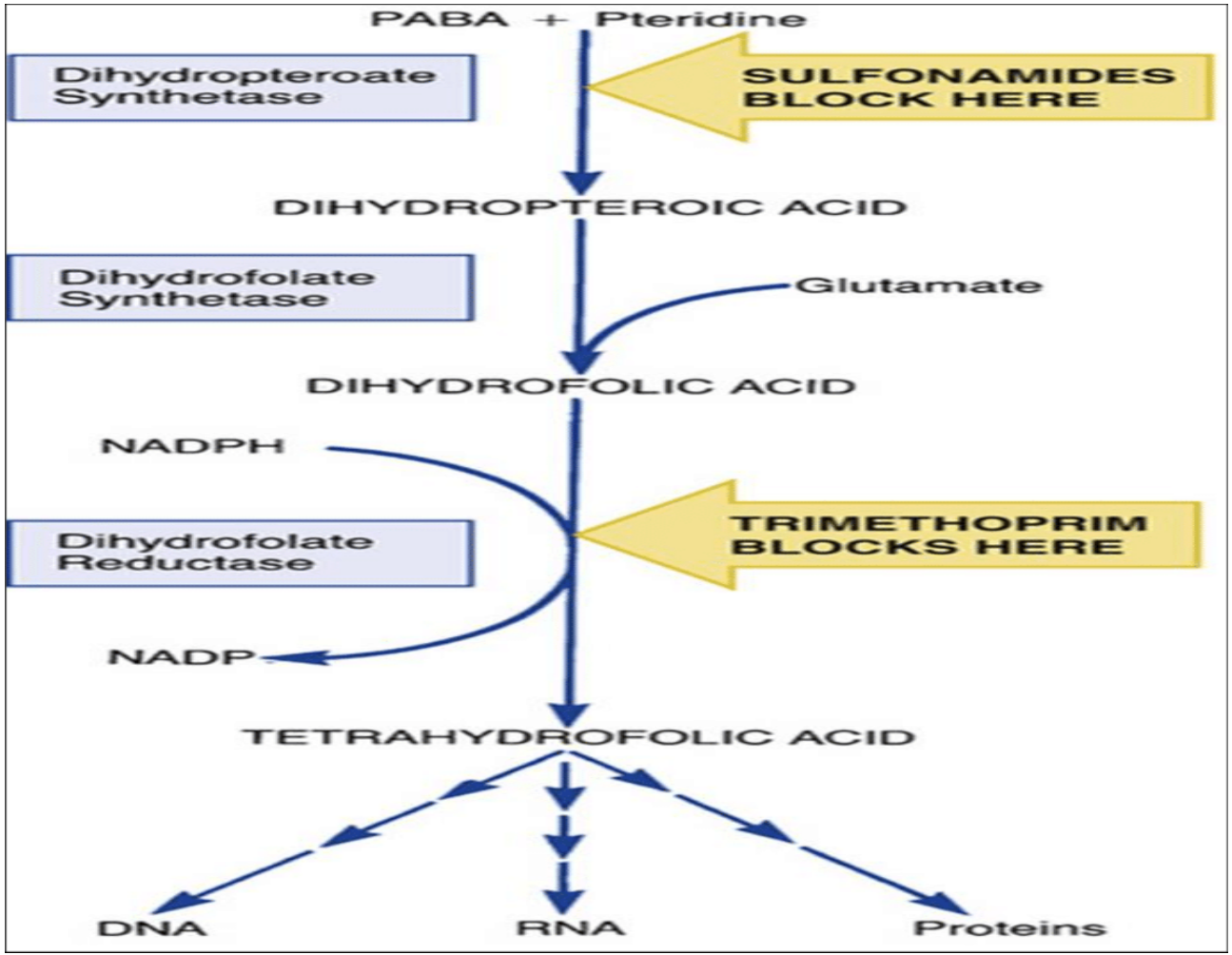
Sulphanilamide group

The **individual members differ in the nature of N1 substitution, which governs the solubility, potency and pharmacokinetic property of the compounds.**

Mechanism of Action of Sulfonamides

- Many bacteria synthesize their own folic acid for which p-aminobenzioc acid (PABA) is an essential constituent.
- Sulfonamides are structural analogs or competitive antagonists of PABA
- competitive inhibitors of dihydropteroate synthetase, a bacterial enzyme responsible for the union of PABA with pteridine residue in bacterial formation of dihydropteroic acid
- Dihydropteroic acid further conjugates with glutamic acid to produce dihydrofolic acid

- The antagonism thus leads to inhibition of synthesis of folic acid and resulting in bacteriostatic effect.
- The organisms, which synthesize their own folic acid and cannot utilize preformed folic acid are sensitive to sulfonamides.
- Sulfonamides do not affect mammalian cells since they require preformed folic acid supplied in diet and need not synthesize it


PABA + Pteridine
Dihydropteroate Synthetase
SULFONAMIDES BLOCK HERE
DIHYDROPTEROIC ACID
Dihydrofolate Synthetase
Glutamate
DIHYDROFOLIC ACID
NADPH
Dihydrofolate Reductase
TRIMETHOPRIM BLOCKS HERE
NADP
TETRAHYDROFOLIC ACID
DNA
RNA
Proteins

- Diaminopyrimidins (Trimethoprim, ormetoprim) inhibits dihydrofolate reductase enzyme. The combination of sulphonamide and trimethoprim inhibits formation of tetrahydrofolic acid at two step. This is known as sequential blocking
- **This action is synergistic**
- Trimethoprim and sulphonamide are bacteriostatic themselves, but together can be bactericidal.

Principles of sulphonamide therapy

- It should be administered as early as possible in the course of an infection.
- In servere infection large dose should be given by parenteral route (IV or IM).
- The initial large dose should be followed by regular smaller maintenance doses.
- Plenty of water and urinary alkaliser (sodium bicarbonate) is to be given with sulfa drugs to prevent crystalluria

Systemically acting Sulphonamides -

- Short acting (duration < 12 hours): sulfadiazine, sulfamerazine, sulfisoxazole, sulfamethizole, sulfathiazole, sulphanilamide,
- Intermediate acting- (duration 12-24 hours): sulphadimidine, sulfamethoxazole, sulfasimazole, sulfamoxole, sulfaphenazole
- Long acting- (duration 24-48 hours): sulphadimethoxine, sulfamethoxypyridazine
- Ultra long acting- sulfadoxine, sulphamethopyrazine

• Locally acting Sulphonamides—

- Gut acting Sulphonamides : sulphaguanidine and sulfasalazine
- Topical agents- Silver sulfadiazine, mafenide, sulfacetamide

- To treat eye infection: Sulfacetamide Sodium
- **To treat burn and wound infections :**Mafenide, silver Sulfadiazine
- Salicylazosulfapyridine (Sulfasalazine) is also hydrolysed in large intestine to **Sulfapyridine and aminosalicyclic acid (anti-inflammatory agent) and is used in ulcerative Colitis in Dogs.**

Interactions affecting Antimicrobial activity/Antagonists of Sulfonamides

- Compounds Containing PABA nucleus such as local anaesthetics (Procaine, butacaine and benzocaine), Procainamide and procaine penicillininamide, folic acid and choline and their precursors, Gelatin, albumin, peptone and serum protein (with which the Sulfa drugs bind)
- Antibacterial action is neutralized in the presence of pus or tissue breakdown products (contain thymidine and purines which are utilized by bacteria by passing the need of folic acid)

Metabolism

- ✓ Herbivores metabolises sulphonamide at a faster rate and more extensively than carnivores and omnivores.
- ✓ Acetylation of –NH2 group at N4 position is a major mechanism of metabolism.
- ✓ Acetylated metabolite is major urinary metabolite in cattle sheep and swine.
- ✓ Canine lack ability to acetylate aromatic amines, and alternative metabolic pathway are involved in metabolism of sulphonamide

Adverse effects

- Renal Toxicity(crystalluria): Most of the N4 acetylated Sulfonamides, except the sulfapyrimidine derivatives **(Sulfadiazine, Sulfamerazine and Sulfadimidine)** are less soluble in acidic urine, precipitate in the tubules and cause crystalluria
- **Keratoconjunctivitis sicca(KCS)**
- **Hypersensitivity**
- Hypoprothrombinemia
- **Blood dyscriasias:** Anaemia and thrombocytopenia due to decreased serum folic acid level which may be due to inhibiting the folate production by intestinal bacteria.
- hypothyroidism in Dog: The effect is caused ability of sulphonamide to inhibit thyroid peroxidase activity.

Potentiated sulphonamide

- ✓ Combination of Diaminopyrimidines and Sulphonamide
- ✓ Diaminopyrimidins: trimethoprim, ormetoprim, aditoprim, tetroxoprim.
- ✓ Causes sequential block of folate metabolism
- ✓ Combination have synergistic effect, Have more activity and bactericidal effect on bacteria and its resistant form.
- ✓ Diaminopyrimidins blocks Dihydrofolate reductase
- ✓ Trimethoprim is >50,000 times more active against bacterial DHFR than against mammalian enzyme
- ✓ Trimethoprim-sulphonamide are formulated in the ratio of 1:5

Nitrofurans

- synthetic antibacterial compounds which contain a furan ring to which a nitro group is attached.
- 5-nitro group is essential for their antibacterial action.
- broad spectrum antibacterial
- act by inhibiting the enzymes necessary for the carbohydrate metabolism of bacteria (also thought to be converted to some metabolites (in bacterial cells) which interfere with the function of DNA)
- Nitrofurazone, Nitrofurantoin, Furazolidone, Sulphones

Beta-Lactam Antibiotics

- antibiotics have a beta-lactam ring as the essential antibacterial component in their chemical structure.
- The antibiotics under this group consist of:
  - Penicillins,
  - Cephalosporins,
  - Cephamycins,
  - Monobactams and
  - Carbapenems.

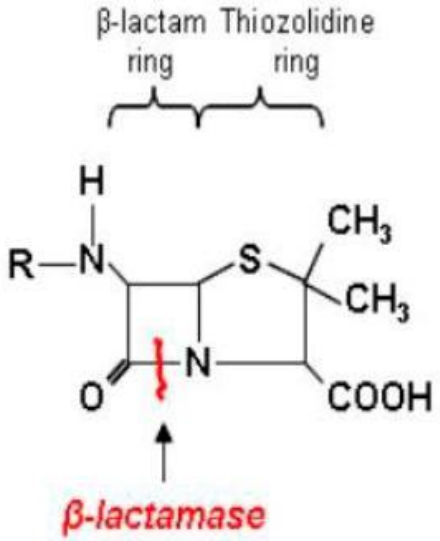
Penicillins

- The penicillins are a large group of naturally occurring and semi-synthetic antibiotics.
- first natural antibiotic discovered by **Sir Alexander Fleming** in the filtrate of culture medium of mold *Penicillium notatum* having bacterial action on *Staphylococcal* in 1929.
- *P. Chrysogenum*, a mutant of ***P. notatum*** **is presently used for commercial production** of the antibiotic.
- Penicillin was the first antibiotic to be used clinically in **1941**
- **Florey and Chain: Nobel prize in medicine for developing penicillin**

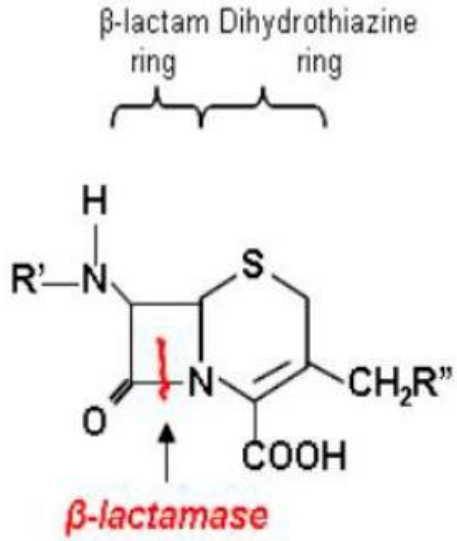
- penicillin comprises of a thiazolidine ring (A) connected to a beta-lactam ring (B), to which a side chain (R) is attached through an amide linkage.

- side chain of natural penicillin can be split off by amidase to produce 6-aminopenicillanic acid (weak antibacterial activity).
- The enzyme breaks the beta-lactam ring (BL) and inactivates penicillin through formation of penicilloic acid, which does not possess antibacterial activity.
- natural penicillin is known as benzyl penicillin or penicillin G

β-Lactam Antibiotics



Penicillins



Cephalosporins

- **Antibacterial Spectrum**:
- Benzyl penicillin has narrow spectrum activity, effective against Gram positive organism especially against cocci. But not against Gram negative organism

- It is bactericidal at 0.5 U/ml concentration. It action is unaltered by blood, pus or tissue breakdown products

- The extended spectrum penicillins are active against both Gram positive and Gram negative organism

Classification

1. Natural penicillins –
- Penicillin G
- Repository Penicillins or Sparingly soluble organic salts of penicillin G:
    - Procain penicillin G
    - Benzathine penicillin G

2. Semisynthetic penicillin:

a) Acid-stable penicillin's

i) Phenoxymethyl penicillin (penicillin v)

ii) Phenoxyethyl penicillin (Phenethicillin)

b) Penicillinase-resistant penicillins :

Acid labile penicillins: Methicillin, nafcillin

Acid resistant penicillins: Oxacillin, cloxacillin, dicloxacillin, flucoxacillin

3. Extended spectrum penicillins: These are not Penicillinase-resistant.

- Amino penicillins: Ampicillin, amoxicillin, and hetacillin
- Carboxypenicillin: Carbenicillin and ticarcillin
- Ureidopenicillins : Azlocillin, Mezlocillin, and Piperacillin

Mechanism of Action
(Inhibition of Peptidoglycan synthesis: cell wall)

- All β-lactam antibiotics interfere with the synthesis of bacterial cell wall
- The bacteria synthesize UDP-N-acetylmuramic acid (NAM) and UDP-N-acetyl glucosamine (NAG).
- The peptidoglycan residues are linked together forming long strands and UDP is split off
- The final step is cleavage of the terminal D-alanine of the peptide chains by transpeptidases

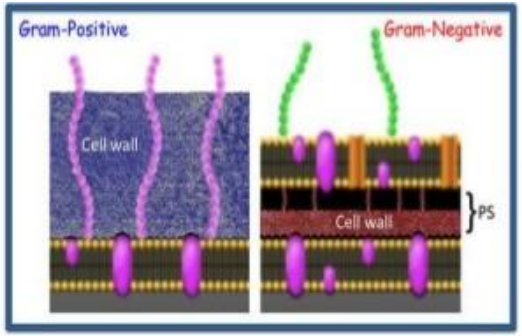
- The bacterial cell wall comprised of peptidoglycan having linear strains of two alternating amino sugars, N-acetyl glucosamine (NAG) and N-acetyl muramic acid (NAM) which are Cross linked by peptide chains (transpeptidation) and give rigid mechanical stability to the cell wall
- The β-lactam antibiotics inhibit the transpeptidases so that cross linking does not take place
- When susceptible bacteria divide in the presence of a β-lactam antibiotic-cell wall deficient (CWD) forms are produced.
- Because the interior of the bacterium is hyperosmotic, the CWD forms swell and burst bacterial lysis.
- This is how β-lactam antibiotics exert bactericidal action.

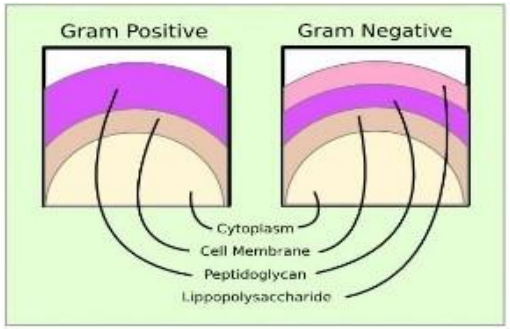
Penicillin binding proteins

- These enzymes and related proteins constitute the penicillin binding proteins (PBPs) which have been located in the bacterial cell membrane.
- Each organism has several PBP_s and PBP_s obtained from different species differ in their affinity towards different β-lactam antibiotics.
- This fact probably explains their differing sensitivity to the various β-lactam antibiotics.

- Penicillin G is ineffective against Gram negative bacteria as it cannot penetrate their cell wall which contains an extra lipopolysaccharide layer.

- In gram-positive bacteria, the cell wall is almost entirely made of peptidoglycan, which is >50 layers thick and extensively cross linked,





Pharmacokinetics

- Penicillin G, its salts and methicillin are destroyed by gastric acid and are orally ineffective.
- Most of the Penicillins including repository Penicillins are administered parenterally (usually IM).
- Penicillins are chiefly excreted through kidney (90%) unchanged in urine.
- Out of which 20% is by glomerular filtration and 80% by proximal tubular secretion
- **Proximal tubular secretion of penicillin is inhibited by probenecid prolonging the effective blood level of penicillins.**

Administration and Dosages of Penicillins

- The dosage of penicillin G is usually expressed as units.
- One standard unit of penicillin is defined as the amount of antibacterial activity present in 0.6 µgm of pure crystalline standard sodium penicillin G (1 mg – 1667 Oxford units).
- The dosage of semisynthetic penicillins is expressed in mg/kg.

Penicillin	Dosage(All Species)	Route	Interval
Benzathine penicillin G	10,000-40,000IU/kg	IM(Horse); SC (cattle)	48-72 hr.
Penicillin V	15,000 IU/kg	Oral	8 hr.
Sodium penicillin G	10,000-20,000IU/kg	IV or IM	6 hr.
Procaine penicillin G	25,000 IU/Kg 10,000-20,000 IU/KG	Oral IM or SC	6 hr. 12-24 hr.
Ampicillin	5-10 mg/kg 10-25 mg/kg	IV,IM ,or SC oral	8-12 hr. 6- 12 hr.
Amoxicillin	4-8mg/kg 12 mg/kg	IM oral	12- 24 hr. 12 hr. (dog)
Cabenicillin	10-20 mg/kg	IV or IM	8-12 hr.
Cloxacillin	10 mg/kg	IM or Oral	6 hr.

Adverse Reaction and Toxicity of penicillin

- **Hypersensitive, allergic or anaphylactic reactions** (mostly along with streptomycin) are reported in dog ,cattle and horse following prior sensitization to the antibiotic,
- The clinical signs noted were Salivation, Shivering, Vomition and Urticaria in cat and dog, laboured breathing ,salivation cutaneous oedema (head and perinial region) and froth from nostril and mouth in cattle and urticaria and pruritis in horse.

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Beta-lactamases

- **Beta-lactamases** are enzymes produced by penicillin-resistant bacteria, which break the antibiotic into inactive penicilloic acid.
- They are named as beta-lactamases as they act by splitting the beta-lactam ring present in beta-lactam antibiotics, penicillins and cephalosporins.
- The enzyme is of two types: Penicillinase and Cephalosporinase.

Beta-lactamase inhibitors

- These potentiate or reestablish the antibacterial potency penicillinase sensitive penicillins.
- It is active against beta-lactamase producing organisms by inhibition of the enzyme (suicidal inhibition).
- These inhibitors are structurally similar to penicillin and act as substitutes for penicillinase (B-lactamase) causing inhibition of the enzyme.

Potentiated Penicillins

- **Potentiated Penicillins:**

  Penicillins + β-lactamase inhibitors = Potentiated Penicillins

- The combinations are:
  - Amoxicillin-Clavulanic acid **(4:1),**
  - Ticarcillin-clavulanic acid- **(15:1)** and
  - Ampicillin-sulbactam.
- Penicillins with sulbactam and tazobactum are administered IV;

  with clavulanic acid are administered orally or IV.

Eagle effect

- The Eagle effect, also known as the Eagle phenomenon or paradoxical zone phenomenon, is a term coined by Harry Eagle in 1948.
- It describes a paradoxical situation where bacteria exhibit reduced susceptibility to certain antibiotics at high concentrations, contrary to the expectation that increased drug levels would enhance their bactericidal effects.
- This phenomenon has been particularly noted with beta-lactam antibiotics like penicillin.

Mechanisms proposed

- Reduced Expression of Penicillin Binding Proteins: Bacteria may down regulate these proteins during stationary growth phases, which are not conducive to penicillin's action since it targets actively replicating cells.
- Induction of Resistance Mechanisms: High concentrations of antibiotics can trigger microbial resistance mechanisms, such as the production of beta-lactamases that degrade the antibiotic.

- Penicillins are classified as time-dependent antibiotics, meaning their bactericidal efficacy primarily depends on maintaining drug concentrations above the pathogen's minimum inhibitory concentration (MIC) for a sufficient duration during the dosing interval.
- This contrasts with concentration-dependent antibiotics (e.g., fluoroquinolones), where higher peak concentrations correlate with greater bacterial kill rates

- Ampicillin Prodrugs: -
  - Pivampicillin
  - Bacampicillin
  - Hetacillin

Cephalosporins

- These are group of Semisynthetic antibiotics.
- Derived from cephalosporin C obtained from a fungus cephalosporium.
- Initially 3 natural cephalosporins viz. cephalosporin P,N,C were isolated from fungus *Cephalosporium acremonium*
- The Cephalosporin molecule contain a **7- amino cephalosporanic acid** consisting of a **beta-lactam ring like Penicillins** & **dihydrothiazine unlike Penicillins.**

CLASSIFICATION

First Generation

- **Oral :** Cephalexin, cephradine, cefadroxil, cephalogylcin
- **Parenteral:** Cefapirin, cefazolin, cephalothin, Cephalonia.
- **Intramammary:** Cefacetrile, cefapirin, cephalonium

Second Generation

- **Oral:** Cefachlor, cefuroxime axetil
- **Parenteral :** Cefamandole, cefonicid, ceforonide, cefuroxime.
- **Intramammary:** Cefuroxime

Third Generation

- **Oral :** Cefixime, cefpodoxime proxetil, cefdinir, ceftibuten
- **Parenteral:** Cefmenoxine, ceftiofur, cefoperazone, cefotaxime, cefsulodin, ceftazidime, ceftizoxime, ceftriaxone

Fourth Generation

- **Parenteral:** cefepime and Cefpirome

Mechanism of Action

- Similar to other β-lactam antibiotics,
- The cephalosporins bind to PBPs and disrupt the cell wall.
- They are usually bactericidal and most often bind the PBP-2 and PBP-3.

- to treat meningitis
  - Ceftriaxone
  - Cefotaxime
  - Ceftazidime
  - Cefepime
- Most cephalosporins are excreted primarily in urine
- Cefoperazone and ceftriaxone - biliary excretion

Resistance

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

- These include :
  - Elaboration of ß-lactamases (cephalosporinases) that destroy cephalosporins.
  - Alterations in target proteins that reduce affinity for cephalosporins.
  - Decreased permeability to cephalosporins so that drugs do not reach their site of action in sufficient quantity.

Cephamycins

- **Cephamycins** are a group of β-lactam antibiotics
- These are closely related to cephalosporins, but have a methoxy group at position 7 of beta-lactam ring of 7 aminocephalosporanic acid nucleus
- Cephamycins are also produced by Streptomyces
- Moxalactam a synthetic cephamycin is similar in action to III generation cephalosporins.

Monobactams

Aztreonam:

- A beta-lactam antibiotic.
- Inhibits Gram negative enteric bacilli, *Haemophilus influenza* and *Pseudomonas*, but not Gram positive cocci and anaerobes.
- Used in serious hospital acquired infections of urinary, biliary, GI and female genital tract.

Carbapenems

Imipenem:

- Extremely potent and broad-spectrum beta-lactam antibiotics
- Effective against Gram positive Cocci, *Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Listeria*, anaerobes etc.
- It is resistant to most beta-lactamases
- It is rapidly hydrolyzed by the enzyme dehydropeptidase I (found in the brush border of renal tubular cells); therefore, combined with cilastin (inhibitor of dehydropeptidase).

Chloramphenicol

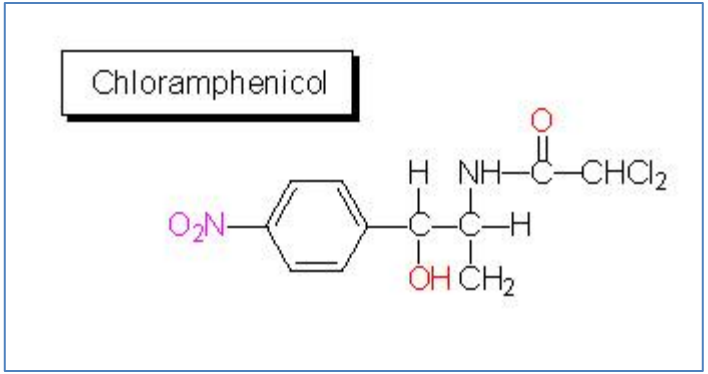
- The isolation of chloramphenicol was reported by Ehrlich, Burkholder and coworkers in the year 1947.
- It was naturally obtained from *Streptomyces* venezuelae and was the first antibiotic to be manufactured synthetically for clinical use.
- highly effective broad spectrum antibioticdrug causes severe blood dyscracias in human so carefully used in pet animals and not approved for use in food animals in many countries
- Two chloramphenicol congeners viz.

  thiamphenicol and florefenicol

  (less toxic to bone marrow)

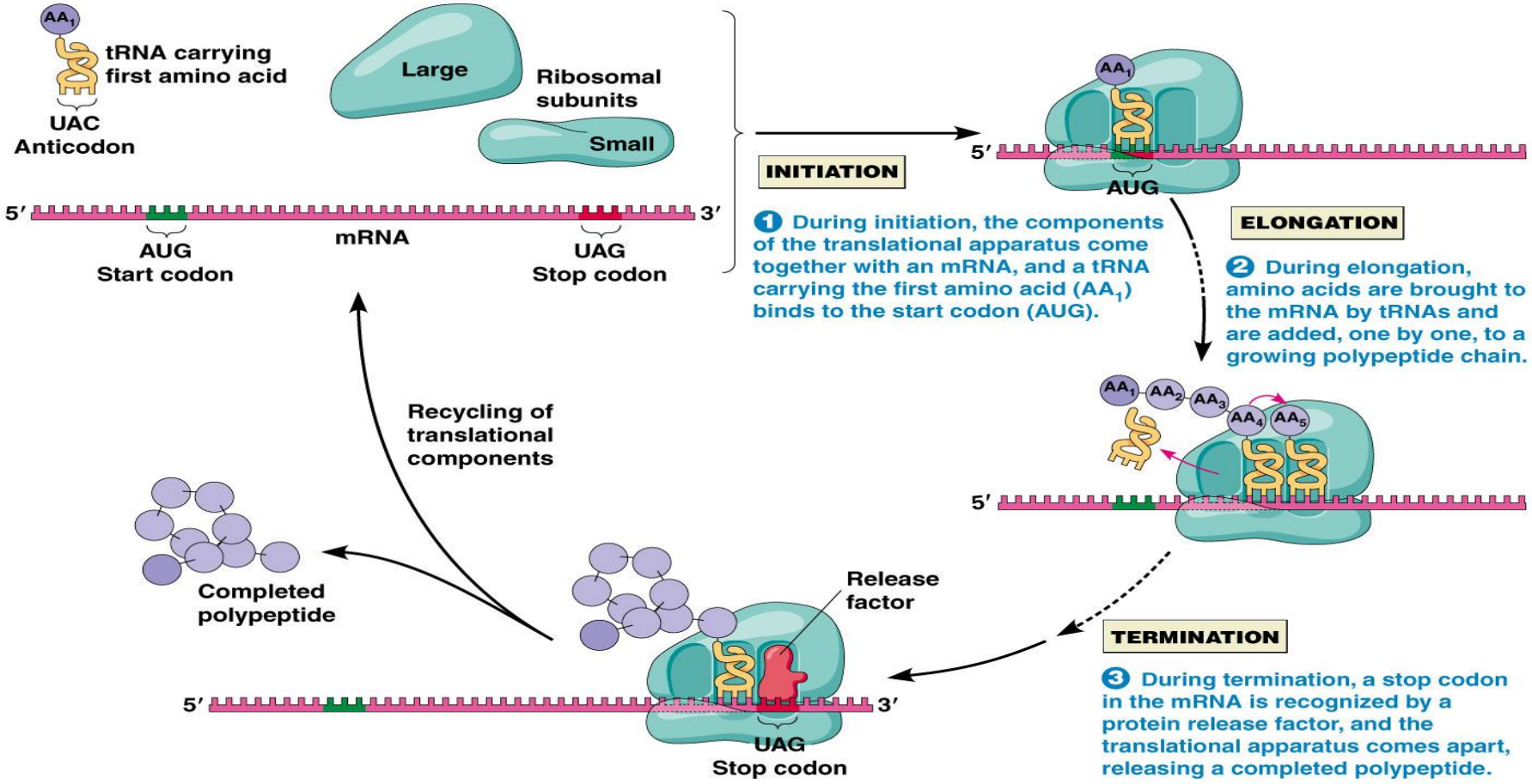
- Chloramphenicol (D-threo-2-dichloroacetamido-l -p-nitrophenyl-l, 3-propanediol) is a derivative of nitrobenzene and dichloroacetic acid.

- The p-nitro group has been implicated in the irreversible suppression of bone marrow.



Mechanism of action

- Chloramphenicol inhibits protein synthesis.
- Chloramphenicol readily penetrates into bacterial cells, probably both by passive and facilitated diffusions.
- binds reversibly to the 50 S ribosomal subunit and prevents the activity of peptidyl transferase enzyme
- interferes with **transfer of elongating polypeptide chain in the newly attached aminoacyl t-RNA** at ribosome-mRNA complex.



- Although host ribosomes do not bind as effectively as do bacterial ribosomes, some host ribosomal protein synthesis is impaired.
- At high doses, it can inhibit mammalian mitochondrial protein synthesis as well.
- Bone marrow cell are especially susceptible.

Antimicrobial spectrum

- It is a broad spectrum antibiotic effective against
  both Gram positive and Gram negative bacteria and
  several anerobes (*Bacteroidesfragilis),*
  as well as *Rickettsia*, *Chlamidia* and *Mycoplasma* like tetracycline.

- It has special efficacy against *Salmonella* including S. typhi, but less action on Gram positive cocci
- Bacterial resistance is due to synthesis of chloramphenicol acetyltransferase (plasmid mediated).

Toxicity

Chloramphenicol in man (but not Thiamphenicol & florfenicol) produces two types syndrome related to bone marrow depression.

Non regenerative anaemia

Reversible aplastic anaemia

Gray baby syndrome:

- inadequate inactivation and execration of the drug result in such toxic syndrome – vomiting flaccidity, hypothermia, and an ashen grey cyanosis followed by CV collapse and death.

- Chloramphenicol (a potent microsomal enzyme inhibitor) inhibits the metabolism of many other drugs like phenytoin, barbiturates, primidone, local anaesthetics and thereby either prolong their action or precipitate toxicity.

- Phenobarbitone and phenytoin enhance chloramphenicol metabolism, reduce therapeutic concentration and cause failure of chemotherapy.

- It should not be combined with bactericidal drugs and drugs that bind to 50S ribosomal subunit (macrolides and lincosamides).

Tetracyclines

- natural and semisynthetic antibiotics having nucleus of four partially unsaturated cyclohexane rings.
- All are obtained from soil actinomycetes
- first member of the group was chlortetracycline
- Doxycycline and minocycline are newer tetracyclines with high lipid solubility and longer duration of action.

- They characteristically fluoresce when exposed to ultraviolet light.
- Tetracyclines form insoluble chelate with divalent and trivalent cations like Ca++, Mg++, and Al+++
- Tetracyclines are stable as powders but their aqueous solutions are not stable
- propylene glycol or polyvinyl pyrrolidine and stabilizers are added to increase stability and prolong elimination half-life.

Classification

- Based on sources
- Natural:

  Chlortetracycline *(streptomyces aureofaciens*),
  Oxytetracycline (*S. rimosus*),
  Demethylchlortetracycline/demeclocycline
  (a mutant strain of *S. aureofaciens*).

- Semisynthetic: Tetracycline, methacycline, rolitetracycline, lymecycline, doxycycline and minocycline.

- Based on duration of action
- Short acting: Tetracycline,
  Oxytetracycline and
  Chlortetracycline.
- Intermediate: Demeclocycline and
  Methacycline.
- Long acting: Doxycycline and
  Minocycline
  (highly protein bound and slowly excreted).

Mechanism of action

- primarily bacteriostatic; inhibit protein synthesis by binding to 30S ribosomes in susceptible organism.
- Subsequent to such binding, attachment of aminoacyl-t-RNA to the mRNA-ribosome complex is interfered.
- As a result, the peptide chain fails to grow.
- The sensitive organisms have an energy dependent active transport process which concentrates tetracyclines intracellularly.

- In gram-negative bacteria tetracyclines diffuse through porin channels.
- The more lipid-soluble members (doxycycline, minocycline) enter by passive diffusion also (this is partly responsible for their higher potency).
- Two factors are responsible for the selective toxicity of tetracyclines for the microbes:
  - The carrier involved in active transport of tetracyclines is absent in the host cell.
  - Moreover, protein synthesizing apparatus of host cell is less sensitive to tetracyclines.

- Tetracyclines are active against:
  - both aerobic and anaerobic Gram +ve and Gram -ve bacteria,
  - Mycoplasma,
  - Rickettsiae,
  - Chlamidia and
- some protozoa like Babesia,
  - Theileria,
  - Anaplasma,
  - Coccidia
  - Entamoeba.

Pharmacokinetics

- Tetacyclines are administered orally (mainly to small animals), parenterally (mostly IM and IV) and also topically.

Absorption:

- Oral administration in carnivores the drugs are absorbed rapidly from GIT reaching peak plasma concentration within 2-4 hr which persists for 6-8 hr.

- Milk and milk products, calcium, magnesium, iron or iron preparations and antacids interfere with the absorption of the tetracyclines in the GI tract due to chelation.

- The absorption of doxycycline and minocycline is complete and highest in undergo enterohepatic cycling.
- Tetracycline should not be administered orally to ruminants as they are poorly absorbed and cause disruption of ruminal microflora.
- Chlorteracycline should not be administered IM because of severe tissue irritation and damage.
- These drugs undergo chelation with calcium and are deposited irreversibly in growing bones and teeth in young animals.

Metabolism :

- Tetracyclines undergo limited metabolism in domestic animals except doxycycline and minocycline (partly).

Excretion:

- They are chiefly excreted by kidney via Glomerular filtration and also excreted unchanged in faeces directly or through bile.
- Most tetracyclines will accumulate if renal function is impaired and increases nephrotoxicity.
- Doxycycline is an exception as it is largely excreted through the GI tract.
- They are also secreted in milk.

- Tetracyclines are deposited in growing teeth and bones and should not be used in growing animals because they cause yellowish and later brownish discoloration of teeth and suppress bone growth.

- Tetracycline should not be used with immunization programme (as they cause immunosuppression).

- Intramammary infusion of chlortetracycline is contraindicated in dry cows (Cause severe tissue irritation and subsequent fibrosis) and if infused. Cows fail to lactate after parturition (due to teat and udder tissue damage).

- Intraarticular injection of tetracyclines are contraindicated (cause severe irritation and inflammation).

- If administered by rapid IV injection, hypotension and acute collapse may occur in cattle and horses due to chelation of blood Ca^{++} and this can be avoided by slow infusion of the drug or pretreatment with IV calcium gluconate.

- Tetracyclines in high doses produce hepatotoxicity particularly in pregnant animals or those having renal abnormality.

- All tetracyclines in high doses are potentially nephrotoxic (due to decrease in host protein synthesis and anti-anabolic effect) except doxycycline and are contraindicated in renal insufficiency.

- Phototoxic dermatitis is most common with demeclocycline and doxycycline in man which is rare in animals.
- Hypersensitivity is rare.
- In human ingestion of outdated tetracyclines produces a syndrome characterized by aminoaciduria, glycosuria, polyuria and polydypsia due to proximal convoluted tubular damage (Fanconi syndrome).
- Demeclocycline induces diuresis (ADH antagonism).

Aminoglycosides

- **Aminoglycosides** are a group of natural and Semisynthetic antibiotics which contain amino sugars linked to aminocyclitol ring by glycosidic bond.
- mostly bactericidal
- The presence of amino group in the structure imparts basic nature and the hydroxyl group on the sugars provide high water solubility (poor lipid solubility) to the drugs.
- Streptomycin - the first member of aminoglycoside antibiotics discovered in 1944 by Waksman and co-workers from a strain of *Streptomyces griseus*.
- Amikacin was the first semi-synthetic aminoglycoside obtained by chemical modification of kanamycin.

Sources

- Streptomycin: *Streptomyces griseus;*
- Neomycin: *S. Fradiae;*
- Kanamycin: *S. kanamyceticus;*
- Gentamicin: *Micromonospora Purpurea;*
- Tobramycin: *S. tenebrarius;*
- Amikacin: Semisynthetic derivative of Kanamycin;
- Sisomicin: *Micromonospora inyoensis*;
- Netilmicin: Senmisynthetic derivative of sisomicin;
- Framycetin: *S. Lavendulae.*
- Aminoglycosides prepared from Streptomyces carry the suffix —mycin, Micromonospora have name ending with —micin.

Classification

- Based on antibacterial spectrum:

Narrow spectrum:

- Streptomycin and dihydrostreptomycin.
- Mainly active aerobic Gram negative bacteria (E.coli, Salmonella, pasturella spp. Brucella spp.)
- Mycobacterium tuberculosis is sensitive to streptomycin.

Broad spectrum: Gentamicin, tobramycin, Amikacin, sisomicin and netilmicin.

- Highly effective against a wide variety of aerobic (both Gram positive and Gram negative) bacteria including Pseudomonas aeroginosa.
- Gentamicin is more potent than streptomycin (MIC 4-8 times lower), but it is ineffective against M. tuberculosis.
- Amikacin and netilmicin are resistant to bacterial aminoglycoside inactivating enzymes and therefore have widest spectrum of activity including against organisms resistant to other aminoglycosides.
- Extended spectrum: Neomycin, framycetin, paromomycin and Kanamycin.

Common Properties of Aminoglycosides

- All are used as sulphate salts that are highly water soluble (stable)
- None is absorbed after oral administration
- None penetrate the brain or CSF.
- All are rapidly excreted unchanged through normal kidney by glomerular filtration
- They are exclusively used in the treatment of Gram negative bacterial infections.

- All act by interference with the protein synthesis in susceptible bacteria.
- They are bactericidal and more active at alkaline pH.
- Partial cross resistance may be seen among them.
- They have relatively narrow margin of safety.
- All share common toxicities (ototoxicity and nephrotoxicity).

Mechanism of action

- The aminoglycosides are bactericidal antibiotics, all having the same general pattern of action which may be described in two main steps:

- 1. Transport of the aminoglycoside through the bacterial cell wall and cytoplasmic membrane.

- 2. Binding to ribosome resulting in inhibition of protein synthesis.

Transport of aminoglycoside into bacteria:

- It is a multistep process.
- They diffuse across the outer coat of gram-negative bacteria through porin channels.
- Entry from the periplasmic space across the cytoplasmic membrane is carrier mediated which is linked to the electron transport chain.
- Thus, penetration is dependent upon maintenance of a polarized membrane and on oxygen dependent active processes.

- Penetration is also favored by high pH; aminoglycosides are 20 times more active in alkaline than in acidic medium.

- Bacterial cell wall inhibitors (β-lactams, Vancomycin) enhance entry of aminoglycosides and exhibit synergism.

Step II

- Once inside the bacterial cell, streptomycin binds to 30S ribosomes, but other aminoglycosides bind to additional sites on 50S subunit, as well as to 30S-50S interface.

- They freeze initiation of protein synthesis,
  - prevent polysome formation and
  - promote their disaggregation to monosomes
  -so that only one ribosome is attached to each strand of mRNA.

- Binding of aminoglycoside to 30S-50S juncture causes distortion of mRNA codon recognition resulting in misreading of the code: one or more wrong amino acids are entered in the peptide chain and /or peptides of abnormal length are produced.

- Different aminoglycosides cause misreading at different levels depending upon their selective affinity for specific ribosomal proteins.

Cidal action of Aminoglycoside

- The cidal action - based on secondary changes in the integrity of bacterial cell membrane,
- Other antibiotics which inhibit protein synthesis (tetracyclines, chloramphenicol, erythromycin) **are only static.**
- After exposure to aminoglycosides, sensitive bacteria become more permeable; ions amino acids and even proteins leak out followed by cell death.
- This probably result from **incorporation of the defective proteins into the cell membrane.**
- This reinforces the lethal action.

- The cidal action of aminoglycosides is concentration dependent, i.e. rate of bacterial cell killing **is directly related to the ratio of the peak antibiotic concentration to the MIC value.**

- They also exert a long and concentration dependent ‘post antibiotic effect’.

Adverse reactions and Toxicity

- The aminoglycosides produce toxic effect which is common to all but the relative intensity may differ.
- The main toxicities are:

Ototoxicity

Nephrotoxicity

Neuromuscular blockade

Ototoxicity

- This is the most related to dose and duration of treatment .
- The ototoxicity involves ---progressive and irreversible damage and destruction the sensory cells in the cochlea and vestibular apparatus of the internal ear.
- Vestibular damage - nystagmus, vertigo and ataxia.
- Cochlear damage -- auditory disturbances which may even lead to deafness
- Cats are particularly sensitive to vestibular toxicity.
- Streptomycin and Gentamicin are more prone to produce vestibular toxicity.
- Neomycin and amikacin cause mainly cochlear damage.
- Netilmicin is less ototoxic and therefore preferred for long term use

Nephrotoxicity

- It is due to damage of kidney tubules and this is more common in patient with preexisting kidney diseases.
- neomycin > gentamicin ≥ tobramycin ≥ amikacin ≥ netilmicin > streptomycin
- Renal damage can be reversed by immediate discontinuation of drugs.

Neuromuscular blockade

- High doses of aminoglycosides may cause neuromuscular blockade (due to chelation of calcium and reduction of Ach release from the motor nerve endings by aminoglycosides) resulting in skeletal muscle paralysis and respiratory arrest which may even lead to death.
- Neomycin and streptomycin are more prone to cause this toxic effect than Kanamycin, Gentamicin or Amikacin.
- Tobramycin is least toxic in this respect.
- The blockade can be partially antagonized by IV calcium gluconate and neostigmine.

FLUOROQUINOLONES

In 1962 nalidixic acid was discovered by George lesher during synthesis of chloroquine and was named as quinolone.

Earlier quinolones were useful only for treatment of UTI.

Fluoroquinolones are quinolone antimicrobials having one or more fluorine substitutions.

Fluorinated derivatives achieve bactericidal levels in blood and tissues so they have improved antibacterial spectrum.

CLASSIFICATION

First generation : Nalidixic acid, oxolinic acid, cinoxacin, resoxacin, Piromidic acid and Flumequine.

Second generation: Ciprofloxacin, ofloxacin, enrofloxacin, norfloxacin, difloxacin, danofloxacin, and flumequine

Third generation: Pefloxacin, marbofloxacin, Sarafloxacin

MECHANISM OF ACTION

The FQs inhibit the enzyme bacterial DNA gyrase

which nicks double-stranded DNA,

introduces negative supercoils and

then reseals the nicked ends.

This is necessary to prevent excessive positive supercoiling of the strands when they separate to permit replication or transcription.

Recent evidence indicates that in gram-positive bacteria the major target of FQ action is a similar enzyme topoisomerase IV which nicks and separates daughter DNA strands after DNA replication.

The bactericidal action probably results from digestion of DNA by exonucleases whose production is signalled by the damaged DNA.

In place of DNA gyrase or topoisomerase IV, the mammalian cells

possess an enzyme topoisomerase II (that also removes positive supercoils) which has very low affinity for FQs— hence the low toxicity to host cells.

GENERAL DISPOSITIONAL CHARACTERISTICS OF FLUOROQUINOLES

Variable but good oral absorption

Complete parenteral absorption

Good tissue distribution

Volume of distribution 2-4 L / kg.

Renal excretion by glomerular filtration and tubular secretion

Hepatic metabolism via oxidation and glucuronidation

Enterohepatic recycling

Terminal phase half-life of 2-4 hrs.

Some are eliminated unchanged (ofloxacin) and some are metabolized in liver and the metabolites (sometimes active ;enrofloxacin to ciprofloxacin) undergoes glucronidation and are mainly excreted by kidneys, both by glomerular filtration and tubular secretion.

In some cases (ciprofloxacin, pefloxacin) the parent drug as well as metabolites are mainly eliminated in bile.

Quinolones also appear in milk when administered to lactating animals. Nitrofurantion (bacteriostatic) interferes with efficacy of quinolones (bactericidal).

TOXICITY OF QUINOLONES

GI disturbances (vomiting, diarrhea etc.) neurotoxicity (convulsions, GABA antagonism) at high doses. Causes.

Fluoroquinolones are relatively safer than older quinolones.

FQs cause arthopathic/ chondro toxicity (erosion of cartilage in weight bearing joint).

Dogs are the most susceptible species (mainly in pups/growing dogs), but also occurs in young foals.

MACROLIDE ANTIBIOTICS

- bacteriostatic

- Due to their basic nature, they are concentrated in acidic fluids such as milk prostatic fluid by process of 'ion trapping'

Erythromycin is the first member discovered in the 1950s.

Oleandomycin, troleandomycin, spiramycin, josamycin, tilmicosin, and tylosin.

Roxithromycin, Clarithromycin and Azithromycin are the later additions.

MECHANISM OF ACTION

Erythromycin is bacteriostatic at low but cidal (for certain bacteria) at high concentrations.

Cidal action depends on the organism concerned and its rate of multiplication.

The action of macrolides can be divided into two processes —

- passage of macrolides into bacterial cell and
- interaction of macrolides with bacterial ribosomes.

Step I : Passage of macrolides into bacterial cells :

Sensitive gram-positive bacteria accumulate erythromycin intracellularly by active transport which is responsible for their high susceptibility to this antibiotic.

The gram-positive bacteria accumulate about 100 times more antibiotics than do gram-negative organisms.

Step II: Interaction of macrolides with bacterial ribosome:

Erythromycin acts by inhibiting bacterial protein synthesis.

It combines with 50S ribosome subunits and interferes with 'translocation'.

After peptide bond formation between the newly attached amino acid and the nascent peptide chain at the acceptor (A) site the elongated peptide is translocated back to the peptidyl (P) site, making the A site available for next aminoacyl tRNA attachment.

This is prevented by erythromycin and the ribosome fails to move along the mRNA to expose the next codon.

As an indirect consequence, peptide chain may be prematurely terminated: synthesis of larger proteins is specifically suppressed.

Tylosin:

Source: A strain of *Streptomyces fradiae.*

Its antibacterial spectrum is similar to erythromycin.

Tilmicosin:

It is mainly used in the treatment of bovin respiratory diseases associated with *Pasteurella haemolytica.*

LINCOSAMIDES

These antibiotics closely resemble macrolide antibiotics in their antibacterial spectrum, mechanism of action and clinical application.

The most important members of this group are:

lincomycin and clindamycin.

Lincomycin contraindicated in horses – causes entero colitis

Clindamycin: Antibacterial + Antiprotozoal effects

POLYMYXINS

Polymyxine B *Bacillus polymyxa*

polymyxine E (colistin) - *Bacillus colistinus*

polypeptide

antibiotics

- bactericidal,
- detergent like action on the bacterial cell membrane

- bind with bacterial cell membrane phospholipids, distort it, amino acids etc leak out and bacterial cells die.

BACITRACIN

It is another polypeptide antibiotic obtained from *Bacillus subtills*.

Its antibacterial spectrum is similar to penicillin G and is mostly limited to Gram positive bacteria and spirochaetes

It is a bactericidal drug and acts by inhibiting the formation of bacterial cell wall peptidoglycan.

binds with the pyrophosphate lipid carrier and inhibits the dephosphorylation reaction required for regeneration of the lipid carrier.

VANCOMYCIN

It is a glycopeptides antibiotic produced by *Streptomyces orientails*.

Vancomycin acts by inhibiting the synthesis of cell wall peptidglycan.

- treatment of methicillin resistant Staphylococcus aureus (MRSA)

VIRGINIAMYCIN

It is an antibiotic produced by *Streptomyces virginiae* and used in the treatment and control of dysentery in piglets as feed additive @ 100 g/ 900kg feed for 2 weeks and @ 50gm/900kg feed thereafter.

It has also growth promoting potentiality in pigs like salinomycin.

RIFAMYCINS

obtained from *Streptomyces mediterranei.*

Microsomal enzyme inducer

active against Gram +Ve organisms (notably, against intra-leucocytic *Staphylococci*), a few Gram -Ve organisms, *Mycobacteria*, some anaerobes, *Chlamydia* and antiviral activity at high concentration

They prevent the DNA dependent RNA synthesis in microorganisms by inhibiting bacterial DNA-dependent RNA polymerase enzyme.

METHENAMINE (HEXAMINE)

It is inactive as such, but decomposes in acidic urine to formaldehyde which provides antibacterial activity.

It may be bactericidal or static depending on the concentration of formaldehyde.

Acidic urine is essential for its action, so some organic acids like ascorbic or mandelic or mandelic acid are frequently administered to carnivores to produce acid urine.

It is available as methenaminemandelate that combines the antibacterial action of methenamine and mandelic acid.

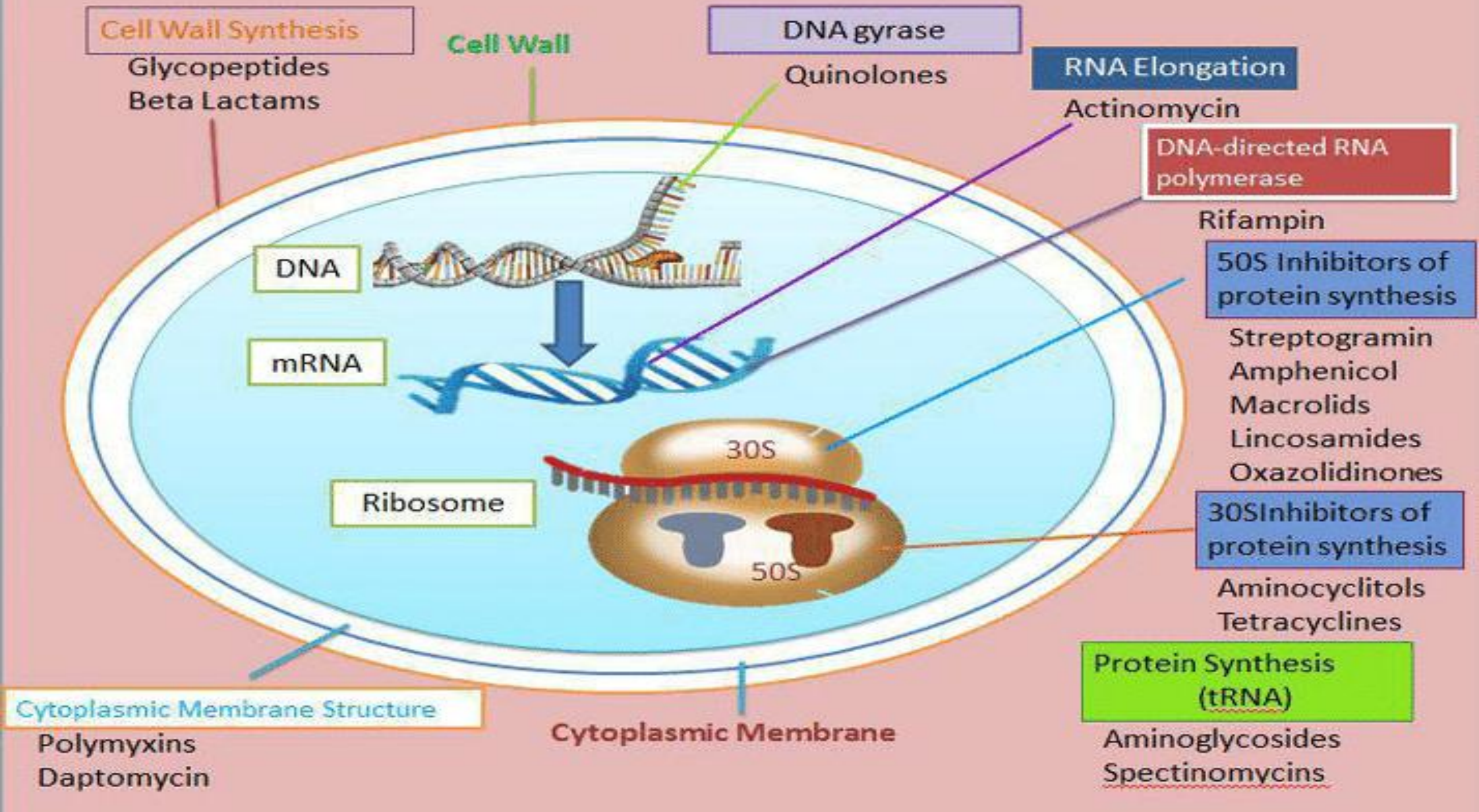
OXAZOLIDINONES

- Drug of last resort

- binding P site, inhibition of initiation complex and also translocation of peptidyl-tRNA from A site to P site

- Linezolid, Posizolid

Aminoglycosides	Streptomycin Gentamicin	Gram (-)	Inhibit Protein Synthesis (30s)
Cephalosporins	Ceftriaxone Cefepime	Gram (+)/(-)	Inhibit Cell Wall Synthesis
Tetracyclines	Tetracycline Doxycycline	Gram (+)/(-)	Inhibit Protein Synthesis (30s)
Penicillins	Ampicillin Amoxicillin	Gram (+)/(-)	Inhibit Cell Wall Synthesis
Sulfonamides	Sulfasalazine Sulfamethoxazole	Gram (+)/(-)	Inhibit Folate Synthesis
Fluoroquinolones	Ciprofloxacin Levofloxacin	Gram (+)/(-)	Inhibit DNA Replication
Macrolides	Azithromycin Erythromycin	Gram (+)	Inhibit Protein Synthesis (50s)
Carbapenems	Meropenem Ertapenem	Gram (+)/(-)	Inhibit Cell Wall Synthesis
Lincosamides	Clindamycin	Gram (+)	Inhibit Protein Synthesis (50s)
Glycopeptides	Vancomycin	Gram (+)	Inhibit Cell Wall Synthesis

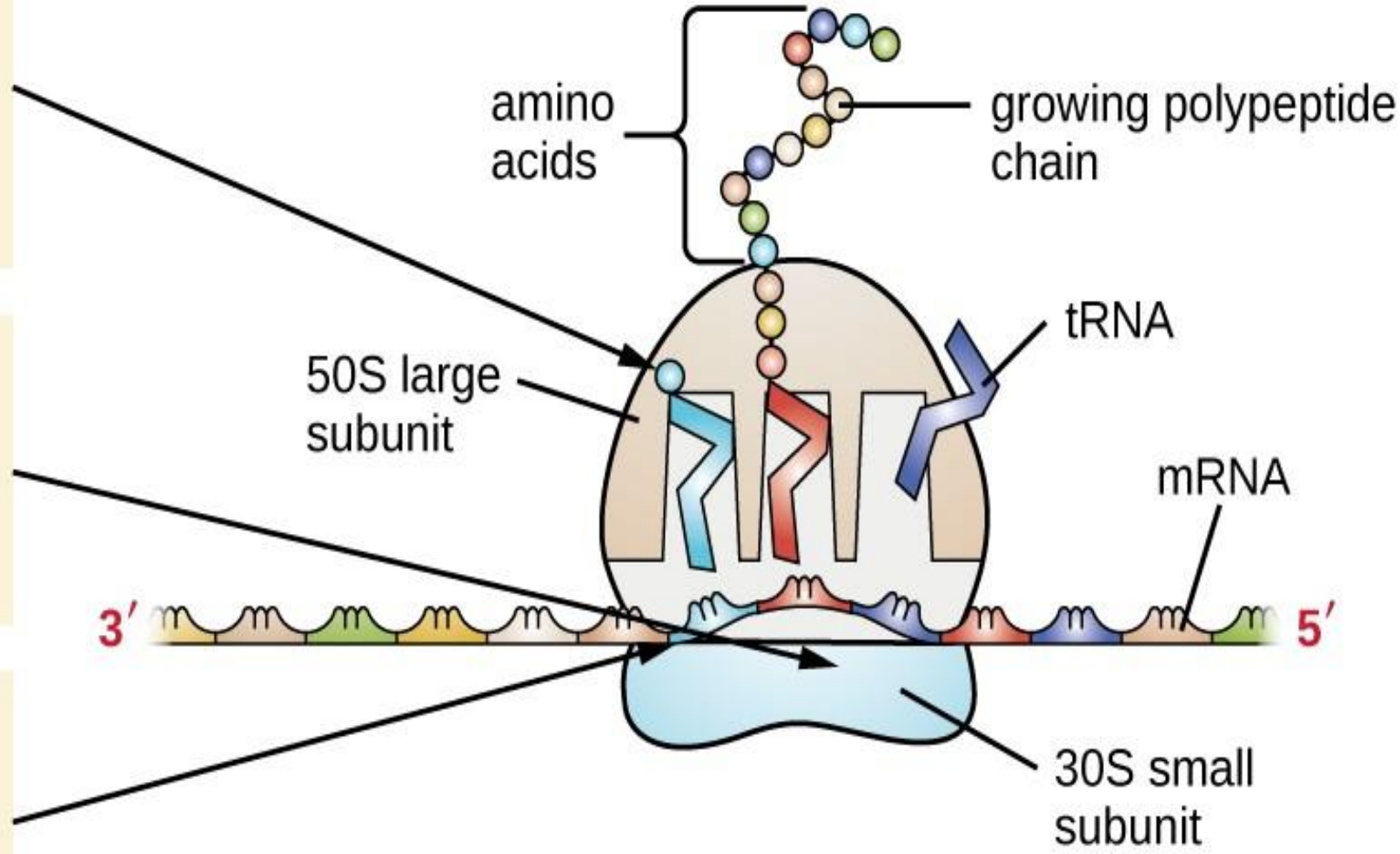

Cell Wall Synthesis
Glycopeptides
Beta Lactams
Cell Wall
DNA gyrase
Quinolones
RNA Elongation
Actinomycin
DNA-directed RNA polymerase
Rifampin
DNA
mRNA
50S Inhibitors of protein synthesis
Streptogramin
Amphenicol
Macrolids
Lincosamides
Oxazolidinones
30S
Ribosome
50S
30SInhibitors of protein synthesis
Aminocyclitols
Tetracyclines
Protein Synthesis (tRNA)
Aminoglycosides
Spectinomycins
Cytoplasmic Membrane Structure
Polymyxins
Daptomycin
Cytoplasmic Membrane

Major classes of protein synthesis–inhibiting antibacterials

Chloramphenicol, macrolides, and lincosamides
- Bind to the 50S ribosomal subunit
- Prevent peptide bond formation
- Stop protein synthesis

Aminoglycosides
- Bind to the 30S ribosomal subunit
- Impair proofreading, resulting in production of faulty proteins

Tetracyclines
- Bind to the 30S ribosomal subunit
- Block the binding of tRNAs, thereby inhibiting protein synthesis

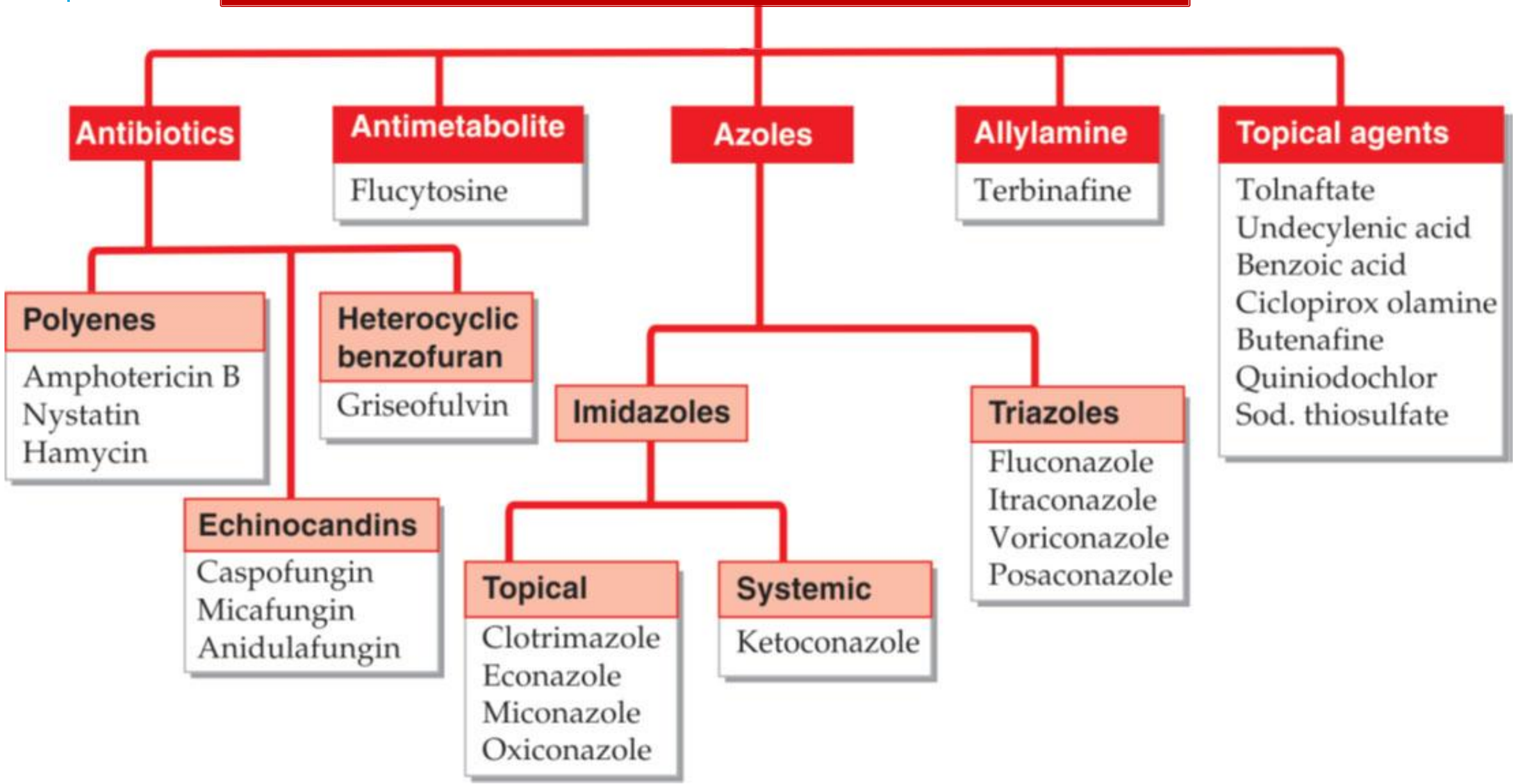


ANTIFUNGAL DRUGS

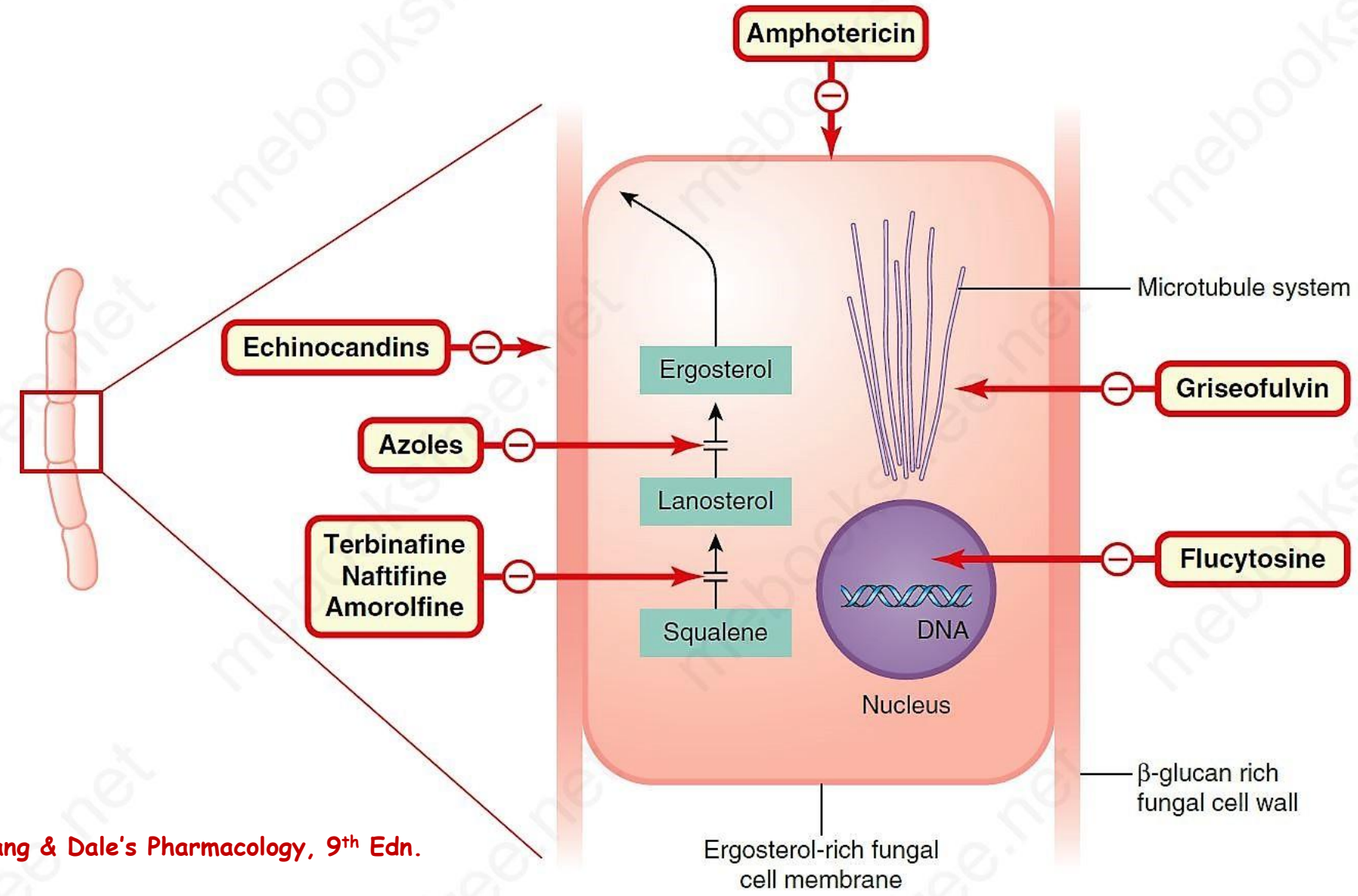
Fungicidal drugs: Destroy parasitic fungi.

Fungistatic drugs: Prevent growth and multiplication of fungi.

Classification of Antifungal Agents



Sites of action of antifungal drugs



Source: Rang & Dale's Pharmacology, 9th Edn.

ANTIFUNGAL ANTIBIOTICS

GRISEOFULVIN

Produced by *Penicillium griseofulvum.*

Mechanism of action: Fungistatic.

- Interferes with mitosis.
- Disrupts the mitotic spindle.
- Daughter nuclei fail to move apart.
- Disorients the microtubules.

AMPHOTERICIN B

A **polyene antibiotic**

Obtained from *Streptomyces nodosus.*

Mechanism of action: **Fungicidal.**

- All polyenes share a common mechanism of action.
- **Binds to ergosterol** in the fungal plasma membrane.
- **Increased permeability results, leakage of cell electrolytes, resulting in cell death (Fungicidal action).**
- The selective toxicity of amphotericin B is based on its decreased binding to the major cell membrane sterol of mammalian cells (cholesterol) as compared to that of fungal cells (ergosterol).

AMPHOTERICIN B
CONTD…

Toxicity:

- Long term toxicity: **Nephrotoxicity** is most important. Azotaemia, reduced glomerular filtration rate, acidosis, hypokalaemia and inability to concentrate urine.
- Slow progressive anaemia is also seen due to bone marrow suppression.

ECHINOCANDINS

Mechanism of action: Inhibit the synthesis of **1,3-β-glucan**, a glucose polymer that is necessary for maintaining the structure of fungal cell walls. In the absence of this polymer, fungal cells lose integrity and lysis quickly follows

Caspofungin (Obtained from *Glarea lozoyensis*)

Micafungin (Obtained from *Coleophoma empedri*).

Anidulafungin (Semisynthetic, Obtained from *Aspergillus nidulans*).

SYNTHETIC ANTIFUNGAL AGENTS

FLUCYTOSINE (5-FLUOROCYTOSINE OR 5-FC)

Synthetic antifungal agent.

Mechanism of action: **Fungistatic**

- A pyrimidine antimetabolite.
- Ineffective as such (Prodrug).
- Taken up by the fungal cells ⇨ converted to the active form, 5-fluorouracil by the fungal ***cytosine deaminase enzyme***.
- 5-FU is either incorporated in RNA disrupting protein synthesis or is converted to a related compound which inhibits DNA synthesis.
- Mammalian cells are deficient in cytosine deaminase enzyme.

5-FC CONTD…

Antifungal spectrum:

- It is a narrow spectrum fungistatic
- **Uses:**
- Not employed as the sole therapy. Rapid development of resistance limits its utility in deep mycosis.
- Flucytosine is used as adjunct therapy with Amphotericin B

Synergy between two medications.

AZOLE ANTIFUNGAL AGENTS

Fungistatic agents.

Broad spectrum of activity.

IMIDAZOLES:

Clotrimazole Econazole Fenticonazole
Ketoconazole Miconazole Tioconazole
Sulconazole Isavuconazole Posaconazole

TRIAZOLES:

Itraconazole Voriconazole Fluconazole

AZOLE ANTIFUNGAL AGENTS

Mechanism of action:

inhibit the **fungal** cytochrome P-450 3A **enzyme**, ***lanosine 14α-demethylase***,

which converts lanosterol to ergosterol, the main sterol in the fungal cell membrane

The resulting depletion of ergosterol alters the fluidity of the membrane, and this interferes with the action of membrane-associated enzymes. The net effect is an **inhibition of replication**.

KETOCONAZOLE

It was the **first azole that can be given orally to treat systemic fungal infections**.

It is well absorbed from GI tract.

Toxicity: The main hazard of ketoconazole is liver toxicity.

Inhibition of adrenocortical steroid and testosterone synthesis has been recorded with high doses

Treatment of Cushing's disease in dogs

TERBINAFINE

Highly lipophilic, keratinophilic **fungicidal** compound active against wide range of skin pathogens.

Mechanism of action – It acts by selectively inhibiting the enzyme ***squalene epoxidase***, which is involved in the synthesis of ergosterol from squalene in the fungal cell wall. The accumulation of squalene within the cell is toxic to the organism.

OTHER TOPICAL AGENTS

BENZOIC ACID:

It is bacteriostatic and fungistatic, hence used as preservative in foodstuffs.

It is the active ingredient of Whitefield's ointment or compound ointment of benzoic acid which contains 6% benzoic acid and 3% salicylic acid.

Benzoic acid is effective against *Trichophyton* infection

SALICYLIC ACID:

It has keratolytic and some fungistatic activity. So, suitable for topical ringworm treatment : It softens the crust and then acts on the organism so revealed. It is applied as Whitefield's ointment.

OTHER TOPICAL AGENTS

UNDECYLENIC ACID:

It is fungistatic esp. against *Microsporum* spp.

At higher concentrations, the acid tends to be irritant, so the zinc or copper salts are often used in combination, both to minimize this effect and to use the antifungal action of copper salts.

COPPER SULPHATE:

It is strongly fungicidal, partly by virtue of its astringent and caustic nature, partly by specific effect by the copper ion.

1 – 2% aqueous solution and 5% ointment can be used.

CLASSIFICATION OF ANTIVIRAL DRUGS

Classification of Antiviral Drugs

1. Inhibitors of Viral Nucleic Acid Synthesis:
   (a) Interfering with Transcription: Idoxuridine, Trifluridine.
   (b) Inhibitors of DNA synthesis: Acyclovir, Ganciclovir, Cytarabine, Vidarabine, Zidovudine, Ribavirin.

1. Preventing virus in host's cell (Inhibition of Assembly of the Virus): Amantadine, Rimantadine.

2. Increasing the host's resistance: Interferons, Gamma-globulins.

NUCLEOSIDE ANALOGS

(ACYCLOVIR, VALACYCLOVIR, PENCICLOVIR, FAMCICLOVIR, GANCICLOVIR,IDOXURIDINE, CYTARABINE, RIBAVIRIN, ZIDOVUDINE)

ACYCLOVIR:

Acyclovir is prototypic nucleoside analog of purine (deoxyguanosine).

Acyclovir acts selectively against herpesviruses.

Valacyclovir is a prodrug that is itself inactive but is rapidly metabolized to its active form, acyclovir, after oral absorption.

Mechanism of action: Acyclovir is converted to its active form acyclovir triphosphate in infected cells by the viral thymidine kinase with 200 times greater efficiency than mammalian enzyme. Its inhibits viral DNA polymerase by competing with deoxyguanosine triphosphate.

ANTIHERPESVIRUS AGENTS: NUCLEOSIDE ANALOGS
CONTD…

IDOXURIDINE:

- Idoxuridine is thymidine analog that is only active against DNA viruses, primarily herpesvirus and poxvirus.

CYTARABINE & VIDARABINE:

Cytarabine (also known as cytosine arabinoside) and vidarabine, are nucleoside analogs of cytosine and adenine, respectively.

ANTIHERPESVIRUS AGENTS: NUCLEOSIDE ANALOGS
CONTD…

RIBAVIRIN:

Ribavirin is a guanosine analogue that inhibits the replication of a wide range of RNA and DNA viruses in vitro.

ZIDOVUDINE, ADEFOVIR:

Zidovudine is a thymidine analog

Selectively inhibits viral reverse transcriptase, preventing viral RNA from making a DNA copy of itself.

FOSCARNET

It inhibits DNA and RNA polymerases as well as reverse transcriptase.

Oseltamivir: competitive inhibitor of the enzyme neuraminidase, which influenza viruses

AMANTADINE, RIMANTADINE

Rimantadine has approximately 3 - 4 times greater in vitro activity against influenza A than amantadine.

Their antiviral activity involves inhibition of late-stage assembly of the virus.

* Interferons interfere with viral multiplication and viral protein synthesis (transcription and translation).

ANTITUBERCULAR DRUGS

Tuberculosis :chronic granulomatous disease.

Mycobacterium bovis -- Ruminants.

M. bovis and M. avium -- Dog.

M. avium -- Pig.

Sheep and horse are rarely affected.

CLASSIFICATION

First Generation

- Streptomycin,
- Isoniazid/isonicotinic acid hydrazide (INH or H),
- Rifampicin,
- Ethambutol (E),
- Pyrazinamide (PZ) and
- Thiacetazone (T).
- Paraaminosaliclic acid (PASA)

Second Generation

- Capreomycin (A),
- Cycloserine (C),
- Kanamycin (K),
- Ethionamde (Et).
- These drugs low anti TB efficacy, but relatively high toxicity.

Fluoroquinolones are also used under reserve category anti-TB drugs.

ISONIAZID

Isoniazid is chemically related to MAO inhibitor iproniazid.

MOA:Exerts bactericidal effect

by inhibiting the synthesis of mycolic acids (essential cell wall constituents in *Mycobacterium*) and

also causing damage to cell membrane by inhibiting phospholipids synthesis.

RIFAMPICIN

semisynthetic derivative of rifamycin B (*Streptomyces mediterranei*).

It has bactericidal action on ***M. tuberculosis, M. para-tuberculosis*** and other subpopulations of TB bacilli.

It acts best on slowly or intermittently dividing bacilli as well as on many atypical mycobacteria.

Both extra and intracellular organisms are affected.

MOA: acts by inhibiting protein synthesis in mycobacteria by inactivating DNA-dependent RNA synthesis.

One of the most effective anti-TB antibiotics; also effective against many other Gram negative or Gram positive bacteria, including *Mycobacterium laprae.*

It imparts orange color to saliva, sputum, tears and sweat.

Adverse effect: Hepatitis.

ETHAMBUTOL

Ethambutol (d-Ethambutol) is a commonly used anti-tubercular drug, possess selective tuberculostatic activity.

MOA: Not fully understood but it has been found to inhibit arabinogalactan synthesis and to **interfere with mycolic acid synthesis and cell wall formation;** ineffective against other bacteria.

STREPTOMYCIN

It was the **first clinically** useful anti- tubercular drug.

It is an aminoglycoside antibiotic obtained from *Streptomyces griseus.*

It is tuberculocidal but less effective than Isoniazide & Rifampin.

It acts only on extracellular bacilli (poor penetration into cells).

PARAAMINOSALICYLIC ACID (PAS)

Paraaminosalicylic acid (PASA) exerts **anti PABA activity like sulfonamides;** has no antipyretic or analgesic or anti-inflammatory action of salicylic acid.

Least active drugs, only delay the development of resistance.

It is tuberculostatic drug active only on TB bacilli and not on other bacteria.

Anthelmintic

Introduction

- **Anthelmintic** are drugs used to either kill (vermicide) or expel (vermifuge) the parasitic worms or helminths that inhabit GI tract and other tissues and organs of the body.

- Vermicide: When Anthelmintic kill the parasitic worms.
- Vermifuge: When Anthelmintic remove the parasitic worms from GI tract by temporarily paralysing them they are called vermifuges

- In this case purgation is required for elimination of worms.

Ideal Anthelmintic

- Should have **high efficacy:**
  - An ideal anthelmintic should have high level of anthelmintic activity.
  - The efficacy is said to be good if it removes 95% of a gastro-intestinal nematodes from ruminant spp.
  - If it removes only 70% of the worm burden it is considered as a poor anthelmintic.
  - It should have effect on both adult and larval stages of worms.
  - If it is effective only against adult worms it is repeated to eliminate adult worms that were unaffected during the first dose.
  - 100% removal of worm load also eliminates the source of antigenic stimulation and animal looses the acquired resistance to parasite.

Classification of Anthelmintics

Based on type of helminthes against which they are effective.

- Antinematodal drugs: Drugs effective against nematodes or roundworms (R).
- Anticestodel drugs: Drugs effective against the cestodes or tapeworms (T).
- Antitrematodal drugs: Drugs effective against the trematodes or flukes (LF).

General Mode of Action of Anthelmintics

Most anthelmintic can be classified into two major categories on the basis of their mechanism of actions.

- Drug affecting the energy production of the parasites
- Drugs Affecting and Neuromuscular System of the Parasites, (Paralysis)

Drug affecting the energy production of parasites

- Biochemical reactions associated with the energy production of the parasites are the most important sites of drug action.
  - Inhibitors of fumarate reductase enzyme and mitochondrial reactions.
  - Inhibitors of tubulin polymerization and glucose uptake.
  - Inhibitors of electron transport mediated oxidative phosphorylation in the mitochondria of the parasites.
  - Inhibitors of glycolysis.

Drugs Affecting and Neuromuscular System of the Parasites

Anthelmintics

↓

Neuromuscular system affected

↓

Inhibiting the destruction of NT or mimicking/enhancing the action of NT or antagonizing the action of NT

↓

Ultimate result is either spastic or flaccid paralysis of the parasite

↓

Paralysed parasite expelled by the normal peristaltic movement of the host.

- The drugs affecting neuromuscular system are classified as below:
- **Cholinergic agonists**
- **Anticholinesterases**
- **Muscle hyperpolarizers**
- **Potentiation of inhibitory neurotransmitters (GABA agonists).**
- **Others**

Other actions:

1. Drugs affecting parasite reproduction: Phenothiazine and benzimidazoles.

2. Drugs affecting the permeability of the cells and cause vacuolation of the tegument

– Praziqunatel and diamfenetide.

3. **Drugs cause disruption of tegument of parasites:**

- Bunamidine, epsiprantel and praziquantel.

4. **Drugs act by unknown mechanism:**

- Bitoscanate, paromomycin, phenothiazine and triclabendazole.

Antinematodal drugs

Simple Heterocyclic Compounds

Piperazine and its Derivatives:

Spectrum

- They are good for ascarid and nodular worm infections of all the species of domestic animals (100% efficacy).
- Moderate for pinworm (Oxyuris sp.) infections, variable effect on other worms like hookworms and stronglyes.
- No effect on whipworms (Trichuris sp), tapeworms and flukes.

MOA:

- Competitive or non-depolarizing type of neuromuscular blockade
- Blockage of succinic acid production by the worm
- Reversible inhibition of neuromuscular transmission in the worm by acting like GABA
- Results – flaccid paralysis – loss motility and ability to maintain position in GIT-passively swept along with intestinal peristalsis.

PHENOTHIAZINES

- The exact mechanism by which phenothiazine destroys the worm is not known, but be due to:

  - Inhibition of certain vital enzymes (succinoxidase, glyoxalase, cholinesterase etc.) in the tissue, cells of the parasites.

  - The drug affect the parasites reproduction and low level of feeding of the drug to animals inhibit the egg production of the parasite remaining in the Gl tract of the host.

  - Ultimately reduce pasture contamination by the helminth eggs, forms the basis of control measure in cattle and sheep management.

Toxicity:

- Cattle and swine are more susceptible. Horses are most susceptible.

- Accumulation of unmetabolized phenothiazine sulfoxide (photodynamic agent) causes photosensitization keratitis

- Manifested by -- ulceration of cornea and blindness, reddening and thickening of ear and muzzle and development of scab.

Benzimidazoles

- These have broad spectrum of antihelmintic activity, high degree of efficacy, good margin of safety and have versatility of administration.

- The first benzimidazole introduced in 1960, was thiabendazole (TBZ).

Mode of action:

All the benzimidazoles act on parasites by interfering with their energy metabolism:

- All benzimidazoles except mebendazole and flubendazole, are inhibitors of fumarate reductase enzyme system and thereby inhibit the generation of mitochondrial ATP.

- Mebendazole and flubendazole primarily act by inhibiting glucose transport
- They bind to free beta-tubulin, inhibiting its polymerization and thus interfering with microtubule-dependent glucose uptake.

- In absence of glucose there is depletion of the worm's glycogen reserve, which renders its unable to produce ATP necessary for survival. But these two do not inhibit fumarate reductase system.

- The primary site of action of cambendazole and fenbendazole is fumarate reductase inhibition.

- Thiabendazole also inhibits egg production by helminths by inhibiting protein synthesis.

Albendazole

- The drug is metabolized to the sulphones and sulfoxide which may provide the liver fluke and tapeworm activity

- High doses may be embryotoxic and teratogenic.

Cambendazole (R, T):

- Mainly used to treat pig and avian roundworms embryotoxic and teratogenic.

Fenbendazole (R, T, LF):

- No embryotoxicity.
- For Ascarids in horses and swine and Moniezia in ruminants @ 10mg/kg.
- Effective against GI nematodes and lungworms.
- Embrytoxic and teratogenic.

Flubendazole (R):

- Mainly used to treat pig roundworms, tape worms (including larvae).
- It has some antifilarial activity.
- No embryotoxicity.

Oxfendazole (R, T, FL):

- Oxfendazole is the sulfoxide metabolite of fenbendazole and responsible for the activity of both these anthelmintics.

Oxibendazole (R):

- Usually employed as horse anthelmintic.
- No teratogenic or mutagenic effects.
- Mainly used in sheep.
- It is an antitrematodal drug.

Luxabendazole (R, FL):

- No teratogenic or mutagenic effects.
- Mainly used in sheep.
- Dosage: Oral: 7.5 mg/kg (10 mg/kg for flukes).

- **Triclabendazole (FL):** It is an antitrematodal drug.

- Parbendazole, cambendazole and albendazole produce a teratogenic effect

- Mebendazole, fenbendazole, oxfendazole, flubendazole, luxabendazole and thiophanate are free from teratogenic effects.

Benzimidazole Pro-Drugs

- These compounds are metabolised in vivo to produce benzimidazoles and need to be administered at doses high enough to produce sufficient active metabolites.

- Their mode of action, pharmacokinetics and spectrum of activity are similar to those of benzimidazoles.
- These drugs are: **Febantel, Netobimin, Thiophanate**

Febantel (R):

- It is a precursor of fenbendazole. Effective against GI nematodes.

Netobimin (R,T,FL):

- It is a pro drug of albendazole.
- Effective against GI nematodes, their larvae, tapeworms and flukes.

Thiophanate (R):

- It products the metabolite lobendazole.
- Active against most nematodes of farm animals.
- Only orally as drench, or as powder or granules in feed.

Imidazothiazoles

Butamisole Hydrochloride:

- It is an injectable anthelmintic used in dogs to treat whip worm (*Trichuris vulpis)* and hookworm *(Ancylostoma caninum)* infections.

Tetramisole and Levamisole:

- Tetramisole is a racemic mixture of two isomers and the anthelmintic activity of mixture rested almost solely with the l-isomer, levamisole.

- Chemistry: Levamisole is the levo-isomer of dl-tetramisole.

- Spectrum: Levamisole is a commonly used antinematodal drug
- The drug affects the neuromuscular system of the parasite by acting as cholinergic agonist
- At high concentration, levamisole, like benzimidazoles interfere with carbohydrate metabolism by inhibiting fumarate reductase enzyme system.

- Host immune System: Levamisole modulates immunity of the host through stimulation of cell mediated immune reactivity Enhancing the rate of T-lymphocyte differentiation and proliferation,

Tetrahydrophyrimidines

Pyrantel:

- It is used as tartrate or palmoate salts.
- Broad-spectrum drug against Sheep cattle, swine, horse and dogs.
- MOA: A cholinergic agonist. sustained muscle contraction and paralysis of nematodes
- Pinworm infection of lower digestive tract in dogs.

Morantel:

- It is a methyl ester of pyrantel.
- Principallly morantel tartrate but also the fumerate salt is used as veterinary anthelmintic.
- The salts of morantel have greater anthelmintic activity than the pyrantel.
- A 4% ointment of the tartrate salt is used to treat Thelazia eye infections of cat.

OP Compounds

- The OP compounds were originally developed as systemic insecticides.
- Subsequently they are found to have also some anthelmintic property, but their safety is often poor.

- The compounds used in farm animals are-
  coumaphos, crufomate, haloxan and naptholphos, and
  In horse, dog and cat-dichiorvos and trichlorphon.
- MOA: Inhibition of acetylcholinesterase (Ache) enzyme.

Macrocyclic lactones

Avermectins

- **Avermectins** produced by the fermentation of actionmycete, Stryptomyces avermitilis
- The avermectins in commercial use are ivermectin, abamectin and doramectin
- Bind to glutamate gated chloride channel causing hyperpolarization, paralysis and death

Ivermectin: It is a very potent nematocide and ectoparasiticide (endectocide) by oral and parenteral routes.

Milbemycin D:

- It is a natural product of *Streptomyces hygroscopicus sp. Aureolacrimosus*, and only used for treating dogs.
- It is active orally against dog roundworms and prophylactic against heartworms at higher monthly doses.
- Higher doses cause neurological disorders in Collie breeds of dogs.

Drugs acting against Heartworms

Thiacetarsamide sodium and melasormine: arsenic based

- Chemically it is an arsenical compound and is the only drug used for the elimination of adult heartworms in dogs.
- The drug does not affect the circulating microfilariae.
- Mode of action: The drug interferes with the energy production of the parasite by inhibition of glycolysis.

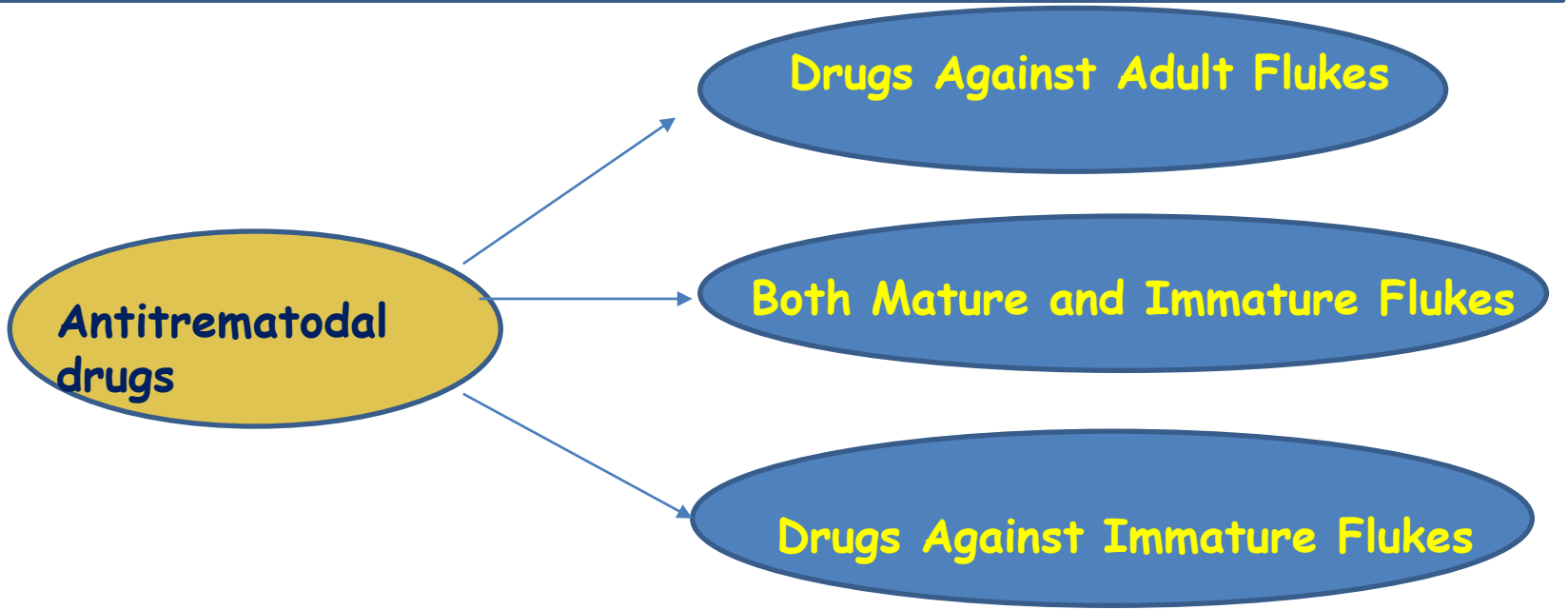
Disophenol (Ancylol):

- Chemically it is 2,6-diiodo-4-nitrophenol.
- It is an injectable antihookworm compound used in dogs and cats.

Hygromycin B:

- This is an antibiotic obtained from *Streptomyces hygroscopicus* with anthelmintic activity.
- Hygromycin B is anthelmintic antibiotic

Classification



Drugs Against Adult Flukes

Carbon tetrachloride (CCl_4):

- First effective drug for treatment of F. hepatica (1920).

- The anthelmintic action of CCl_4 is thought to be indirect through its metabolites or by inducing formation of toxic methylsterol in the host liver due to interference with the cholesterol biosynthesis.

- **Carbon tetrachloride** —(in liver)→ **Methylsterol**

- In the host - methylsterol is an intermediate metabolite in biosynthesis of cholesterol.

- CCl_4 blocks the cholesterol biosynthesis at a point that results in the formation and accumulation of toxic methylsterols in the liver, bile and urine of treated animals.

- It also uncouples oxidative phosphorylation in the mitochondria and interferes with anaerobic generation of ATP by the flukes.
- This results in death of the flukes.

- After oral administration CCI_4 is absorbed in the intestine (increased by fats and oil), metabolized in liver and the active metabolite is excreted in bile and urine.

- So the adult flukes (12 weeks or older) living in the bile ducts are killed but the immature flukes living in the liver parenchyma are not affected.

Hexachlorophene (Distodin):

- It is used in the treatment of mature liver fluke infections in human and ruminants and cestode infection in canines.

- The drug is 100% effective against adult *F.hapatica* and *F. gigantic* in sheep and cattle.

Bithinol sulfoxide:

- Besides anticestodal properties, bithinol and its sulfoxide has excellent efficacy against rumen and liver flukes
- Bithionol sulfoxide @30mg/kg + Hexachlorophene @ 50 mg/kg:

  100% effective against mature *F.hepatica* in cattle and sheep.

Oxyclozanide:

- It is a salicylanilide compound having fasciolicidal activity.
- *In Vivo*, it is only active against adult liver flukes that live in the bile duct.
- Like hexachlorophene and nitroxinyl, It is also not effective against immature flukes because of protein biding in blood.

Rafoxanide:

- Effective against adult and young (6-10 weeks old) liver flukes in sheep.

Clorsulon:

- Oral fasciolicide adult and young immature liver flukes (6-8 weeks old).

- MOA: Embden-Myerhop glycolytic pathway in the parasite and deprives the fluke of essential metabolic energy.

Closantel:

- Closantel has a broad range of anthelmintic activity, affecting both endoparasites as well as ectoparasites (endectodcide) of animals.
- The drug is effective against adult and juvenile (6-10 weeks old) liver flukes, blood sucking nematodes, parasitic larvae of files and to some extent against tapeworms, mange, mites and ticks.

Benzimidazoles:

- Highly effective against adult *F.hepatica* and *Fascioloides* magna in sheep and cattle and used therapeutically.

Drugs Against Immature Flukes

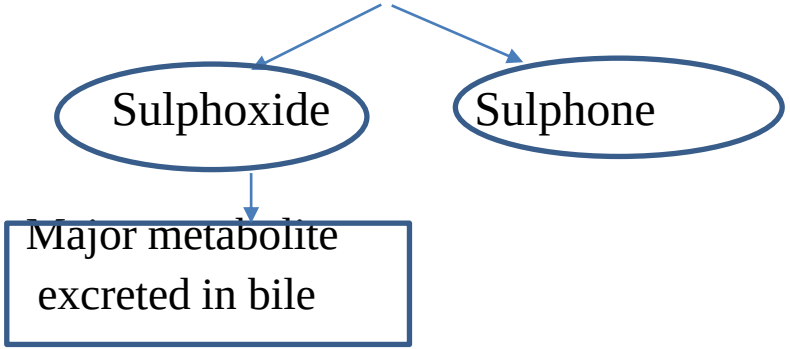
Diamfenetide: Exceptionally high activity against the immature stages of liver flukes especially in sheep and comparatively less activity against adult flukes.

- De-acylation in the liver of the host by hepatic enzymes active amine metabolite is formed in the hepatic parenchyma which is responsible for its activity.

Both Mature and Immature Flukes

Triclabendazole:

- It is highly potent against liver fluke *F. hepatica* from day old to adult.
- But it has no antinematodal activity.
- Mode of Action: Not known. Different from that of other benzimidazoles.
- Pharmacokinetics: Triclabendazole



- **Diamfenetide :** Exceptionally high activity against the immature stages of liver flukes especially in sheep and comparatively less activity against adult flukes.

- **Triclabendazole** is highly potent against liver fluke *F. hepatica* from **day old to adult.**

- **Hexachlorophene (Distodin)**: The drug is 100% effective against adult *F.hapatica* and *F. gigantic* in sheep and cattle.

Anticestodal Drugs

- Natural compounds
- Inorganic compounds and
- Synthetic organic compounds.

Anticestodal Drugs

These are the drug effective against **cestodes or tapeworms** and are of two types:

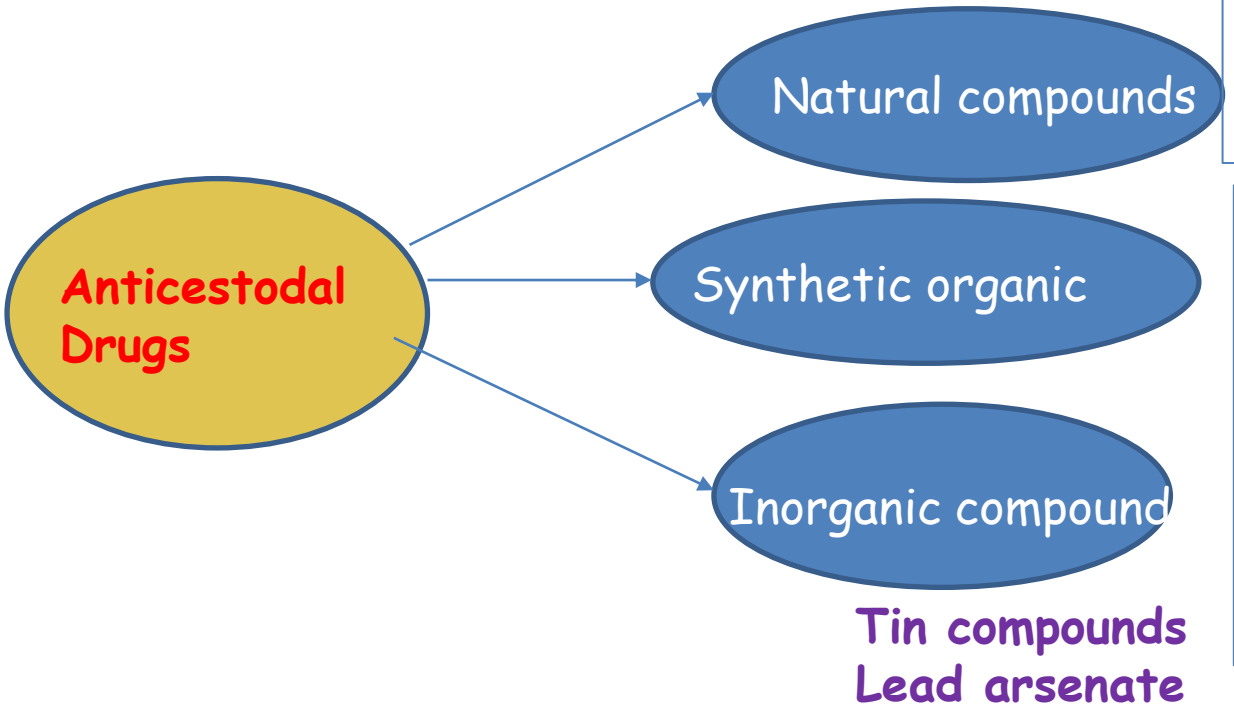
Taeniafuges:

- These drugs simply cause **expulsion of tapeworms**.
- They generally **paralyze the tapeworm** and are combined with purgative to facilitate expulsion.
- e.g. older natural organic anticestodal drugs like arecoline.

Taenicides:

- They cause actual death of the tapeworms in situ. e.g. synthetic organic compounds like bunamidine.

Classification



Arecoline hydrobromide: Areca catehu

- Against all tapeworms of dogs (*Taenia*, *Dipylidium)* including Echinococcus

- It has two fold action. Act as cholinergic agonist, paralysis detachment of the worm and also increase the peristaltic movement of the intestine so that the detached worm is expelled by purgation.

Synthetic organic compounds

Bunamidine hydrochloride:

- Good activity against all tapeworms of dog and cat including *Echinococcus granulosus.*

- MOA: disrupt the tegument of the parasite resulting into reduced rate of glucose uptake and ultimate death of the parasite.

Niclosamide:

- Tapeworm infections (mainly for Taenia) of dog, cat and man but it has poor efficacy against *Echinococcus* and variable for *Dipylidium*

- Safe for all stages of pregnancy and in debilitated animals
-
- Niclosamide is extensively used as a taenicide both in human and **vety. Medicine.**

Dichlorophen:

- It is mainly used as a narrow spectrum taenicide in veterinary medicine.
- It is effective against *Taenia* and Dipylidium in dogs and cats.
- But it is ineffective against *Echinococcus*, thus it is not the drug of choice for this tapeworm.
- The drug has bactericidal and fungicidal properties.

Hexachlorophene:

- It is mainly used as an antitrematodal drug for the treatment of liver fluke infection in sheep and cattle.

- The main anticestodal use of this drug is for the control of chicken tapeworms, especially of *Raillietina cesticillus*.

Resorantel:

- It is an anticestodal for ruminants
- It is highly effective against *Moniezia* in both sheep and cattle and against *Thysaniezia gardi* in sheep
- 90% efficacy in sheep and cattle against adult and immature rumen flukes *(Paramphistomum spp.).*

Bithionol:

- It has anthelmintic as well as bacteriostatic and antifungal activities.

Bithionol sulphoxide:

- The special advantage of this drug is that it has equal anticestodal efficacy to bithionol in dogs, sheep at lower therapeutic dose level of 60 mg/kg.

Uredophos:

- A OP compound
- The most important feature of the drug is that it is 100% efficacy against *Dipylidium caninum* that is resistant to most other anticestodal drugs excepts praziquntel

Praziquantel:

new broad spectrum anthelmintic effective against all species of Schistosomes pathogenic to humans and has unique, extremely high activity wide range of adult and larval cestodes of both animals and man *(*including *Cysticercosis).*

Benzimidazoles:

The cestocidal benzimidazoles are:

- Mebendazole:

  Taeniasis in Dog and Cat: @ 22 mg/kg/day for 5 days;
  For adult Echinococcus @ 160 mg/kg.
  For Moniezia in ruminants: @ 20 mg/kg.

- Fenbendazole:
  - Taeniasis in Dog and Cat: @ 50mg/kg/day for 3 days.
  - Both drugs are ineffective against D. caninum.

- Oxfendazole, Cambendazole and Albendazole:

  For Moniezia in ruminants: @ 7.5-15 mg/kg.

ANTIPROTOZOAL DRUGS

Disease	Therapeutic drug
Anaplasmosis	Imidocarb, tetracyclines
Babesiosis	Trypan blue, Acriflavin, Diminazene, Amicarbalide Imidocarb, Phenamidine
Theileriosis	Parvaquone, Buparvaqone, Tetracycline
Trypnasomiasis	Suramin, Trypan blue, Diminazine, Quinapyramine
Rickettsiae	Tetracycline

- ANTI TRYPS
- Antrycide prosalt: 5mg/kg b/w S/c
  - Quinapyramine sulphate- Therapeutic agent
  - Quinapyramine chloride- prophylactic agent
- Suramin: 8-10 mg/kg b/w
- Diaminazine aceturate: 3.5-7 mg/kg
- Homidium bromide: 1mg/kg
- Isometamidium chloride: 0.5-1 mg/kg
- Melasormine in Camels: 2.5mg /kg

ANTICOCCIDIAL

- Ionophores : Lasalocid, Monensin, Narasinm Salinomycin, Semduramicin
- Chemicals - Quinolone drugs (Decoquinate and nequinatem buquinolate) - Pyridones (Meticlorpindol) - Sulphonamides - Amprolium Diclazuril, Halofuginone, and Robenidine, Nicarbazin

ANTISEPTICS AND DISINFECTANTS

- Sterilization: destroys or eliminates all forms of life, especially microorganisms.
- Disinfection: The killing of pathogenic organisms by direct application of
- physical or chemical agents
- Disinfectant: An agent, usually chemical, that frees from infection by destroying the disease causing microorganism. This refers to substances applied to inanimate objects.
- Antiseptics: A substance that prevents or arrests the growth or action of micro organism on living tissue either by inhibiting their activity or by destroying them.

- Oxidizing agents: H_2O_2, $KMnO_4$, Chlorine, Iodine , Benzoyl peroxide (Keratolytic)
- Reducing agents - Formaldehyde, Glutaraldehyde, Sulphur dioxide
- Acids and Alkalis - H_2SO_4, NaOH, Boric acid, Na_2Co_3, Benzoic acid, Quick lime, Salicylic Acid
- Alcohols - Ethyl alcohol (70%), Isopropyl alcohol (50%)
- Phenols and cresols
- Phenols: First disinfectant and antiseptic used by Joseph Lister in 1867
- general disinfectant(1-2% solution) and chemical sterilizer (5%)
- standard to measure the effectiveness of other disinfectants and antiseptics - phenol coefficient.

Dyes - Acriflavine, Gentian violet

Detergents

Anionic - soap

- Sodium lauryl sulphate
- Ca and Ammonium mandelate

Cationic - Quarternary ammonium compounds

- Cetrimide
- Benzalkonium chloride

Chlorhexidine hydrochloride - 0.5% alcoholic or 1% aqueous solution

INDIGENOUS PLANTS

- *Rauwolfia serpentina*: Reserpine – Antihypertensive
- *Vinca rosea*: Vincristine and Vinblastine - Anticancer drug
- *Withania somnifera*: Somniferine – Immunostimulant
- *Leptadenia reticulata*: Laptadine – Galactagogue
- Atropa belladona: Atropine – Anticholinergic
- *Gingiber officinalis*: Gingerol - Carminative and Stomachic
- *Ricinus communis*: ricin - Purgative

Anti neoplastic drugs

- ALKYLATING AGENTS:

* Cyclophosphamide: converted to aldophophamide

- Toxicity - Damages the bladder, Necrotising haemorrhagic cystitis
- Treatment : Acetyl cysteine and MESNA

* Melphalan

*Chlorambucil

* Busulfan : Toxicity – lung fibrosis (Busulfan lungs)

* Lomustine

* Mechloethamine

* Streptozocin: mainly treatment for tumours of β cells of pancreas

ANTIMETABOLITES

- **Folic acid analogues – Methotrexate** – inhibition of enzyme Dihydrofolate reductase
- **Pyrimidine analogues:**
  - **Cytarabine/Cytosine arabinoside**
  - **5-Flurouracil[5-FU]**
- **Purine analogues**
  - **6-Mercaptopurine** - structural analogue of natural purine hypoxanthine
  - **thioguanine**

Mitotic Inhibitors

- **Vinca alkaloids-** vinca rosea/*Canthranthus rosea* plant
- Blocks mitosis in metaphase, m-phase specifc
- Vincristine: Dose rate-In Dogs and cats-0.5-0.75mg/m2, IV bolus 0.025mg/kg
- Possesses immunosuppressant action, neurotoxicity
- Vinblastin: Dose rate-2-2.5mg/m2, I/V

- **Taxanes/Inhibitors of microtubule disassembly :** **Paclitaxel-** Source- Bark of pacific west yew plant-*Taxus brevifolia*
- **Epipodophyllotoxins**-Contains 2 imp. Cytotoxic drugs
- Etoposide, Teniposide
- Prepared from Podophyllotoxin, a toxic extracted from mandrake plant (*Podophyllum peltatum*)
- Enzyme: L asparginase – G1 phase specific

Antitumor antibiotics:

Doxorubicin

adverse effects including myelosuppression, GI disturbances, cardiotoxicity, hypersensitivity, alopecia and extravasation injuries.

Daunorubicin

Dactinomycin/Actinomycin D

Miscellaneous:

Glycopeptide – Bleomycin – lung toxicity

Platinum compounds: Cisplatin, Carboplatin

- **Anti estrogens** – **tamoxifen** - estrogen dependant mammary tumors
- **Antiandrogens** – **flutamide** - prostate gland tumour
- **Finasteride: 5a-reductase inhibitor**
- **Estrogens** – eg, diethylstilbestrol.
  - Uses- prostate gland tumor, testosterone induced prostate gland tumour
- **Androgens**—eg, testosterone, danazol Uses- mammary tumours
- **Progestogens**—eg, hydroxyl progesterone
  - Uses- endometrial tumour, prostate gland tumour

TOXICOLOGY

- Toxicology is the study of poisons and their effects on living organisms

- Xenobiotics: substances that are foreign to the body and are biologically active.

- **Poison/ Toxicant:** any substance which when taken inwardly in a very small dose or applied in any kind of manner to a living body depraves the health or entirely destroys life (M.J.B. Orfila) – father of toxicology

- *"All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy"* --- Paracelsus.

Disasters related to toxicology

- Thalidomide in pregnant women – phocomelia
- Minamata disease due to Methyl mercury in Japan
- Itai – itai disease: due to Cadmium toxicity
- Bhopal gas tragedy - methylisocyanate in 1984
- Chernobyl nuclear accident – Ukraine
- Ginger Jake paralysis: OPIDN

Sources of toxicity

- Plants: Lantana, Bracken fern etc
- Animals: poisonous animals like snake, toad
- Micro-organisms: Toxins produced by certain fungi and bacteria
- Minerals: Metals and non metals
- Agrochemicals
- Radiations
- Environmental pollutants

Factors affecting/influencing toxicity

- Solubility: high lipid solubility - more readily absorbed through the lipid- protein matrix of the cell membrane. So more toxic than those which are water soluble.
- Oxidation state of the compound: Trivalent arsenic is more toxic than the pentavalent arsenic.
- CO is more toxic than CO 2 .
- Nitrates (NO3 -) are reduced to nitrites (N02 -) by ruminal and intestinal micro flora and toxicity is produced by nitrites.

Species variation

- Atropine is nontoxic to rabbits due to presence of atropinase
- No glucuronide formation in cat due to lack of enzyme uridinediphosphate glucuronyl transferase
- No etheteal sulphate in pigs due to lack of enzyme Phenolsulphotransferase
- Carnivorous animals - glucouronide formation common, Herbivorous animals – amino acid conjugation common
- Acetylation: dogs do not acetylate due to the presence of a natural inhibitor in liver of the enzyme arylamine transacetylase

- Ivermectin is more toxic to Collie breed of dogs as it readily crosses blood-brain barrier in this breed.
- Greyhound Dog - More susceptible to barbiturate toxicity
- Bedlington Terrier –Genetic predisposition for Cu toxicity

- Sheep - more susceptible to chronic copper poisoning
- Response of horse or rat to Bracken poisoning is clinically and biochemically different from that of cow or sheep.
- Thiaminase enzyme present in bracken fern destroys Vitamin B1 essential for horse and rat. In ruminants, the vitamin is synthesized by ruminal organisms and an exogenous source is not required.

DIAGNOSIS AND GENERAL TREATMENT OF POISONING

- History
- Clinical evidence
- Circumstantial evidence
- Pathological evidence:
  - Cherry red/pink m.m. : CO, cyanide poisoning;
  - Brown/cyanotic m.m.: nitrite poisoning
  - Yellow color: nitric acid poisoning
  - CN poisoning: Bitter almond smell (it is HCN gas)
  - H2S poisoning- rotten egg smell
- Analytical evidence
- Experimental evidence
- Response to treatment

Analytical evidence: Samples for Diagnosis

- Quantity of material:
- Blood- 60ml
- Brain- whole (useful for lipid soluble poisons)
- Liver- 500g for large animal and 200g for small animal
- Kidney- 1 kidney
- Stomach/intestine contents- 500-1000 g separately
- Hair- 5 g
- Bone- 1long bone
- Urine- entire quantity (both sides of urinary bladder be tied and send as such)
- chemical preservative is used, 95% ethyl alcohol
- suspected CN poisoning- 1% mercuric chloride

Specimens required for specific poisons

1. Liver: Cu, fluoroacetate, thallium, warfarin, Zn, CCl_4, chloroform

2. Kidney: As, OC insecticides, Cu, ethylene glycol, fluoroacetate, oxalates, thallium, Zn, Hg, sulfonamides.

3. Stomach and intestinal contents: ammonia, ANTU, As , OP and OC compounds, fluoroacetate, phenols, plant poisons, CN.

4. Whole blood: NH_3, Ca (serum), CO, OC, OP (heparinized), Cu, CN, NO_3/NO_2, PO_4 (serum), chlorate

5. Urine: NH_3, As, ethylene glycol, fluoroacetate, OP compounds, thallium
6. Faeces: Cu
7. Vomitus: Acid/alkalies, As, Pb, NO_3/NO_2, chlorate, ANTU, fluoroacetate
8. Bone: Lead, fluoride, selenium
9. Hair: Chronic As poisoning
10. Fat: OC (DDT) about 100 g, OPI about 50 g, thiobarbiturates
11. Milk: Se, F

Treatment

(i) To prevent further absorption of poison
(ii) Use of supportive and non-specific agents
(iii) Specific treatment (antidotal treatment)

Use of emetics: In dogs and cats, vomition may be induced to empty the stomach. e.g. Apomorphine HCl

Universal adsorbent mixture (universal antidote)

- Activated charcoal- 10 g
- Light magnesium oxide- 5 g
- Kaolin- 5 g
- Tannic acid- 5 g

Therapeutic Index (TI)

- quantifies the safety and efficacy of a drug
- ratio of the dose that produces lethal effect (LD50) to the dose that produces the desired therapeutic effect (ED50) in a population
- TI = LD50/ED50
- higher TI - safer drug

LD_{50}	Classification
<5 mg/kg	Extremely toxic
5–50 mg/kg	Highly toxic
50–500 mg/kg	Moderately toxic
500–5,000 mg/kg	Slightly toxic
5000-15,000 mg/kg	Practically non-toxic
>15,000 mg/kg	Relatively harmless

Loomis & Hayes, 1996

Arsenic Toxicity – King of Poisons

* inorganic and organic arsenical compound. Inorganic form is more poisonous than organic.

*Order of toxicity is **Arsine> As+3 > As+5**

* Herbivores are more prone because they are more likely consumed contaminated forage.

* It is used as rodenticides, herbicide and pesticide.(Lead arsenate is used as taenicide in sheep and growth promoter in poultry)

* Used in mining operations (for smelting), so in industrialized area air is polluted with arsenic.

Toxicokinetic

- route of entry is generally by ingestion
- The **highest levels found in liver (primary),** kidneys, heart, and lungs.
- In chronic exposures, arsenic accumulates in skin, nails, hooves, sweat glands, and hair.
- It does not crosses blood brain barrier (BBB).
- It crosses placental barrier & cause foetal damage.
- The majority of the absorbed arsenic is excreted in the bile, milk, saliva, sweat urine & faeces by process of methylation.

Mechanism of action

- Trivalent arsenic compounds : inhibition/slowing of glycolysis and TCA cycle by interacting with **sulfhydryl group of enzymes(alpha-lipoic acid) , Pyruvate dehydrogenase system**
- may combine with SH group of glutathione peroxidase (GSH)

- Pentavalent arsenic - uncouple oxidation phosphorylation.
- may produce demylination and axonal degeneration (due to interference with vitamin B).

- Arsine gas: hemolytic agent and cause pulmonary oedema
- most toxic form of As and there is no treatment.

Clinical signs

Acute poisoning :-

- Poisoning is usually acute with major effects on the GI tract and cardiovascular system.
- watery diarrhoea (rice water diarrhoea)
- severe fall of B.P and hypovolemic shock

- Subacute: staggering gait, paralysis of hind quarter, dehydration etc

- Chronic: brick red mucous membranes, poor condition, animal become thirsty, pulse weak and irregular, reproductive disorder. Tying up in horse

- Pentavalent As salts: Nervous symptoms like motor incoordination, ataxia, and blindness. Animal assume dog sitting posture.

Post-mortem changes

- intense rose-red inflammation of alimentary tract
- Garlic like odor in arsine toxicity
- Diagnosis :
- (a) Liver- most useful material for chemical analysis
- (b) Kidney: considered better in organic As poisoning
- In chronic As poisoning: Levels of As are analyzed in Hair and can be very high (even μg)
- Marsh Test – to detect As toxicity

Treatment

- **Dimercaprol (BAL, British Antilewsite) - Classical antidote**
- Sodium thiosulphate
- Thioctic acid
- MDSA (Meso dimecaptosuccinic acid) and DMSA (Dimercaptosuccinic acid) - water soluble and derivative of BAL

Mercury

- Aristotle named it **"Quicksilver"**.

- Mercury exists in a variety of chemical forms, including ---
  Elemental mercury (Thermometers, light bulbs),
  Inorganic mercurial (Mercuric or Mercurous)
  Organic mercury called organomercurials, found in 2 forms - aryl (e.g. phenyl) and short and long chain alkyl (more toxic than aryl)
- organic mercurials - more toxic than inorganic mercury compounds.

* Methyl mercury - can bioaccumulate in certain edible freshwater and saltwater fish.

* The release of methyl mercury into an ocean bay (Minamata) in Japan in the 1950s led to a massive health disaster, and the clinical syndrome was named **Minamata disease**. Thousands of people were poisoned, and hundreds of them had severe brain damage.

Inorganic mercury :-

- Absorption is poor to the extent of 2- 10%.
- It is distributed non-uniformly after absorption; highest concentration of mercury is found in kidney where it is retained for a long period.
- Concentration of mercury are similar in whole blood and placenta.
- Inorganic mercury do not crosses blood brain barrier.
- excreted via urine and stool.

Continue…

Organic Mercury :-

- It is more completely absorbed from the GIT then inorganic form. Intestinal absorption of organic mercury may be as high as 95% of the dose given.
- It crosses the placental barrier and blood brain barrier hence produce more neurological & teratogenic effect than inorganic form.
- Major route of excretion is through faeces; they are also readily excreted via urine.

Mechanism of Toxicity

Inorganic mercury

due to its interaction with sulfhydryl/ dithiol (SH) group of protein and precipitate it, i.e. it interferes with protein metabolism and their corrosive action directly damage the GIT mucosa.

organic mercury : similar to inorganic additionally

Methyl Hg inhibits choline acetyl transferase (CAT) enzyme leading to acetylcholine (Ach) deficiency which leads to motor dysfunction

* **easily absorb through GIT**
* **crosses different cellular membrane**
* **crosses PB & BBB hence causes harmful teratogenic & neurotoxic effects**

Clinical signs

- **Organic mercury: Neurological Signs**
- **Inorganic mercury:-**

❑ **Acute – mainly the effect GIT & Kidney**

GIT – The symptoms are metallic taste in mouth, abdominal pain, diarrhoea with blood in the faeces leading to dehydration

Kidney – Oligouria followed by anuria, albuminuria, and uraemia.

❑ **Chronic –** kidney damage is the main symptom. Increase urinary excretion of alkaline phosphatase is found to be sensitive indicator of kidney damage

❑ **mercurial ptyalism** - to profuse salivation, swelling of gums, loosening of gum and teeth and necrosis of jaw bones

Treatment

Specific treatment:-

- **BAL (British anti-lewisite)** @ 3 mg/kg, IM, every 4 hr for the first 2 days, every 6 hr for the third day, and 12 hrly for the next 10 days or until recovery.

- D-Penicillamine is used as an antidote in the human being

- **Non-specific treatment:-**

* Gastric lavage for removal of poison from the GIT.
* Administration of proteinous liquid to protect the GIT.
* Selenium and Vitamin E reduces toxicity

Diagnosis: Grunwald test

Lead Toxicity

- **plumbism, colica Pictonum or Saturnism**
- most common cause of metallic poisoning in dogs & cattle.
- Goats, swine and chickens are more resistant
- animals ingest lead-based paints
- Vegetation grown in lead smelters areas and near highways where plants accumulate lead are other important source of lead poisoning.

Toxicokinetic

Absorption:-

- GIT & respiratory system
- GIT is very limited (1-2%) and therefore 98% of lead is eliminated in the faeces
- After absorption a large proportion (85-90% in sheep & 65-70% in cattle) of lead in blood is carried to erythrocytes membrane as Lead phosphate

Distribution:-

majority bound to RBC only small fraction is present in unbound form & cause toxicity

About 95% of the total body burden of lead is present in the bone & hence **bone** is considered to be a **"sink" for lead**

crosses placental barrier & blood brain barrier

Excretion:-

- Lead is normally excreted via kidney small amount excreted through bile & sweat.
- excreted in dangerous amount through milk

Mechanism of toxicity

- Leads depresses **aminolevulinic acid(ALA) dehydratase enzyme** (copper containing enzyme)
- resulting in increase serum level of δ-aminolevulinic acid and its excretion in urine
- inhibit **haem synthetase/ Ferrochelatase**, a thiol containing enzyme which is required to incorporate iron in the haem molecule.
- prevent entry of iron from cytosol to mitochondria.

Clinical Sign

gastrointestinal, central nervous system & hematological system.

GIT Symptoms :-

Anorexia, colic, dullness and transient constipation frequently followed by diarrhea

CNS symptoms :-

- In cattle - depression, weakness and ataxia can progress to more severe clinical signs of muscle tremors head pressing ,blindness, jaw champing, muscle tremor and convulsion.

- Horses develop acute lead toxicosis & show clinical signs of **pharyngeal paralysis (roaring) and dysphagia** frequently resulting in aspiration pneumonia.

- **Hematological symptoms:-**

  Blood capillaries congested with enlarged and increased endothelial cells.

* **Basophilic stippling** (the aggregation of ribonucleic acid) of erythrocytes

* inhibition of hemoglobin synthesis are characteristic hematological features of lead poisoning.

Treatment

Specific antidotal therapy

Disodium calcium EDTA(**Ethylene diamine tetra acetate**)

Thiamine - treatment lead poisoning in ruminants and is recommended for other species as well.

Corticosteroids and osmotic diuretics may reduce cerebral oedema in cattle and horses.

Diazepam and barbiturates may be used to control muscle tremor and convulsion.

Copper

- Dietary requirement in ruminants: 8-11 ppm
- Cu poisoning is common in sheep, while cattle & swine are somewhat resistant, poultry – most resistant
- sheep are affected most often because they accumulate copper in the liver
- Dog breed like Bedlington terrier breed is highly sensitive to Cu toxicosis, as genetic defects in breed cause excess storage of Cu in liver resulting in liver damage.
- Bordeaux mixture (contain 1-3% CuSO4) - fungicide

- Low levels molybdenum and sulphate increase toxicity of copper. Ideal ratio of **Cu-Mo in diet is 6:1**
- toxic signs occurs if ratio in excess of 10:1. High SO4 level helps in more excretion of Cu and vice versa

- Prolong ingestion of certain plants which are hepatotoxic with normal amount of Cu and low level of Mo.
- **Cu accumulator plants– *Heliotropium Europeum, Senecio sp., Trifolium subterraneum***

Toxicokinetic

- absorbed through intestine in cuprous (cu+) form
- absorption Cu in the intestinal epithelial cells binds with metallothionein a cysteine rich protein
- From intestine Cu is transported to liver by **transcuperein** (high affinity to Cu) and albumin (low affinity to Cu)
- In liver Cu combines with metallothionein and is stored in lysosomes, mitochondria & nucleus for further utilization
- For the transport from liver to peripheral tissues it combines with blood **ceruloplasmin,** an a- globulin protein produced in liver

Mechanism of toxicity

- Excessive accumulation in hepatic mitochondria and lysosome which cause progressive hepatocyte damage and cellular degenration or necrosis
- inhibition of **dichlorolipoyl dehydrogenase**, which leads to inhibition of pyruvate dehydrogenase system
- causes weakening of erythrocyte membrane increasing there fragility leading to hemolysis
- Oxidation of hemoglobin by copper leads to methemoglobin **(Hemolytic crisis)**
- In swine in addition to the above feature copper inhibit the absorption *Fe* from the GIT leading to *Fe-Deficiency* anaemia (microcytic hypochromic anaemia)

Clinical Sign

Acute Toxicity:-

Severe gastroenteritis, abdominal pain , diarrhoea, anorexia, dehydration and shock

Faeces may appear deep green in colour due to presence of Cu-chlorophyl compound

Chronic Toxicity:-

- Due to hemolytic crisis there will be free hemoglobin – which causes clogging of renal tubules leading to renal tubular and glomerular necrosis
- Signs in affected animals include generalised icterus, hemoglobinuria ,methemoglobinemia, hemoglobinemia
- Faeces & Vomitus- green to bluish in color
- Severe hepatic insufficiency is responsible for death.

P.M finding

- Pale yellow liver **(bronze coloured liver)**
- Enlarged pulpy spleen **(Black berry jam spleen)**
- **Bluish black kidney (Gun metal kidney)**
- Blood – may be chocolate coloured due to met Hb
- Port wine colored urine

Diagnosis

- **Estimation** in body fluids and tissues
- Level in faeces is around 8000-10000 ppm
- Increased values of Liver function test
- Chronic poisoning - 5-20 µg/ml in blood and >150 ppm in liver

- Liver to be sent for analytical examination

Treatment

- **Ammonium or sodium molybdate (50–500 mg) and sodium thiosulfate (250 – 1000 mg)** should be used daily as a drench for up to 3 weeks.

- D-Penicillamine or Calcium versenate may be useful if administered in early stages of toxicosis.

- Molybdenum in the diet can be increased to 5 ppm and zinc can be supplemented at 100 ppm to reduce copper absorption.

Molybdenum Toxicity- PEAT SCOURS, TEART, Alkalied

- Mo: **oxygen transfer reactions** of aldehyde oxidase, sulfite oxidase, and xanthine oxidase
- The normal level requirement in Cattle is 5-6 ppm and for Sheep is 10-12 ppm
- ratio of 2 : 1 to 3 : 1 is borderline. The animal show toxic signs if it is

< 2 : 1.

- Dietary molybdenum of 10 ppm can cause toxicity regardless of copper intake
- Cattle are most susceptible.

Toxicokinetic

- inverse relationship with Cu
- High dietary sulphate increases Mo toxicosis by decreasing copper absorption
- increase in dietary Zn may increase the Mo toxicity
- **Water soluble form of Mo (tetramolybdate)-** more toxic than water insoluble from (Mo disulfide)

- absorption and excretion is rapid
- Mainly stored in kidneys and to some extent in bones
- also excreted in milk and may affect young calves suckling the dams
- eliminated very rapidly via the kidneys (>80%) and bile

Mechanism of toxicity

- Mo produces toxicosis as a results of Cu deficiency (Secondary hypocuprosis)
- Thiomolybdates bind to copper in the digestive tract & prevents absorption of copper
- Microcytic Hypochromic anaemia is characteristic due to inhibition of enzyme sulfide oxidase
- Cu deficiency produces falling disease in cattle and sheep
- progressive atrophy of myocardium with replacement of fibrous tissue, weakening the heart and causes sudden death after excitement or exercise

Teart

- Persistent scouring with passage of liquid faeces full of gas bubbles (teart)
- due to complex formation between molybdenum and catechols (bacteriostatic and control the activity of bacteria in the gut)
- excessive activity of bacteria which will cause diarrhea with liquid feces with lot of gas bubbles

Clinical Sign

- severe scouring making a 'parabola' (shooting diarrhoea)
- liquid faeces with lot of gas bubbles and unpleasant odors (called as **peat scours or teart)**
- Depigmentation of hair coat, noticeable in black animals specially around eye spectacled appearance

- **Hypochromic anemia,** Joint pain, Osteoporosis, and decreased fertility.
- Sheep and young animal show stiffness of the back and legs with reluctance to rise this condition is called "**Enzootic ataxia**" in Australia and "**Swayback disease**" in the UK.
- In sheep, there is development of pica while Horses are generally resistant
- Osteoarthritic changes give the animal abnormal look and gait – called **pacing disease**

Treatment

- The two primary mechanisms of treating Mo toxicosis involve removal from the source of high Mo and copper supplementation
- Scouring can be controlled by daily administration **of Copper sulphate** 1gm for calves and 2 gm for cattles.
- Copper glycinate injection S/C @ of 60mg. For calves and 2 0f 120m mg. for cattle can be given as an adjunct therapy
- 'Anti-teart cake' (containing prophylaltic amount of CuSO4)

*Mo level in blood > 0.1 ppm (and less than 0.6 ppm Cu) indicates Mo toxicity.

*Analysis of Mo in liver > 5 ppm (and less than 10 ppm Cu) indicates Mo toxicity

Selenium toxicity –

Blind Staggers,

Alkali disease,

DOG MURRAIN

*** Obligate indicator plants :**

10,000 – 15000 ppm for growth and survival.

accumulate high concentrations of selenium as water-soluble amino acid analogs of cysteine and methionine.

E.g - *Astralagus , Oonopsis* & Xylorhiza.

*** Facultative indicator plants:**

Absorb and tolerate large amounts of selenium (1500 ppm) if it is present in the soil

E.g - *Sideranthus, Aster* & *Atriplex* .

***Passive accumulator plants:**

May accumulate selenium if grown on seleniferous soils (20 – 60 ppm) E.g - Corn, Wheat & Barley

Toxicokinetics :-

- Se is readily absorbed from the gut and distributed throughout the body particularly to the liver kidney and spleen.
- Chronic exposure results in large concentration in hairs and hooves.
- Se can cross the placental barrier in mammals and also enters into avian eggs causing foetal malformation and embryonic defects.
- natural organo selenium> selenite (+4) = selenate (+6) > selenide (-2) > elemental selenium
- Se toxicity is most common in areas that have arid or" semi-arid climates (less than 20 inches annual precipitation)
- Se toxicity is most common in areas that have soils with pH levels above 7.0

Mechanism of toxicity

- The main mechanism of selenium is due to the incorporation of Se instead of Sulphur in some amino acids (Cysteine & Methionine) that's why hoof & hair defects in chronic Se Toxicosis.

- Se causes depletion of glutathione (GSH, GSH is required for cell integrity)

- Chronic selenosis depresses ATP formation due to inhibition of –SH containing enzymes viz. succinic acid dehydrogenase

Subacute (Blind staggers)

- In the second stage depression, in-coordination and fore leg weakness, animal goes down on its knees.

- In the third stage colic, subnormal temperature, emaciation, swollen eyelids, near blindness. Salivation, lacrimation, severe abdominal pain, inability to swallow, complete paralysis, collapse and death

- **rooted to one spot**

Continue…

Chronic (Alkali disease)

- Lameness, hoof and hair abnormalities, partial blindness, paresis, in-coordination, emaciation and lethargy may be noticed.
- Lameness is due to erosion of the articulate surface of long bones.
- Hoof begins to shed. Shedding is incomplete and old hoof fuses with new hoof and form **abnormally long rocker shaped hoof.**
- In horses there will be loss of long hair from the mane and tail will occur
- "**bob" tail and "roached" mane appearance**, cracking and sloughing of hoof

Diagnosis & Treatment

Diagnosis

- Diagnosis is based on clinical signs and estimation of selenium in whole blood and liver.
- Elevated glutathione peroxidase level in liver and blood suggest Se poisoning.
- Laboratory analysis of Se in:
- Feed >5 ppm → indicate toxicity.
- Bovine Hoof → 5-20 ppm (in chronic toxicity),
- Bovine Hair → 5-10 ppm (in chronic toxicity)
- Blood → 4-25 ppm – acute toxicity
  1-4 ppm – chronic toxicity

Treatment

- There is no specific antidote for Se toxicosis symptomatic & supportive care of affected animals should be started as early as possible.
- Addition of inorganic arsenicals enhances biliary excretion of selenium and increasing the dietary levels of sulphur containing proteins is also beneficial.
- CONTRAINDICATIONS:
- BAL (dimercaprol) → alleviates Liver damage but worsens kidney damage.
- Vit E →Synergistic action with Se

PHOSPHORUS (P) POISONING

- 4 different forms i.e. white, yellow, red and black.
- Yellow form is most toxic. White form can be converted into yellow and can cause toxicity
- in the body P circulates first as element and then is oxidized to phosphate.
- **eliminated by lungs and this provides the exhaled air a smell of phosphorus (garlic-like) and a glow in dark.**
- Similarly, the **vomitus of GI tract contents may be luminous** and have the same odour.
- Main excretion of phosphorus is in the urine and expired air

Mechanism of action

- phosphorus acts as a protoplasmic poison
- direct cardiotoxic effect resulting in cardiovascular collapse. Phosphate formed in body due to oxidation of phosphorus causes hepatic necrosis
- On dermal exposure, white phosphorus results in painful chemical burn injuries by the heat of flame as phosphorus ignites when comes in contact with air

- gastrointestinal irritation and abdominal pain, colic, profuse vomiting (occasionally haematemesis), severe diarrhoea (often haemorrhagic), and a **garlic-like odour from the breath**
- **hepatic failure is followed by convulsions and death**
- **Pigs vomit profusely and the vomitus show luminous in dark and gives a characteristic garlic odour**
- **Luminescence is due to presence of phosphorus trioxide**
- **In chronic phosphorus poisoning, the main clinical feature is necrosis of jaw (mandible) called "Phossy jaw" or "Lucifer's jaw".**

Cadmium Toxicity

- impair Vitamin D metabolism in the kidney with deleterious impact on bone
- This effect, coupled with direct Cd impairment of gut absorption of calcium and derangement of collagen metabolism, can produce osteomalacia and/or osteoporosis .
- Occupational toxicity due to inhalation of cadmium fumes
- ***itai-itai* disease in Japan**
- **EDTA significantly increased urinary elimination of cadmium**

Fluorine (F) Poisoning

- non-metallic halogen
- feed-grade phosphates should not contain more than 1 part of fluorine to 100 parts of phosphate
- species susceptibility is as follows: calves, dairy cows, beef cattle, sheep, horses, pig and poultry (cattle most sensitive)
- Mainly distributed into calcified tissues **like bone and teeth**
- Bone is a natural sink for fluoride (like lead) with 96-99
- Normal adult bones contain about 1000-1500 ppm fluoride.

Acute toxicity

- Gastroenteritis action
- Disrupting ionic balance : interfere with Na+ K+ channels
- Enzyme inhibition: Fluoride impairs utilization of glucose by inhibiting pre glycolytic and phosphatase enzymes (Enolase)
- Anticoagulant action: Fluoride acts as anticoagulant because it precipitates the calcium in the form of calcium fluoride (CaF_2).

Chronic toxicity/ fluorosis

- **Dental fluorosis**: Excessive amount of fluoride damages ameloblasts and odontoblasts
- deposition in teeth occurs only during the formative stages
- teeth lesions are the earliest and most severe in young and growing animals.
- Mottling of teeth

- **Osteofluorosis**: interferes with the osteoclast activity and damage the osteoblast cells
- **Intermittent shifting lameness**
- F in Bones – 4000-5000 ppm of ash indicate flurosis
- urine in live animals- Urine levels of F:>15 ppm indicate fluorosis

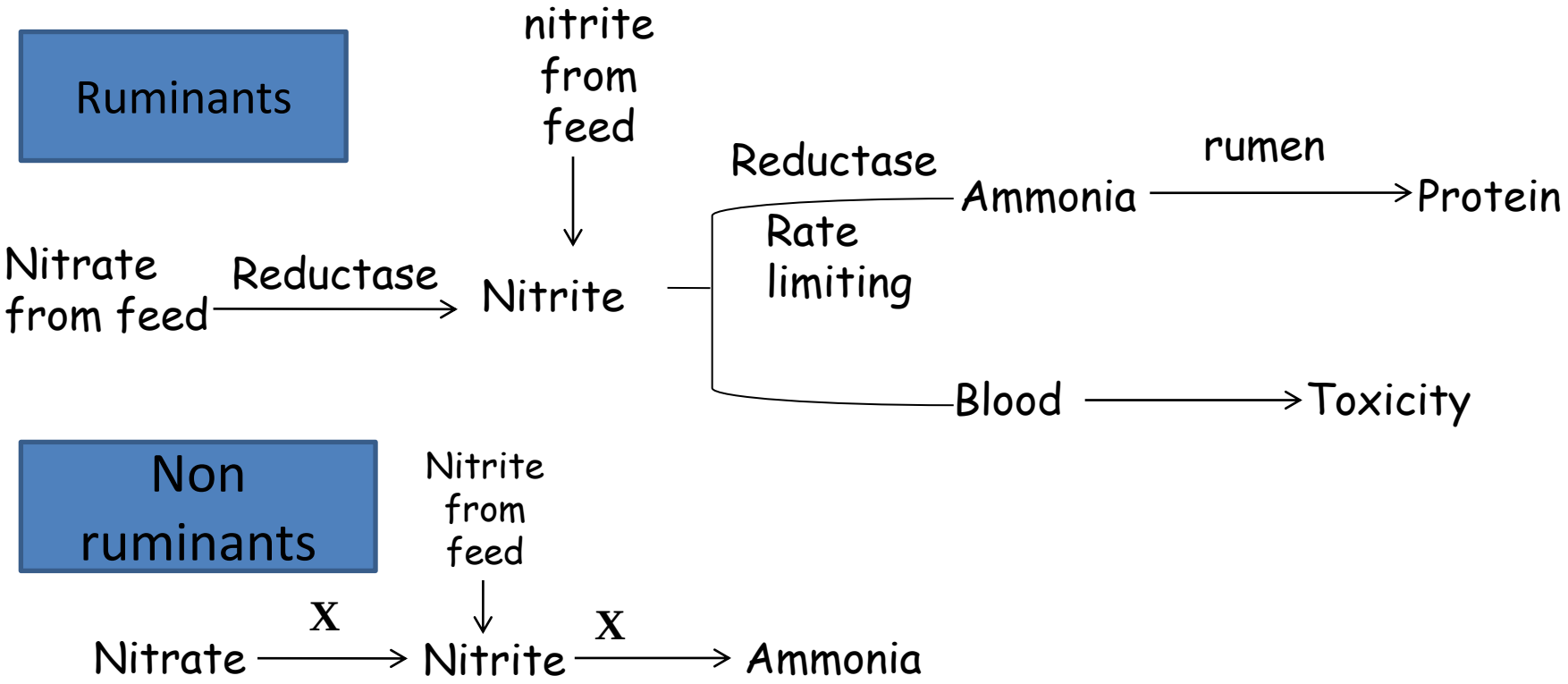
SALT POISONING- Water deprivation toxicity

Sodium ion poisoning/ Water deprivation induced sodium chloride toxicosis

- Salt hunger
- Na+ causes an extracellular hyperosmolality resulting in very significant intracellular dehydration and development of brain or cerebral oedema.
- Dragging of hindfeet while walking & Knucking of fetlock joints
- **Eosinophilic meningoencephalitis:** Cerebral vascular endothelial proliferation & distended perivascular space in pigs – is a pathognomonic lesion of salt poisoning.

Nitrate and Nitrite Poisoning

- Heavy use of nitrogen fertilizers (e.g. ammonium nitrate, potassium nitrate and urea) and herbicides (e.g. 2, 4-D)
- cereal grasses (especially oats, millets and rye), corn (maize), sunflower and sorghum readily accumulate nitrate
- Water: accumulation in water bodies due to increased water run off from nitrate rich soil, decaying manure, silo pits, and freshly fertilized fields
- toxicity of the nitrate ion is approximately 10 times lower than that of the nitrite ion


Ruminants
nitrite from feed
Nitrate from feed
Reductase
Nitrite
Reductase
Rate limiting
Ammonia
rumen
Protein
Blood
Toxicity
Non ruminants
Nitrite from feed
Nitrate
X
Nitrite
X
Ammonia

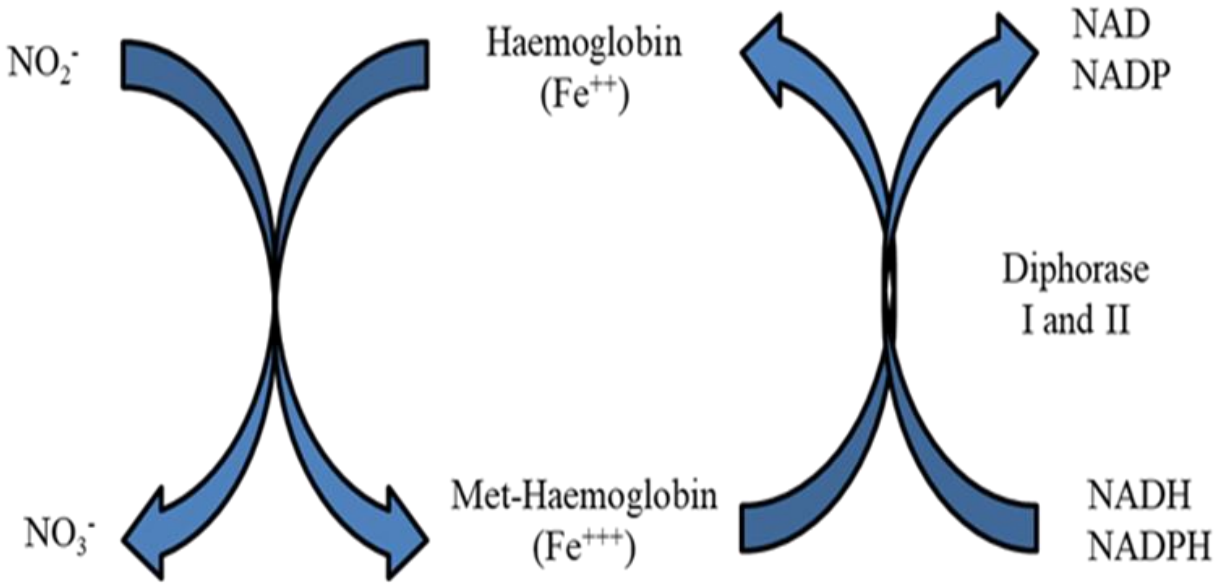
- Ruminants are much more susceptible to nitrate poisoning than monogastric animals
- Cattle- affected most frequently by nitrates
- Pigs are most susceptible to nitrite poisoning than cattle and sheep
- cloudy weather or decreased sunlight enhances nitrate levels in plants due to decreased activity of plant NO_3-reductase enzymes
- cut hay or green relatively late on sunny days to minimize concentrations of nitrate

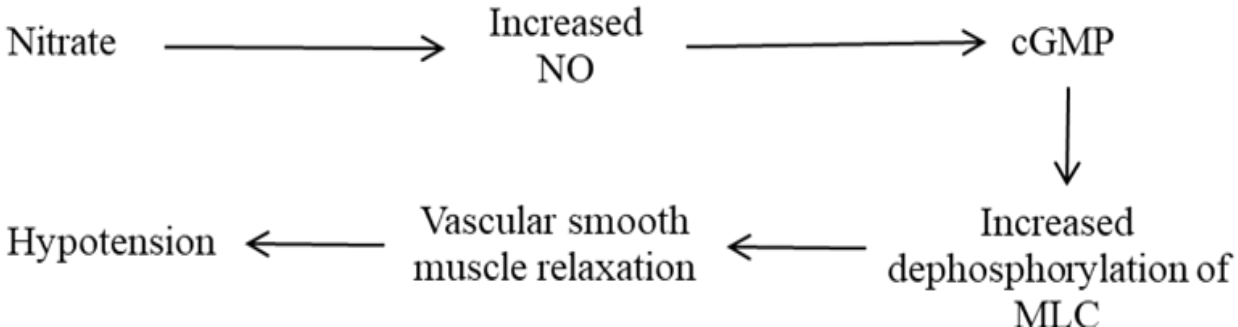
Mechanism of action

- Nitrite: ingestion of large amount of nitrate or nitrite and this is due to mainly nitrite ions
- a. Methaemoglobin formation: One nitrite combines with 2 Hb molecules producing Met-Hb by oxidation

- Normally some Met-Hb (1-2%) is always present which is converted back to ferrous haemoglobin by two reducing enzymes in blood viz. NAD-dependent diaphorase I and NADP-dependent diaphorase II

b. Vascular smooth muscle relaxation (Vasodilation): hypotension and decreased cardiac output


NO_2^-
Haemoglobin
(Fe^{++})
NAD
NADP
Diphorase
I and II
NO_3^-
Met-Haemoglobin
(Fe^{+++})
NADH
NADPH


Nitrate
Increased
NO
cGMP
Increased
dephosphorylation of
MLC
Vascular smooth
muscle relaxation
Hypotension

- Nitrate: primary action of large doses of nitrate is different from nitrite ions and resembles effect of excess common salt poisoning

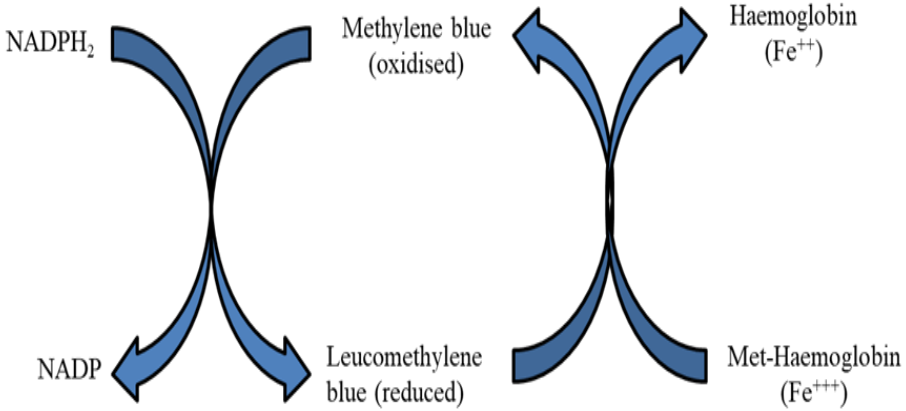
- The signs include disturbed osmotic conditions in the body and death may occur shortly after ingestion of very large doses of nitrate, even before the nitrite and methaemoglobin stages are reached

- Dark chocolate brown or coffee brown color of blood (dark tarry chocolate colored blood) due to methaemoglobin formation in nitrite poisoning

Methylene blue: antidote for treating methaemoglobinaemia caused by nitrite/nitrate (chlorate poisoning also)

- After i/v, converted in blood and body tissues to a **reducing agent leucomethylene blue**

- Leucomethylene blue also activates Diaphorase I and II systems.



Cyanogenetic Plants/Prussic acid poisoning

- poisoning occurs due to ingestion of cyanogenic plants which yield HCN upon acidic or enzymatic hydrolysis by beta glycosidase and lyase

- *Sorghum helepense* (Baru grass, Johnson grass), *Sorghum vulgare* (Jowar, Millet), *Sorghum sudanensis* (Sudan grass), *Sorghastium nutans* (Indian grass)

- *Triglochin maritima* (Arrow grass), *Zea mays* (Maize), *Linum usitatissimum* (Linseed, Flax), *Prunus laurocerasus* (Cherry laurel, Milk laurel), *Lotus spp.*,

- Linamarin----------linseed
- Dhurrin----------sorghum (Millet, Jowar, sudan grass etc.)
- Amygdalin----------bitter almond, wild cherry (Prunus spp.)
- Lotusin or lotaustralin from Lotus spp

- Minimum lethal dose of HCN --- 2mg/Kg

- Plant materials >20mg of HCN per 100gm (200ppm) may have toxic effects. Highly poisonous plants ---- 6000ppm

- Ruminants are more susceptible ; Among ruminants, cattle are more susceptible than sheep

- Horses, dogs and pigs - less susceptible to HCN poisoning than ruminants

- endogenous **thiosulphate** react with HCN to form thiocyanate catalyzed by enzyme known as **rhodanase**

- Small amount of absorbed CN- is eliminated through lungs **(exhaled air has bitter almond smell)**

- Cyanide has strong affinity **for trivalent iron** of the **cytochrome oxidase** molecule and **inhibits enzymatic activity and hence the cellular respiration**

- death is primarily from tissue anoxia in the brain

- As oxygen of arterial blood cannot be utilised, venous blood retains the bright colour of oxyhaemoglobin.

Diagnosis

- In case of suspected CN poisoning, the liver/muscle/stomach contents should be preserved with a solution of 1% mercuric chloride and refrigerated.
- For urine, phenyl mercuric nitrate is used as preservative. It prevents enzymatic degradation.

Post-mortem findings

- Bright cherry red color of venous blood
- Plants containing 200 ppm or more of HCN are potentially toxic
- Rumen contents and liver showing more than 10 ppm and 1.4 ppm of HCN, respectively, are indicative of cyanide poisoning

Sodium nitrite: antidote to cyanide poisoning, often **in conjunction with sodium thiosulphate.**

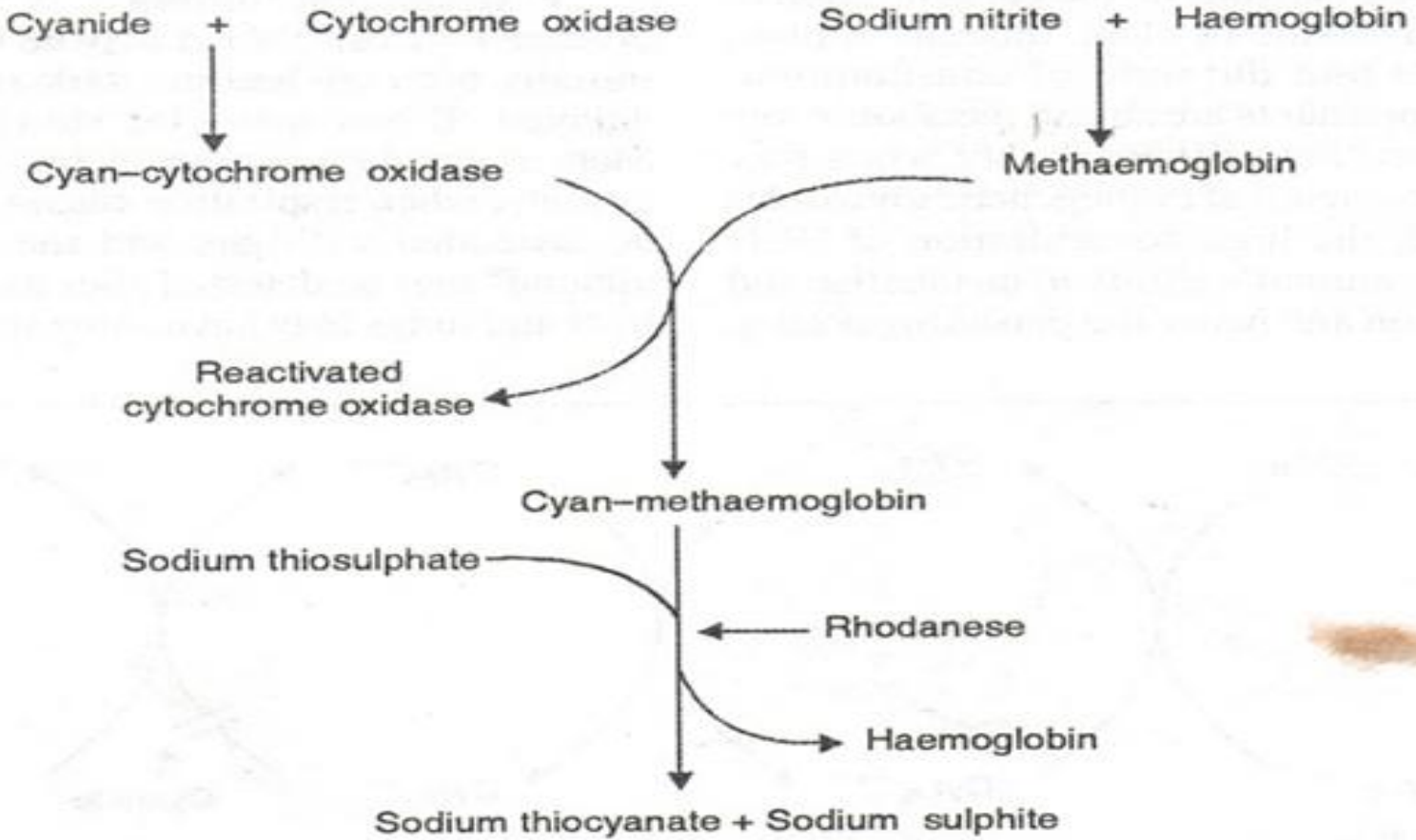
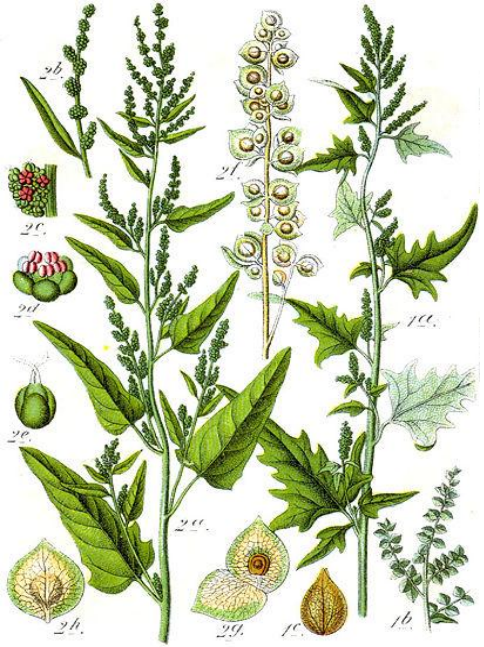


Fig. Proposed mechanism of action of sodium nitrite in cyanide poisoning.

Oxalate rich plants

The oxalate rich plants are:

- *Amaranthus retrflexus,*
- *Atriplex spps.,*
- *Beta vulgaris,*
- *Calandrina spp,*
- *Oxalis spp.,*
- *Rumexs spp.,*
- *Setaria spp.*
- and *Triantema spp.*



Atriplex spps.,

Mechanism of Toxicosis

- Calcium metabolism is upset (oxalates chelate Ca^{++} causing acute hypocalcaemia), interfering with milk production in lactation in lactating animals and foetal bone growth in pregnant animals.
- Blocking of renal tubules by calcium oxalate crystals – renal injury.
- Failure of blood clotting mechanisms and haemolysis.
- Oxalates also crystallize and cause neuronal damage in brain – CNS signs and paralysis.

Treatment

- Shift to oxalate-free pastures.
- Oral administration of **dicalcium phosphate** (25% in salt ration) or given as grain or alfalfa hay pellets containing 10% dicalcium phosphate @ 225 G/animals/day for **elimination of oxalates (calcium oxalate) through faces.**
- Prior treatment with dicalcium phosphate before allowing sheep to graze in oxalate rich pastures, does not result in oxalate poisoning.

Plant producing thiamine deficiency

(i) *Pteridium aquilinum* (Bracken fern)
(ii) *Equisetum arvense* (Horse tail, bottle brush)

Pteridium plant:

1. Cyanogenetic glycoside - harmless
2. Thiaminase - responsible for poisoning **in non-ruminants**
3. Aplastic anemia factor (Ptaquiloside): bone marrow suppression **in cattle and sheep**
4. Haematuria factor: enzootic haematuria and haemorrhages **in cattle and sheep**
5. A carcinogen (Ptaquilosid (Japanese) / Aquiloside A (Dutch)

Equisetum contains enzyme Thiaminase and alkaloid Equisetine.

- Chronic poisoning: Chronic enzootic haematuria in cattle characterised by intermittent haematuria and ultimate death due to anaemia

- In sheep, a bright blindness may occur due to progressive retinal atrophy that is characterized by permanent blindness.

a. Administer **DL - Butyl alcohol**: It stimulates bone marrow

b. Toluidine blue

LANTANA CAMARA

- Lantana hepatotoxins -Lantadenes – Lantadene A, B, C, D. (Major)
- Lantadene A is toxic to sheep (ruminants) & guinea pig (most susceptible species)

- **causes hepatotoxicity & secondary photosensitization**

i) absorbed from whole GIT with max absorption from small intestine and transported to liver mainly in portal blood. (GIT Phase)

ii) Toxins interact with biomolecules on/in hepatocytes, followed by cascade of biochemical reactions → cholestasis (hepatic phase)

iii)Cholestasis leads to regurgitation of bile → causes marked increase in levels of bilirubin & phylloerythrin (biodegradation product of chlorophyll) in blood

undergo phytochemical reaction on exposure to light & causes photosensitization

- Hepatogenous photosensitization:
  - Lantana camara
  - Blue green algae
  - Pithomyces chartarum fungus

Teratogenic plants

- ***Veratrum californicum*:** alkaloids like **cyclopamine, Jervine and** Veratrosine
- ***'Cyclopian Disease' or Cyclopian eye'***

- ***Lupine (Lupinus sericus, L. caudatus):*** the alkaloid 'Anagyrine' LUPININE
- **CROOKED CALF DISEASE**

Ipomoea carnea (Behaya). I. batata: Sweet Potato, Shakarkhand

Toxic Principles:

Phytotoxins like lysergic acid alkaloids (hallucinogenic), resins (cathartic), toxic saponins, nitrates etc

SCAMMONIN (JALAPIN) – I. orizabensis

TURPETHIN – I. turpethum (Indian Jalap)

PHARBITISIN – I. hederaceae

Sorghum vulgare (Jowar).

Toxic Principles: HCN

Toxicity:

Cytotoxic anoxia.

Treatment: Sodium nitrite 20mg/kg slow i.v. as 1% solution and sodium thiosulphate. 500mg/kg

Thevetia peruviana (Yellow Kaner) *Nerium oleander* (Red Kaner)

Toxic Principles:

N. odorum has one glycoside called 'Nerin'. *Cerebra thevatia (Thevatia nerifolia*, yellow oleander) has two glycosides called Thevitin, Cerberin.

Mechanism of action: oleander glycosides act on heart like digitalis and inhibits the Na^+-K^+-ATPase pump.

Datura stramonium, Atropa belladonna (Deadly nightshade)

Toxic Principles: Atropine, Hyoscyamine, Hyoscine- Antimuscarinic action

Animals affected: Cat>Dog>Birds>Horses>Cattle>Sheep>Goat.

Clinical signs: Dryness of mouth & mucous membranes, thirst, anorexia, mydriasis, visual disturbances, depression, tachycardia.

Treatment: Parasympathomimetic agents, e.g. physostigmine, pilocarpine etc.

Ricinus communis (Redi, Andi).

Toxic Principles: **Phytotoxin Ricin I & II (more toxic).** Ricin is one of the most powerful phytotoxins known.

Animals affected: Horses are most susceptible

Toxicity: Cytotoxic (hydrolytic fragmentation of ribosomes and inhibits protein synthesis, disrupts CM) and Gastrotoxic.

Treatment: Anti-ricin serum. Symptomatic & supportive

Abrus precatorius (Rati) Rosary Pea Poisoning

Toxic Principles: **Abrin**

Animals affected: All species of animals. Used for Malicious poisoning

Toxicity: A potent cytotoxic phyto protein

Argemona mexicana

Toxic Principles: alkaloid – sanguinarine; berberine; protopine

Animals affected: Poultry

Toxicity &Clinical signs: Drop in egg production, cyanosis of comb, hemorrhagic enteritis and death in poultry

Gossypol: pigment found in cottonseed cake, occurs in 2 forms i.e. free form (toxic) and bound form (non toxic)

Young calves, swine and poultry are affected

Supplement feed with iron (Ferrous sulphate) – prevention

Ourecus incana (Oak).

Toxic Principles: Tannins, Gallic and Pyrogallic acids, phenols

Toxicity: Precipitation of proteins and binding of =SH groups of enzymes

***Lathyrus Sativus*(Grass Pea)**.

Toxic Principles:
β-oxalyl aminoalanine (BOAA)--**Neurolathyrism**
β-N aminopropionitrile (BAPN) -- **Osteolathyrism**

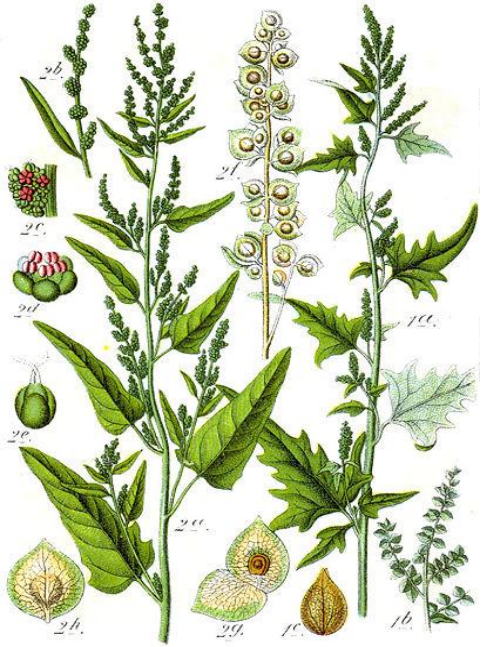
***Strychnos nuxvomica*:**

- Strychnine poisoning occurs in farm animals as a result of accidental ingestion of seeds of plant or powdered form of nuxvomica used as bait to kill rats, foxes or dogs.
- **Mechanism of toxicity**: Main site of action of strychnine is the recurrent inhibitory inter neurons (Renshaw cells) of the reflex arc in the spinal cord and medulla.
- Convulsant action

Oxalate rich plants

The oxalate rich plants are:

- *Amaranthus retrflexus,*
- *Atriplex spps.,*
- *Beta vulgaris,*
- *Calandrina spp,*
- *Oxalis spp.,*
- *Rumexs spp.,*
- *Setaria spp.*
- and *Triantema spp.*



Atriplex spps.,

Mechanism of Toxicosis

- Calcium metabolism is upset (oxalates chelate Ca^{++} causing acute hypocalcaemia), interfering with milk production in lactation in lactating animals and foetal bone growth in pregnant animals.
- Blocking of renal tubules by calcium oxalate crystals – renal injury.
- Failure of blood clotting mechanisms and haemolysis.
- Oxalates also crystallize and cause neuronal damage in brain – CNS signs and paralysis.

Treatment

- Shift to oxalate-free pastures.
- Oral administration of **dicalcium phosphate** (25% in salt ration) or given as grain or alfalfa hay pellets containing 10% dicalcium phosphate @ 225 G/animals/day for **elimination of oxalates (calcium oxalate) through faces.**
- Prior treatment with dicalcium phosphate before allowing sheep to graze in oxalate rich pastures, does not result in oxalate poisoning.

Plant producing thiamine deficiency

(i) *Pteridium aquilinum* (Bracken fern)
(ii) *Equisetum arvense* (Horse tail, bottle brush)

Pteridium plant:

1. Cyanogenetic glycoside - harmless
2. Thiaminase - responsible for poisoning **in non-ruminants**
3. Aplastic anemia factor (Ptaquiloside): bone marrow suppression **in cattle and sheep**
4. Haematuria factor: enzootic haematuria and haemorrhages **in cattle and sheep**
5. A carcinogen (Ptaquilosid (Japanese) / Aquiloside A (Dutch)

Equisetum contains enzyme Thiaminase and alkaloid Equisetine.

- Chronic poisoning: Chronic enzootic haematuria in cattle characterised by intermittent haematuria and ultimate death due to anaemia

- In sheep, a bright blindness may occur due to progressive retinal atrophy that is characterized by permanent blindness.

a. Administer **DL - Butyl alcohol**: It stimulates bone marrow

b. Toluidine blue

LANTANA CAMARA

- Lantana hepatotoxins -Lantadenes – Lantadene A, B, C, D. (Major)
- Lantadene A is toxic to sheep (ruminants) & guinea pig (most susceptible species)

- **causes hepatotoxicity & secondary photosensitization**

i) absorbed from whole GIT with max absorption from small intestine and transported to liver mainly in portal blood. (GIT Phase)

ii) Toxins interact with biomolecules on/in hepatocytes, followed by cascade of biochemical reactions → cholestasis (hepatic phase)

iii)Cholestasis leads to regurgitation of bile → causes marked increase in levels of bilirubin & phylloerythrin (biodegradation product of chlorophyll) in blood

undergo phytochemical reaction on exposure to light & causes photosensitization

- Hepatogenous photosensitization:
  - Lantana camara
- Blue green algae
- Pithomyces chartarum fungus

Teratogenic plants

- ***Veratrum californicum*:** alkaloids like **cyclopamine, Jervine and** Veratrosine
- ***'Cyclopian Disease' or Cyclopian eye'***

- ***Lupine (Lupinus sericus, L. caudatus):*** the alkaloid 'Anagyrine' LUPININE
- **CROOKED CALF DISEASE**

Ipomoea carnea (Behaya). I. batata: Sweet Potato, Shakarkhand

Toxic Principles:

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- Convulsant action

Insecticides

Organochlorines- DDT, BHC

Organophosphates- malathion, sarin

Carbamates- Carbaryl, propoxur

Pyrethrins and pyrethroids- allethrin, deltamethrin

Formamidine insecticides- amitraz

Natural products- rotenone, nicotine

Organochlorines

- Organochlorines were the first major class of synthetic organic chemical to become widely used as insecticides

Diphenyl aliphatic agents - DDT, methoxychlor, perthane, dicofol

Hexachlorocyclohexane – Lindane, mirex, kepone,BHC

Cyclodiene agents – Aldrin, dieldrin, chlordane, endrin, endosulpahan, toxaphene, heptachlor

Mechanism of Toxicity

- These drugs are *neurotoxic*.
- easily enter in the nerve membrane interfere with Na^+ Channel
- Prolong the time of sodium channel opening during depolarization.
- Sodium inflow is enhanced and potassium outflow is inhibited
- Results in enhanced action potential and **increased neuronal excitability** (seizures).

Clinical symptoms

- Initial stimulation of CNS followed by depression and death due to respiratory failure.

- **Behavioural symptoms-** like anxiety, aggressiveness, abnormal posturing, jumping over unseen objects, wall climbing and madness syndrome.

- **Neurological symptoms** - hypersensitivity to external stimuli, fasciculation and twitching of facial and eyelid muscles, spasm and twitching of the fore and hind quarter muscles, champing of the jaws, seizures and hyperthermia.

- Cholinergic symptoms - vomiting, marked salivation, mydriasis, diarrhoea and micturition are noticed.

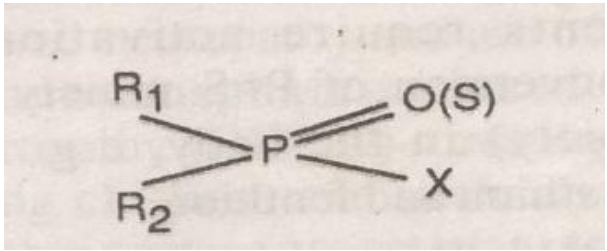
Treatment

- Diazepam, phenobarbital or pentobarbital in dogs.

  Chloral hydrates, Phenobarbital or pentobarbital in farm animals.
- Activated charcoal (1-2g/kg).
- If exposure is by dermal suspected, scrubbed (bathe) the animal with soapy water.
- Supportive and symptomatic therapy.

Organophosphates

- **OP compound are esters of phosphoric, phosphonic, phosphorothioic or related acids**
- **which have ability to inhibit cholinesterase enzyme**
- 1st OPI - tetraethyl pyrophosphate (TEPP).



Classification of OPI

Based on chemical structure –

- **Phosphate & pyrophosphate-** Paraoxon, TEPP, schraden, dichlorvos
- **Phosphorothioates -** Parathion, fenthion, diazinon, runnel
- **Phosphonates** - Trichlorphon
- **Phosphoramidates-** Phospholan, mephospholan
- **Phosphorothiolates-** Echothiophate, profenophos
- **Phosphorohalides-** Diisoprophylfluorophosphate (DFP), sarin
- **Phosphorocyanides-** Tabun

Based on mode of action
(Classification)

Direct acting OP insecticides

- These insecticides contain **P=O group**
- **directly inhibit cholinesterase enzyme** and produce toxicity
- TEPP, trichlorphon and dichlorvos.

Indirect acting OP insecticides

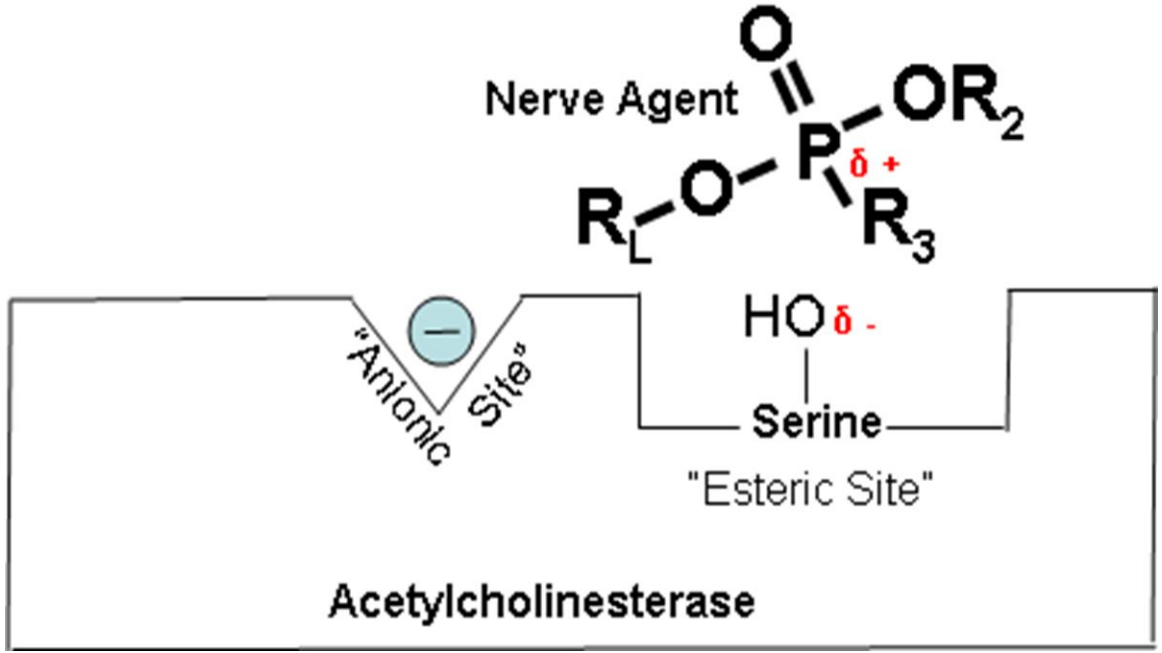
- phosphorothioates containing **P=S groups**.
- Require **activation to oxon** (conversion of P=S moiety to a P =O moiety) in the body.
- Malathion, parathion and fenthion.

Mechanism of action

- OPI owe their toxicity by **irreversible inhibition of AChE enzyme**, which is responsible for hydrolytic degradation of acetylcholine

- This leads to **Ach accumulation in nerves and neuro-effector junctions**, which causes excessive synaptic neurotransmitter activity in the parasympathetic nervous system and at neuromuscular sites and affected animals show **parasympathetic or chlolinergic signs.**

- OP compounds interact with only the active **esteric site** of the enzyme and the enzyme – OP complex formed is extremely stable that does not undergo significant spontaneous hydrolysis



- However once covalent modification of enzyme occurs and the phosphorylated enzyme looses one of its alkyl group (called aging), it is impossible for chemical re activators to break the bond between the inhibitor and the enzyme.

- Aging is very **rapid for nerve gases.**

  soman (aging half life 2 minutes),

Delayed Toxicity (delayed neurotoxicity):

- occurs after several days produced by the inhibition of NTE (**Neuropathy Target Esterase**),membrane bound enzyme.
- NTE facilitate axonal transport of nutrients
- its inhibition results in demyelination of of axon leading to paralysis called as organophosphate induced delayed neuropathy (OPIDN) or dying back axonopathy.
- "**Hind leg paralysis**"/ "**Ginger Jake Leg/ Jake Leg Paralysis**
- Mipafox is a classical example causing OPIDN
- Charolin's cattle and SUFFOLK sheep genetically predisposed

Treatment

- Specific antidotes: a) Muscarinic blockers

  b) ChE reactivators

- **Atropine SO_4:**

Dogs and Cats: 0.2-2 mg/kg 1/ iv and rest sc.

Repeat every 3-6 hr as required.

Horse and Pig: 0.1-0.2 mg/kg I/V,

repeat every 10-15 min as needed;

Cattle and sheep: 0.5-1 mg/kg 1/3 iv and rest im or sc,repeat as needed.

- **Oximes/ cholinesterase reactivators** : **2-PAM** (2-Pyridine aldoxime methiodide, 2-PAM chloride), DAM, MINA – Binds to anionic site
- @ 20-50 mg/kg as 10% sol im or slow
- ChE activation decreases with time (after exposure), better to use within 24-48 hr.
- **If ingestion**: Emetics, purgatives, activated charcoal (3-6 g/kg as slurry in water.
- **If dermal:** wash with soap and cool water.

Carbamates

- **Naphthyl carbamates-** Carbaryl (sevin)
- **Phenyl carbamates** – Propoxur
- **Heterocyclic methyl carbamates-**pyrolan and isolan.
- **Heterocyclic dimethyl carbamates** Carbofuran and furadan, aldicarb, methomyl and thiodicarb.

Differences from OP compounds

Carbamates differ from OP compounds in following aspects:

--They are **reversible inhibitors** of cholinesterase (ChE) enzyme

- They inhibit cholinesterase at both anionic and esteratic sites
- They are selective inhibitors of cholinesterase enzyme
- Decarbamoylation (reactivation) of inhibited ChE enzyme is easier
- Cholinesterase enzyme reactivators like 2-PAM are ineffective (contraindicated) in the carbamate intoxication.

Mechanism of action

- Carbamate inhibit acetylcholinesterase enzyme, but these insecticides occupy **both anionic and esteratic sites of AChE.**

- The inhibition in case of Carbamate results from a chemical reaction between the **carbamoyl moiety of carbamate compound and the active site serine hydroxyl group of AChE to form carbamoylated enzyme** rather than phosphorylated as with the organophosphate.

- The carbamoylated enzyme is **relatively less stable and susceptible to hydrolysis,** although rate of hydrolysis is not very fast as with acetylcholine.

- Therefore, the **decarbamoylation is easier** in comparison to dephosporylation (OPs).

- Because of relatively rapid reactivation of carbamoylated AChE, the carbamate insecticides are often called reversible anticholinesterase agents.

- Toxicosis develops when the amount of carbamate pesticide in the body is so large that the **rate of carbamoylation of AChE exceeds the rate of hydrolysis of pesticide by the enzyme**.

Diagnosis:

- History, circumstantial evidence,
- Clinical signs,
- Estimation of blood ChE activity (25% or more decrease in OPI and carbamate toxicity) and
- Identification of the insecticide in feed, water, ruminal content or tissues.

Treatment:

- **Atropine sulphate** only
- Not ChE-reactivators.

Pyrethrins

- This is a closely related group of naturally occurring compounds that are the active insecticidal ingredients of pyrethrum.

- Pyrethrum is extracted from the **flowers of *Chrysanthemum cinerariaefolium*** and has been an effective insecticide for many years.

- Synergists, such as piperonyl butoxide, sesamex, piperonyl cyclonene, etc, are added to increase stability and effectiveness.

Pyrethroids

These are synthetic derivatives of natural pyrethrins and include –

- Allethrin,
- Cypermethrin,
- Decamethrin,
- Fenvalerate,
- Fluvalinate,
- Permethrin
- Type I pyrethroids – Tremors (T syndrome)
- Type II pyrethroids - choreoathetosis-salivation syndrome (CS)

Mechanism of action

- Nerve poisons like DDT.
- Prolonged depolarization **(delayed closure of Na channels)** and repetitive discharge.
- Piperonyl butoxide and piperonyl cyclonene potentiate pyrethoid insecticidal and mammalian toxicity (inhibition of mixed function microsomal oxidases i.e. by preventing detoxification of pyrethroids).
- Pyrethroids are relatively less toxic in mammals and birds, but highly toxic to fish.

Herbicides

- Dinitro compound- dinitro ortho cresol (DNOC), dinitrophenol
- Phenoxyacetic acids - 2,4-D, 2,4,5-T etc.
- Bipyridium compounds- diquat, paraquat etc.
- Heterocyclic compounds or triazenes- atrazine, propazine, simizine.
- Chloroaliphatic acids - dalapon, sodium chloroacetate, sodium trichoroacetate etc.
- Substituted urea - monouron, diuron, isoproturon etc.
- Substituted dinitroaniline - pendimethalin.

Chlorophenoxy Compounds (Phenoxyacetic acid compounds): 2,4-D

- The most important and most frequently used herbicides.
- It can potentiate the toxic effects of some plants .
- Increases the nitrate content of certain plants and increases the palatability of certain toxic plants, thus increases the poisoning risk.
- Dogs are most sensitive animals.

Bipyridal/Bipyridinium Compounds

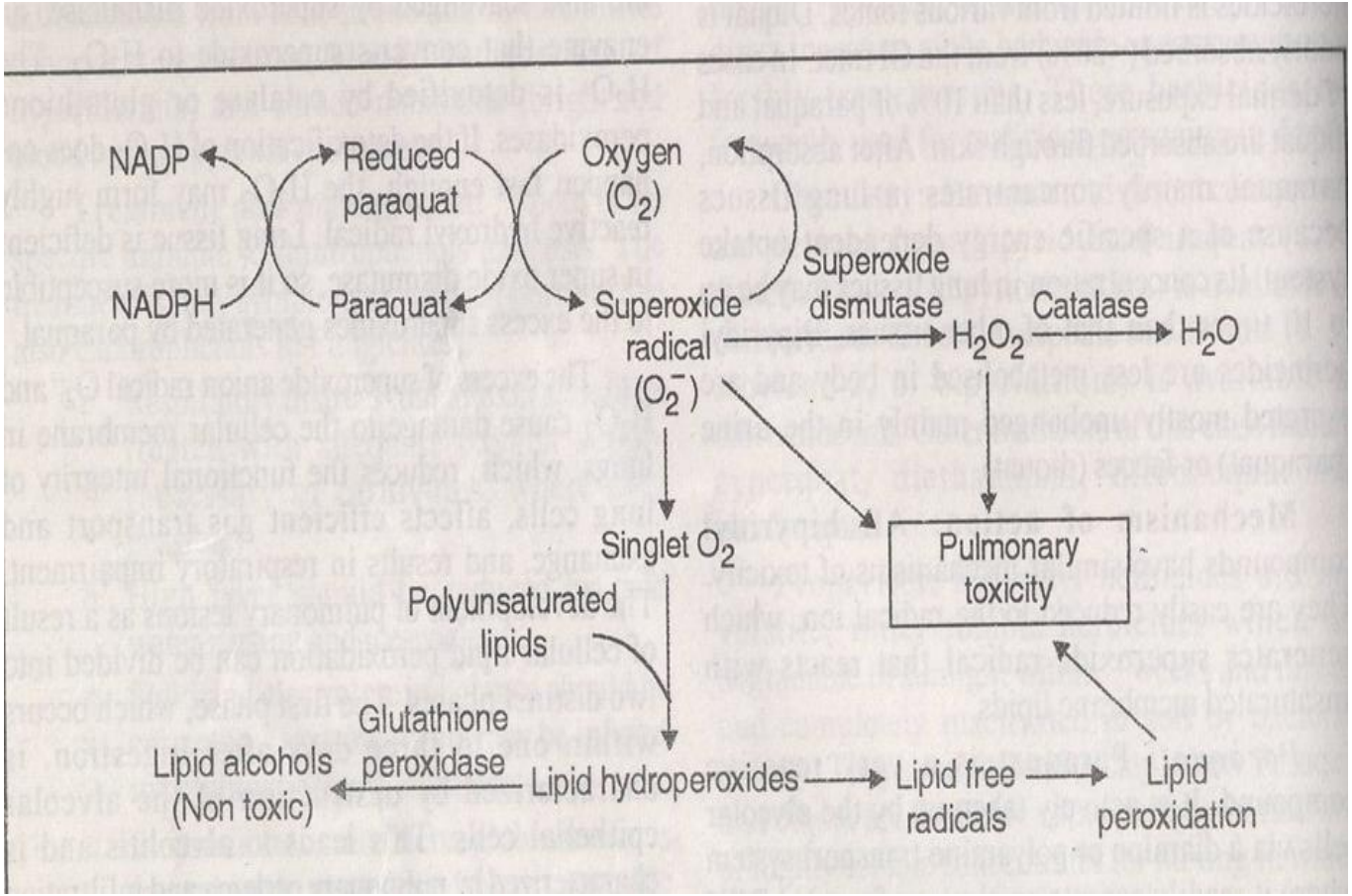
- Paraquat

- actively taken up by the alveolar cells via a diamine where it readily accepts an electron from NADPH to become reduced paraquat.

- When the reduced paraquat is reoxidized by loss of electron, a superoxide anion radical O_2- is generated.

- The superoxide radical is unstable and spontaneously breaks down to the reactive singlet oxygen.

- The reactive singlet oxygen attacks the polyunsaturated lipids associated with cell membranes to form lipid hydroperoxides.


NADP
Reduced paraquat
Oxygen (O_2)
NADPH
Paraquat
Superoxide radical (O_2^-)
Superoxide dismutase
H_2O_2
Catalase
H_2O
Singlet O_2
Pulmonary toxicity
Polyunsaturated lipids
Glutathione peroxidase
Lipid alcohols (Non toxic)
Lipid hydroperoxides
Lipid free radicals
Lipid peroxidation

- These lipid hydroperoxides are normally converted to non toxic lipid alcohols by the selenium – containing enzyme glutathione peroxidase.

- Selenium deficiency, depletion of glutathione or excess lipid hydroperoxides allow the lipid hydroperoxides to form lipid free radicals.

- The action of paraquat in lungs is similar to that produced by carbon tetrachloride in liver.

Rodenticides

Inorganic rodenticides:

- Arsenic compounds arsenic trioxide and sodium hydrogen arsenite.
- Elementary phosphorus
- Thallium sulphate
- Zinc phosphide

Organic rodenticides:

- Anticoagulants- warfarin, diphacinone, difenacoum and brodifacoum.
- Fluoroacetic acid and its derivatives – sodium fluroacetate and fluroacetamide.
- Alphanaphthylthiourea (ANTU)
- Bromothalin
- Strychnine
- Red squill
- Pyriminil
- Norbormide
- Crimidine
- Chloralose

Zinc phosphide

- It is one of the most widely used rodenticides in developing country because it is cheap and very effective.

- It is often recommended as the **rodenticides of choice** because it is fairly specific for rodents and there is no true secondary poisoning, except possibly in dog and cat.

- Liberation of **phosphine gas in acid pH in stomach** – irritates GIT and causes CVS collapse.

Mechanism of action:

- Acute zinc phosphide toxicosis is due to the phosphine gas. phosphine gas is said to act as a general protoplasmic poison.
- It causes direct damage to membranes of blood vessels and erythrocytes leading to cardiovascular collapse.
- Phosphine also causes depression of CNS, irritation of lungs and damage to liver and kidneys.

Clinical Signs:

- Vomiting, acidosis, abdominal pain, aimless running, howling, ataxia, dyspnoea, gasping and convulsions.

Treatment:

- **Calcium boro-gluconate and fluid therapy to reduce acidosis (2-4 litres of 5% soda bicarb. PO).**

Warfarin and Congeners

- Pindone, coumafuryl, coumachlor etc. are most commonly used potentially dangerous compounds.

Mechanism of Toxicosis:

- It is also called as anticoagulant rodenticides.
- It has basic **coumarin or indanedione nucleus.**
- Act as anti-vitamin K and interfere with synthesis of coagulation-Factors I, II, VII and X in liver.
- Prothrombin ~~——~~ thrombin

(failure of blood clotting)

↓

generalized haemorrhages.

Clinical Signs:

Anaemia, hematomas, hemothorax, epistaxis and hematuria, weakness ataxia, colic and polypnoea.

Treatment:

- Vitamin K_1 @ 2.5-5 mg/kg iv or sc smallest possible needle at several locations to speed up absorption for 2 – 4 weeks.
- Fresh or frozen plasma @ 9 ml/kg or whole blood 20 ml/kg iv to replace clotting factors.
- Thoracocentesis to relieve dyspnoea due to hemothorax and artificial respiration with oxygen.

Alpha Naphthyl Thiourea (ANTU)

Mechanism of Toxicosis: Animal drowned in own fluid

- It interferes with effective uptake of O_2 from pulmonary alveoli by producing massive oedema of lungs due to increase capillary permeability.

- ANTU undergoes metabolism by microsomal mixed function oxidases releasing atomic sulphur which damages the endothelium of alveolar capillaries – leakage of fluid into alveoli (airways)– pulmonary oedema
- It causes vomiting on empty stomach due to intense local gastric irritation, but poisoning occurs if ANTU is ingested after feeding.

Red Squill

- It is the ground bulbs of *Urgenia maritime.*
- Contain cardiac glycoside- *proscillaridin*.
- Considered as the safest rodenticide (nontoxic to poultry, unpalatable to livestock, vomiting if cats/dogs ingest, rats are incapable of vomiting).

Formamidine insecticides- Amitraz stimulation of alpha2-adrenoceptors and inhibition of monoamine oxidase (MAO) enzyme

- **NEONICOTINOID INSECTICIDES: IMIDACLOPRID**
- **Mechanism of action:**

acts and binds selectively to nicotinic cholinergic receptors on the post-synaptic membrane.

- nicotinic receptors of mammals are less sensitive to imidacloprid than are insect receptors

Urea Poisoning

- **Toxic dose:** Cattle, sheep: 1 g/kg (lethal dose), 0.5 g/kg (Toxic), 0.3 g/kg (Mild toxic)
- Horse: 4 g/kg (Oral LD_{50})

- rumen pH is elevated to 11, more and more NH_3 will be released and present in non-ionized form (NH_3) which is diffusible into systematic circulation

- Toxic conc.: rumen NH_3 concentration 80 mg% and BUN 0.84 – 1.3 mg %

- NH_3 inhibits TCA (citric acid) cycle. There is decrease in energy production and cellular respiration.
- presence of urease in soyabean potentiate toxicity

- **5% acetic acid/(vinegar)** given (2.5-5 litres) with sufficient cold water
- **Bovine bunker syndrome: NPN/ ammonia poisoning**

Carbon tetrachloride

- anti trematodal drug against fascioliasis in ruminants
- reference hepatotoxic agent
- Pigs are most susceptible of all mammals and sheep is quite tolerant

- $CCl_4 \rightarrow CCl_3^-$ (trichloromethyl free radical) $\rightarrow CCl_3COO^-$ (trichloromethyl peroxy free radical)

- reactions are catalyzed by cytochrome P450 dependent monooxygenase

Phenothiazine

- cause **photosensitization in animals**
- In horses causes hemolysis of RBC (Blood enzyme – lysolecithin is activated)
- Sensitization to sunlight is more frequent problem because **of phenothiazine sulfoxide (metabolite of phenothiazine)**
- Hemolysis in horses leading to icteric membranes and presence of Hb in urine
- Calves show photosensitization, keratitis. In sheep, keratitis accompanied by reddening and thickening of muzzle and ears

Disease	Fungus	Crop or substrate	Mycotoxin	Animals affected
Aflatoxicosis	*Aspergillus flavus* *Aspergillus parasiticus*	Ground nut, maize and nut crops	Afaltoxins B1, B2, G1,G2	Cattle, pig, poultry and dogs
Ergotism	*Claviceps purpurea*	Seed heads of many grasses and grains	Ergotamine and ergometrine	Cattle, Sheep, Pig, Horse and Poultry
Facial Eczema	*Pithomyces charatarum*	Pasture, litter	Sporidesmin	Sheep and Cattle
Oestrogenism	*Fusarium graminareum*	Maize, Barley and cereals	Zearalenone	Pigs
Leukoencephalo malacia	*Fusarium moniliforme*	Maize	Fumonisins B1 (A1, A2, B2)	Horses and Donkey
Trichothecane toxicosis	Many *Fusarium* species	Cereals	T-2 toxin, diacetoxy - seripenol	Many species
Ocharatoxicosis	*A. ochraceus* *P. viridicatum*	Barley, wheat and Maize	Ochratoxin -A	Pigs and Poultry

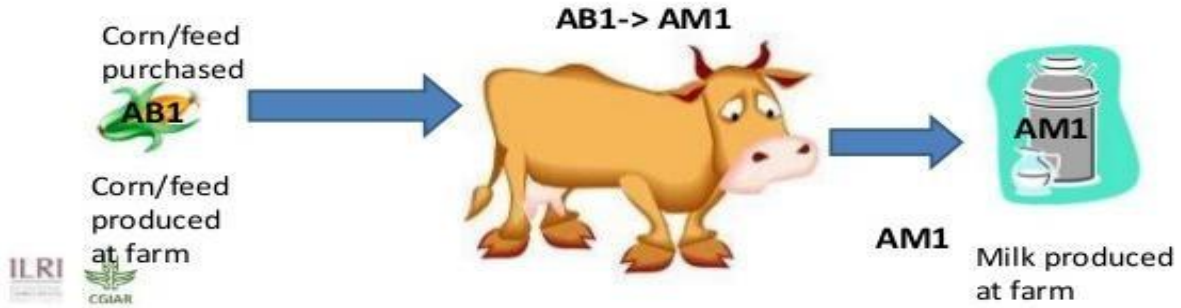
Species	Toxins
A.flavus and A.parasiticus	Aflatoxins
A. ocheraceus	Ochratoxin
Fusarium roseum	Trichothecane (t-2) toxin
Penicillium citrinum	Citrinin

Target organs/ tissues	Toxins
Vascular system	Aflatoxins
Digestive system	Aflatoxins
Mucous membrane	Trichothecane (t-2) toxin
Urinary system	Ochratoxin
Reproductive system	Zearalenone (Fusarium toxin)
Cutaneous system	Sporidesmin

AFLATOXICOSIS

- Afalatoxins produced by *A. flavus* and *A. parasiticus*
- Four major aflatoxins are B1, B2, G1 and G2
- B1and B2 produce blue color and G1, G2 gives green fluorescence.
- Aflatoxins M1, M2 are hydroxylated metabolites of B1 and B2 ---- excreted in the milk of lactating animals

- Young animals are highly susceptible
- Aflatoxin B1 produce the most hepatogenic, carcinogenic, teratogenic and embryotoxic effects
- Calves- blindness, circling, grinding of teeth, diarrhoea, tenesmus & convulsions



- **Ducklings- most susceptible avain species**
- In birds over three weeks of age, subcutaneous haemorrhages of legs and feet

PM Lesions

Principle target organ is liver causes hepatomegaly with necrosis & bile duct hyperplasia

Chronic toxicity, in additon to liver damage, degenerative changes in the kidney, thymus cortical aplasia leading to decreased cell mediated immune response

DIAGNOSIS

- Biological assays for toxicity are important confirmatory steps
- **Concentration of aflatoxin B1 in excess of 100µg /kg of feed are considered toxic for cattle**
- Thinlayer chromatography and HPLC are more sensitive analytical methods for determing afaltoxins levels in the food.
- Radio immuno assay & ELISA
- **Biological assays**- Ducklings are mostly susceptible. Bile duct proliferation in one-day-old ducklings and chick embryo bioassay

Erogtism

- Fungal species of the genus *Claviceps*, notably *Claviceps purpurea*
- toxic alkaloids - ergotamine and ergometrine
- Two forms of ergotism- gangrenous & convulsive ergotism
- Ergot alkaloids may exert an oxytocin like effects causing abortions
- Gangrenous ergotism - Gangrenous necrosis of the extremities – nose, ears, tail, teats & limbs
- Tail gangrene

Fusarium Toxicoses

- Estrogenic metabolites – DON, **zearalenone (F-2 toxin) and** Trichothecene toxins by Fusiarium graminearum and other Fusiarium species

- Zearalenone - oestrogenic activity

- Target organ system- reproductive tract of pigs causing vulvovaginitis, associated with the consumption of moldy maize by gilts.

DON and T-2 Toxin

- Deoxynivalenol (DON), also known as vomitoxin
- necrosis and hemorrhage of the digestive tract, decreased blood production in the bone and spleen, and changes to reproductive systems.
- In poultry, causes reduced egg production, beak lesions, and abnormal feathering
- Advisory level of DON/ Vomitoxin is 1 ppm

Ochratoxicosis and Citrinin Toxicosis

- Several *Aspergillus and Penicillium species*, particularly toxigenic strains of *Aspergillus ochraceus, A. alutaceus and Penicillium verrucosum produce ochratoxins*

- Group of related iso coumarin derivatives

- Ochratoxin A is the principal nephrotoxic mycotoxin in this group

- The mycotoxin citrinin, which can also be produced by *A. ochraceus as well* as by *Penicillium citrinum, P. viridicatum and P. expansum*, is nephrotoxic.

Toxicity caused by poisonous animals

- **Zootoxins:** Toxins produced by lower animals, e.g. snakes, fish, toads, scorpions, bees, wasps, spider, ticks etc.

- **Venomous animals:** Animals capable of producing a poison in a highly developed secretary gland or group of cells and deliver toxin during a stinging and biting act

- Spider, scorpions, bees, wasps, ants, beetles, caterpillars etc.

- Venom may be composed of proteins (polypeptides and enzymes) of both high and low molecular weight.

Snake Venom Toxicity:

- Snake venom - colloidal solution of toxic components-mainly enzymes and non enzymatic peptides and amino acids, (in addition to K^+, Na^+, Ca^{++}, Mg^{++}, Ni^{++} etc.)
- more than 3500 different species out of which more than 400 are poisonous and dangerous
- 1. **Elapidae:** Elapids, Cobras, Kraits, Cora snakes, Mombas
- 2. **Crotalidae:** Crotalids, Pit vipers, rattle snakes, bush master, water moccasins, copper heads
- 3. **Viperidae:** Viperids, vipers, adders
- 4. **Hydrophidae:** All sea snakes, water snakes
- 5. **Colubridae:** Colubrids includes poisonous and non-poisonous snakes – Boomslang, bird snake, rednecked, keelback snake.

- **Active principles of snake venoms:**
- Hyaluronidase, Cholinesterase, proteolytic phosphates, phospholipase A
- Protein and amino acids : toxin
- also contain some different fractions like necrotizing, anticoagulant, coagulant, neurotoxic, cardiotoxic and haemolytic fractions.

- venoms of cobra and krait are mainly neurotoxic while that of vipers and rattles snakes are haemotoxic

- components which itself are not toxic help to increase toxicity of others e.g. Hyaluronidase helps in spreading the toxin

- . Horse > Sheep > Cattle > Goat > dog > Pig > Cat

- **Antihistaminic are contraindicated as they enhance the action of venom/potentiate the effect of venom**

S.No.	Viperine	Elapine
1.	Mainly haemotoxic	Mainly neurotoxic
2	Local swelling at the site of bite which develops very rapidly	No local swelling. Symptoms take about 1 hr to appear
3	Excitement with anxiety	Excitement with convulsions. Nervous signs – Paralysis, Death – respiratory paralysis.
4	Coagulability of blood is completely lost, therefore haemorrhages	Coagulability of blood is not affected
5	Death due to extensive haemorrhages leading to shock or pulmonary thrombosis	Death due to paralysis of respiratory centre.

Spider venom toxicity

- Black widow spiders (Latrodectus mactans) Black recluse spider (Loxoscales reclusa)

- i) Neurotoxin – it affects neuromuscular junctions and cause the release of ACh from pre-synaptic nerve fibers and enhances depolarization.
ii) Lipoproteins, Hyaluronidase, High content of leucine and isoleucine and low tyrosine

* neurotoxin of black widow spider is α-latrotoxin

- death occurs in 4 to 6 hrs in acute cases to few days in mild ones. (due to paralysis of respiratory muscle)

Scorpion toxicity

- stinger located on the tip of tail.
- Venom causes muscular stimulation and hemorrhage.

- **Toxic components:** Heterogenous mixture – neurotoxin, cardiotoxin, nephrotoxin, haemolysin, agglutinins, phospholipases, hyaluronidases, histamines, serotonin etc. The most potent is the neurotoxins

- **Mechanism of action:** Neurotoxin interacts with voltage dependent Na+ channel and stabilizes it in the open position, which leads to prolonged and repetitive firing of somatic, sympathetic and parasympathetic neurons.

Toads

- *Bufo vulgaris* (common toad), *B. marinus* (marine toad), *B. alvarius* (River toad). Out of these, *B. alvarrius, B. marinus* are most toxic and B. vulgaris is least toxic

- Toxins secreted by glands in their skin located above and posterior to eyes (produced in the parotid glands)

- Different toad toxinsn1. Bufodienolides which include Bufogenins and their derivative bufotoxins: Bufotalins, Bufotenidin, Bufotenin, Bufoviridin, 2. Serotonin, 3. Catecholamines.

- **Bufogenins are cardiac glycosides and effect heart and other smooth muscles.**

- toxin binds with specific receptor site on Na^+-K^+-ATPase pump in cardiac cell membrane and inhibits its function causing excessive cardiac stimulation and ventricular fibrillation.

- Death occurs rapidly from heart failure.

Fish toxins (Ichthyotoxins)

- **1. Shellfish toxicity: produces saxitoxin**
- Interfere with ionic transport across the axonal membrane. It inhibits inward current of Na^+ across axonal membrane

- **2. Puffer fish toxicity (Fugu fish toxicity):** produces Tetrodotoxin

- **Mechanism of Action:** Tetrodotoxin is a potent neurotoxin that blocks the inward conduction of Na^+ through Na-channels across the cell membranes of excitable cells.
- direct paralyzing effect on striated muscle and nerve fibers. It also provokes hypotension and has deleterious effects on respiration.

Bees and Wasps Toxicity

- Honey bee venom also contains i) hyaluronidase and ii) proteins – melittin, aparmin.
- Hyaluronidase cause hypotension and increased vascular permeability
- Mellitin is antigenic in nature and produce hypersensitivity (allergic) reactions mainly in human beings and horses.
- Multiple stings result in death due to anaphylactic shock. Allergic responses also observed.
- Wasp venom also contains a variety of amines and kinins.

Radiation toxicology

- study of adverse effects of radiation on living organisms.

- **Mechanism of action:** DNA strands break, point mutation and chromosomal aberrations, then loss of gene products which leads to cell death. rate of chromosomal aberrations is directly related to radiation dose.

- **Pathogenesis:** The rapidly and undifferentiated cells are most sensitive. Skin, GI tract and haematopoietic system are worst affected (with exception of human lymphocytes).

- Biological systems irradiated in presence of O_2 are more susceptible to injury as it results in formation of hydroperoxy or H_2O_2 radicals which damage more due to their long half-lives. The response is termed as "Oxygen effect".

• **Thyroid:** Radioactive isotopes at iodine (^{131}I) are accumulated in the thyroid gland, which destroy thyroid gland.

• **Bones:** Nuclides deposited preferentially in bone or on bone are collectively known as "Bone Seekers"- ^{89}Strontium, ^{90}Strontium, ^{140}Barium, radium isotopes etc. They suppress bone marrow and result in lymphopenia, leucopenia, anaemia.

• **Reproductive organs:** Stops cell division of testicular germinal epithelium. Acute dose of 600 rad in testes produce permanent sterility. But fully developed sperm cells and primary spermatocytes relatively radio-resistant. Atrophy and degeneration of ova occurs in ovary. It may cause death of embryo.