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

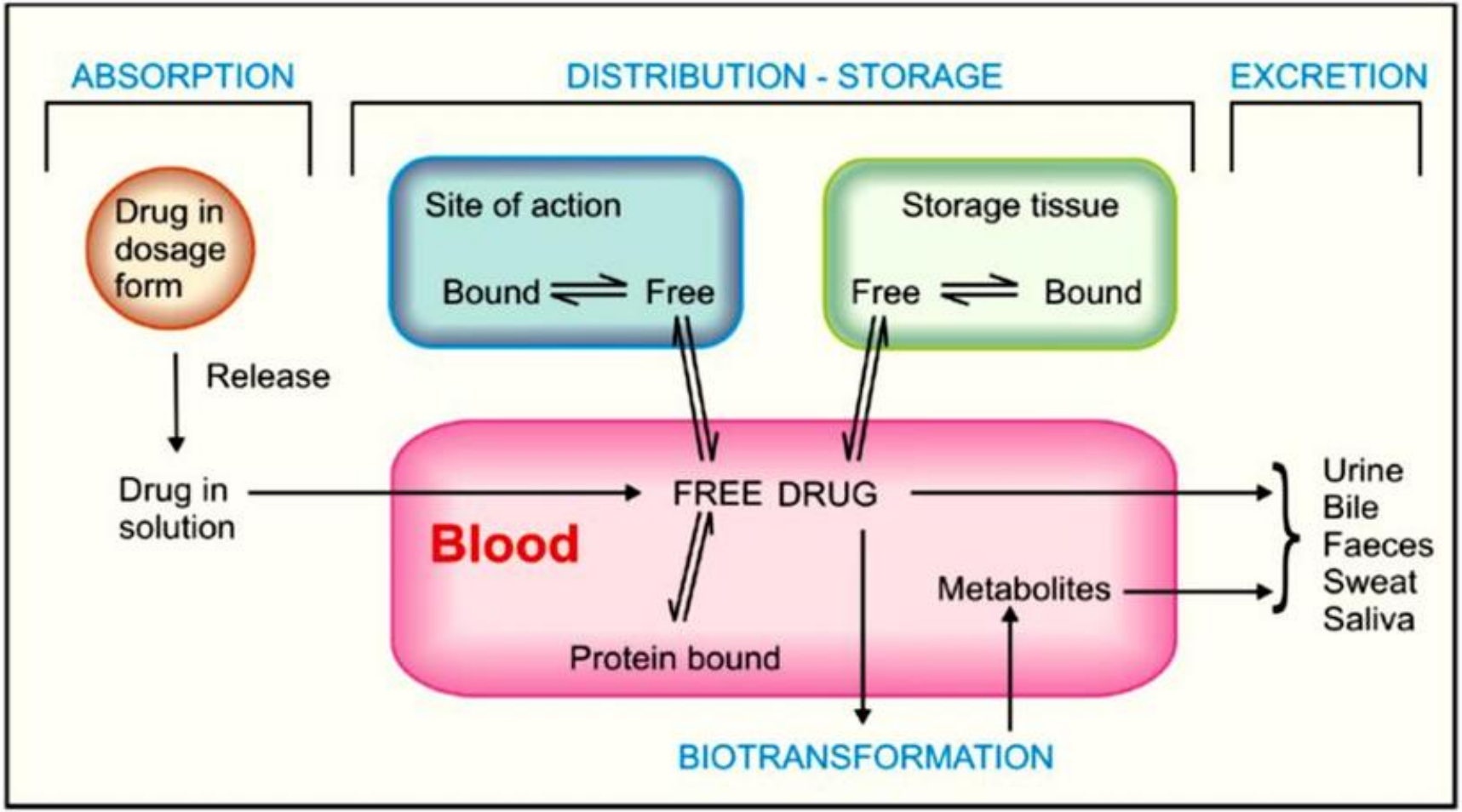
- Saponin: These are non-nitrogenous substances soluble in water which form foam or froth when shaken with water.
- Saponins upon hydrolysis, split into a sugar and a non-sugar (sapogenin), hence considered as a sub class of glycosides
- Examples– Quillaris, Senega etc.

- 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.

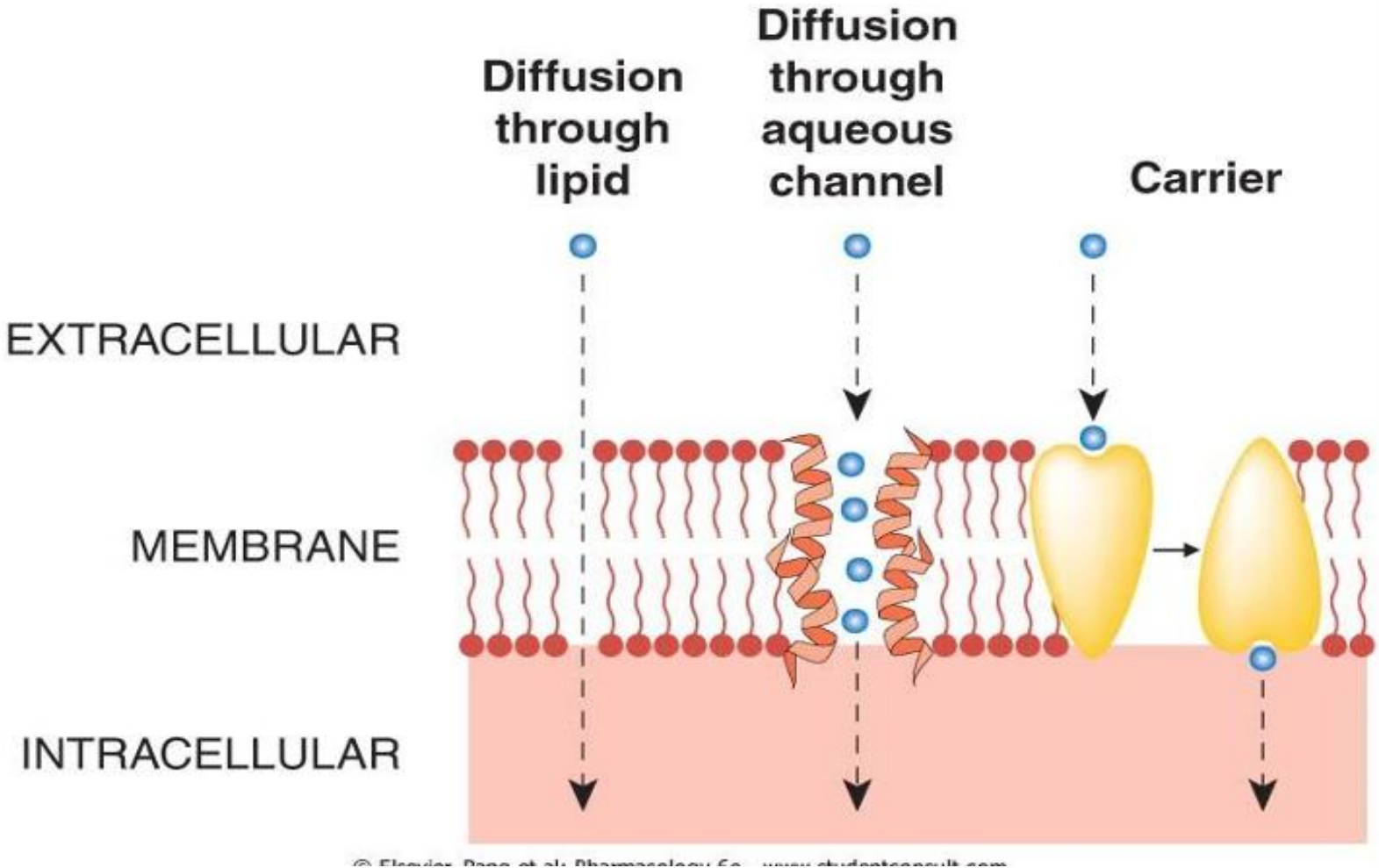
- Structure of Cell membrane:
  - **Bilayer of amphipathic lipids** i.e. contains both hydrophilic and hydrophobic portions. The hydrophilic heads are oriented outwards and hydrophobic hydrocarbon chains oriented inwards to the centre of the bilayer to form a continuous hydrophobic phase.
  - **Individual 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
- Drugs ————> phase-1 ————> metabolites
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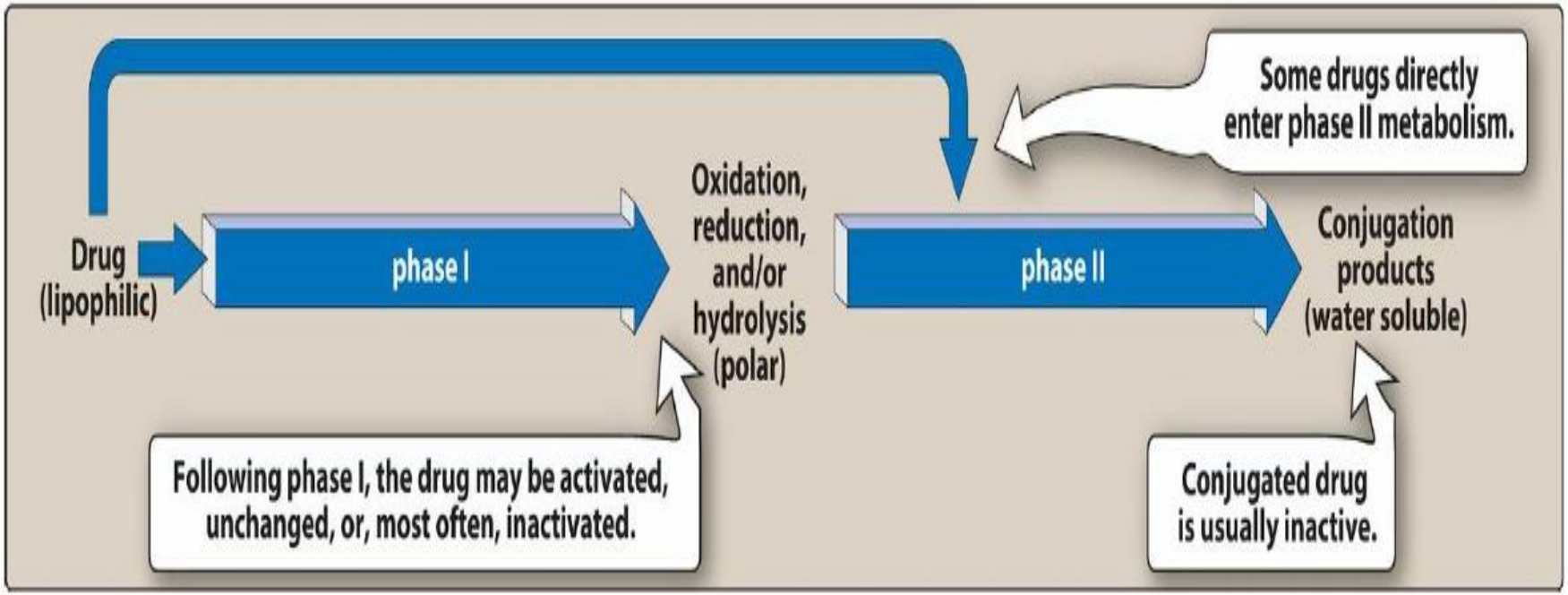
Some drugs directly enter phase II metabolism.
Drug (lipophilic)
phase I
Oxidation, reduction, and/or hydrolysis (polar)
phase II
Conjugation products (water soluble)
Following phase I, the drug may be activated, unchanged, or, most often, inactivated.
Conjugated drug is usually inactive.

- 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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Various oxidative reactions of drugs :

Oxidative reaction	*Drug*	*Metabolite*
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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 :
- Hydrolysis of Acetylcholine (ACh) by acetylchonesterase (AChE)
- 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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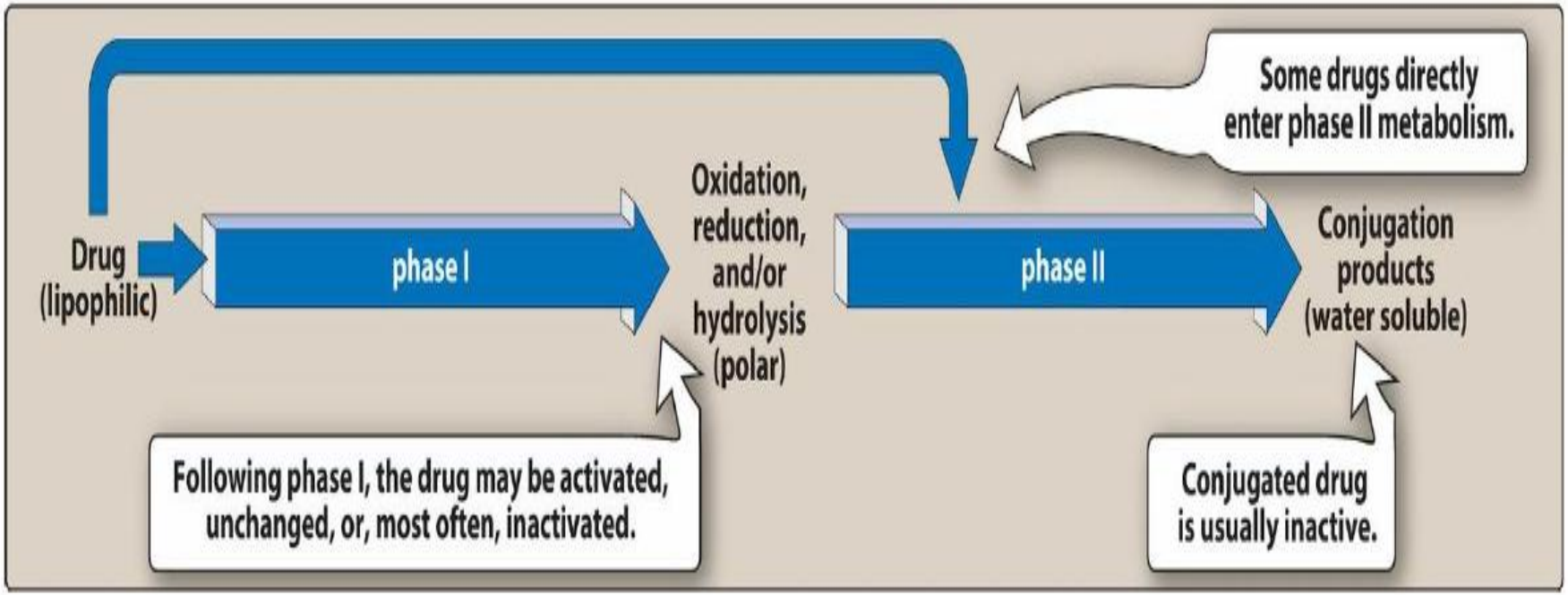
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- Lignocaine (liver) by non-microsomal hepatic amidase.

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.

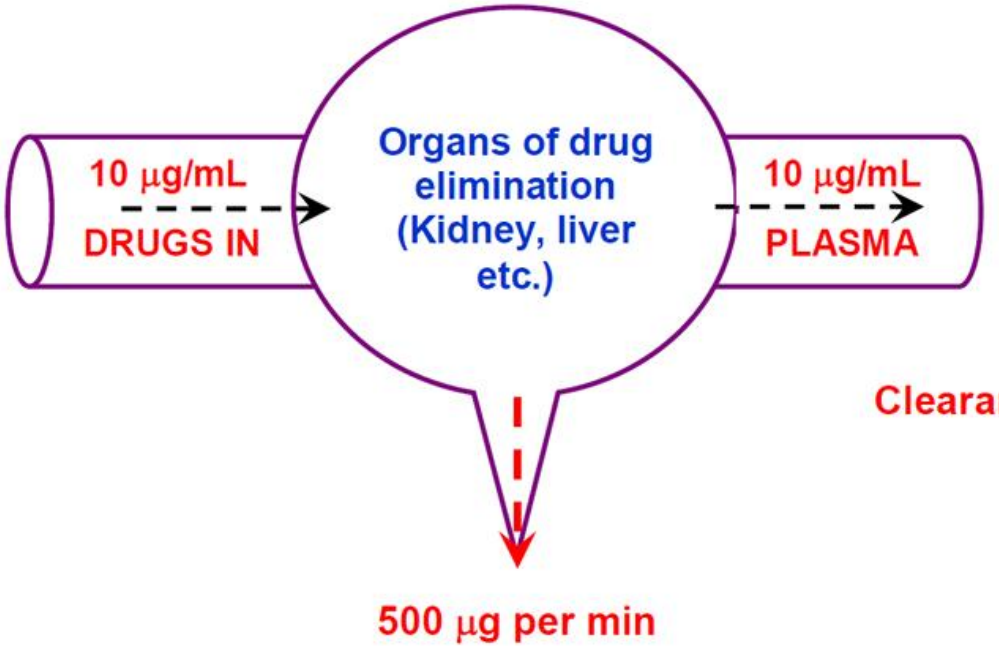
Zero order Kinetics

- 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)

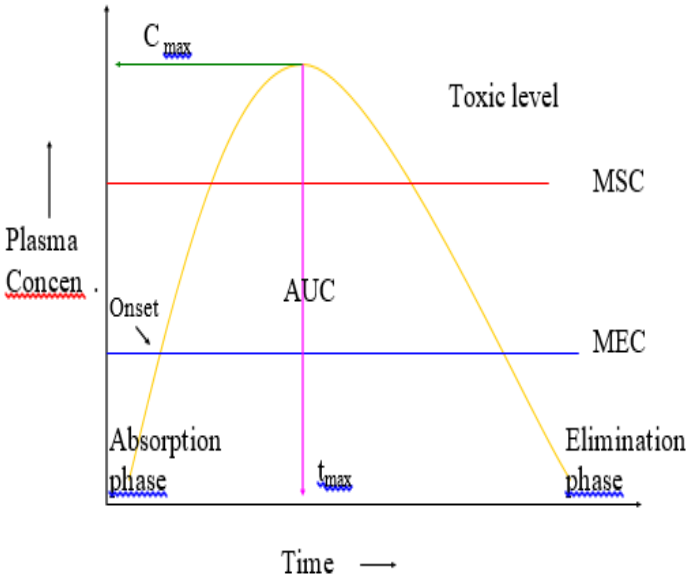
- Clearance (CL): It is the theoretical volume of plasma from which the drug is completely removed in unit time.
- Clearance = Rate of elimination/ Plasma concentration



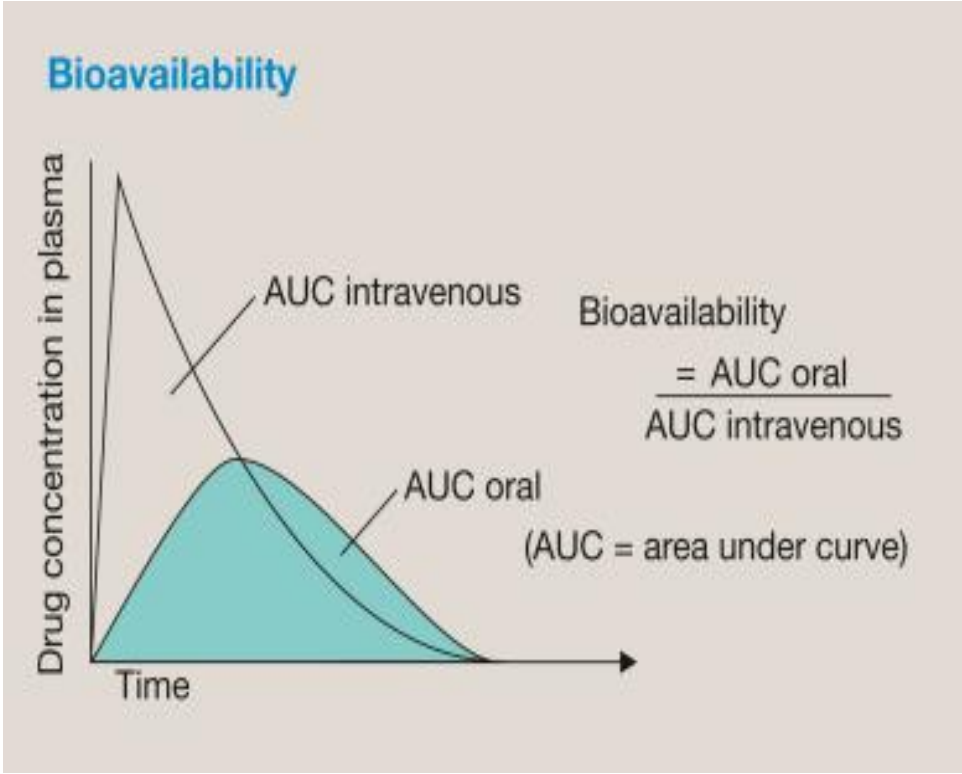
$$\text{Clearance} = \frac{500\ \mu g/min}{10\ \mu g/mL}$$

$$= 50\ ml/min$$

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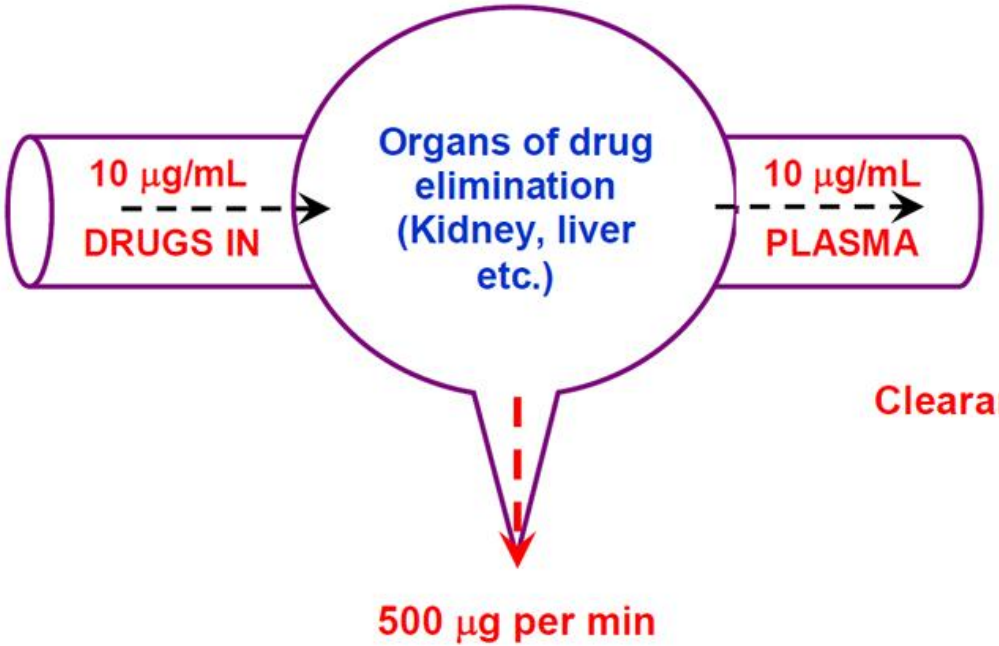
- Volume of Distribution (L) = Amount of drug in the body (mg) / Plasma concentration of drug (mg/L)

- **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.

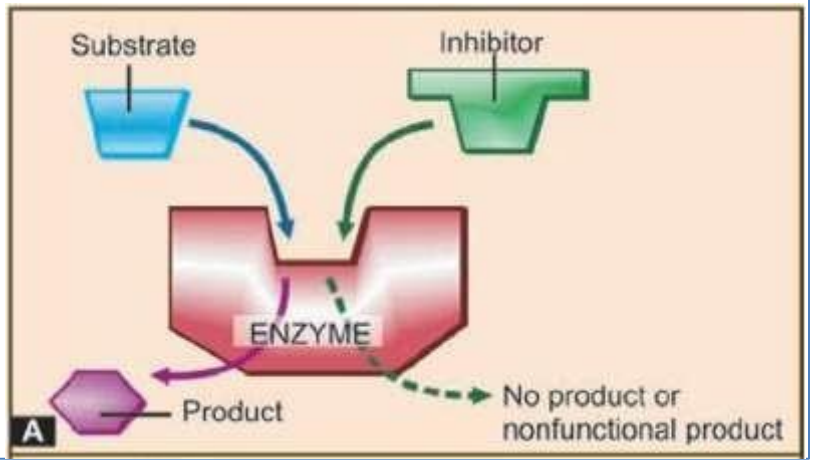
- A few examples include, local anaesthetics that bind to components of the sodium channels in excitable membranes and prevent depolarization, calcium channel blockers that inhibit the entry of calcium into cells.

- 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

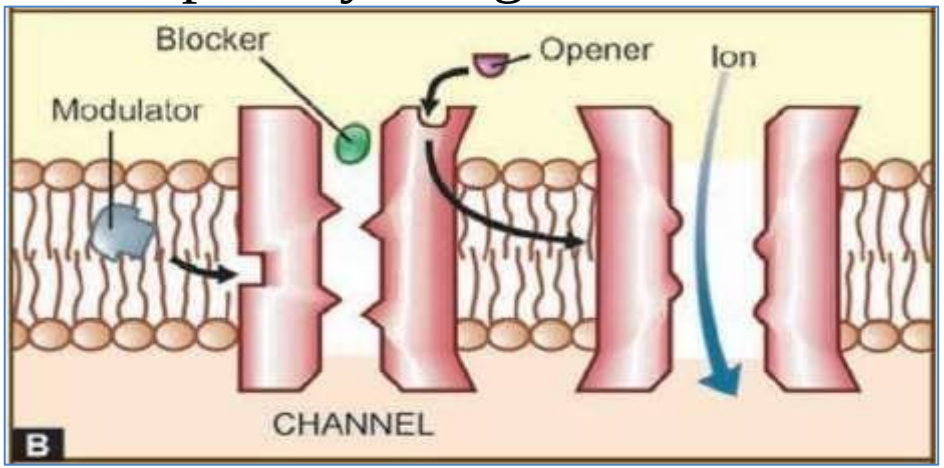
- Almost all biological reactions are carried out under catalytic influence of enzymes;
- Drugs can either increase or decrease the rate of enzymatically mediated reactions.
- Enzyme Inhibition:
  - Non-selective & Selective.
- Selective enzyme inhibition:
  - Competitive & Non-competitive.



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

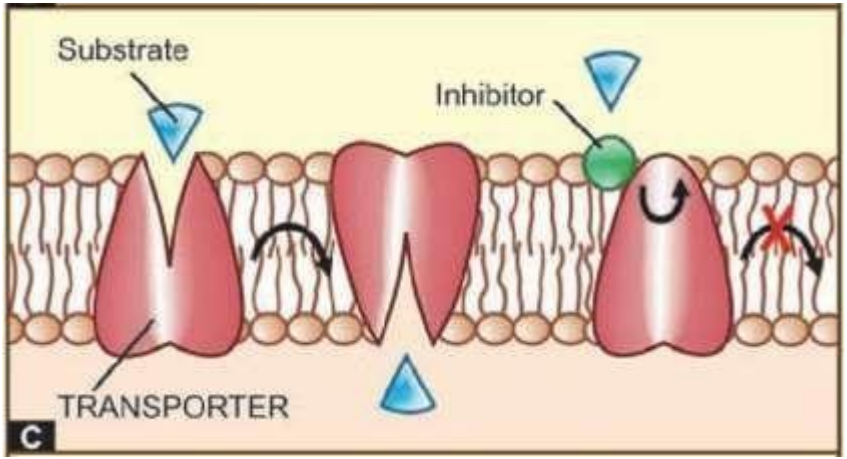
- Some ion channels (known as ligand gated channels) are directly linked to a receptor and they open only when the receptor is occupied by an agonist



- 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)

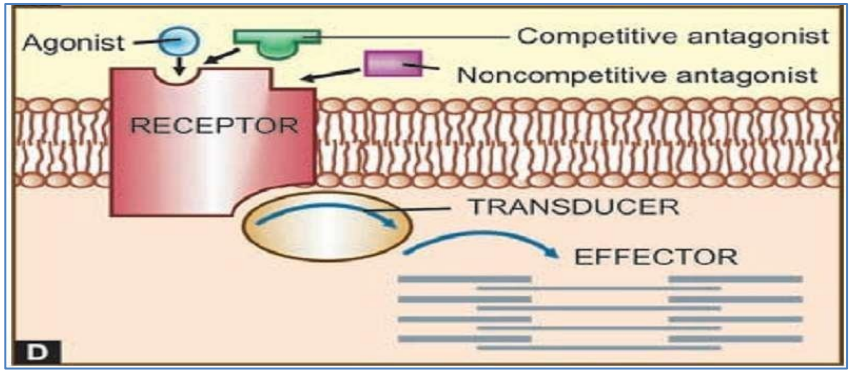
- The transport of ions and small organic molecules across cell membranes generally requires a carrier protein (transporter), the since permeating molecules are often polar, to penetrate lipid membranes on their own.



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.

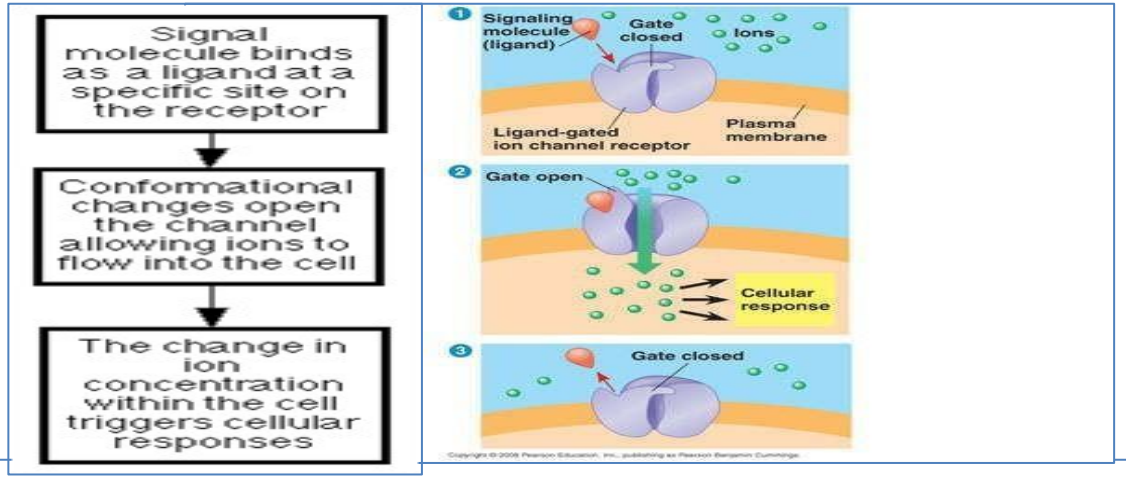


Properties of Receptors

- 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

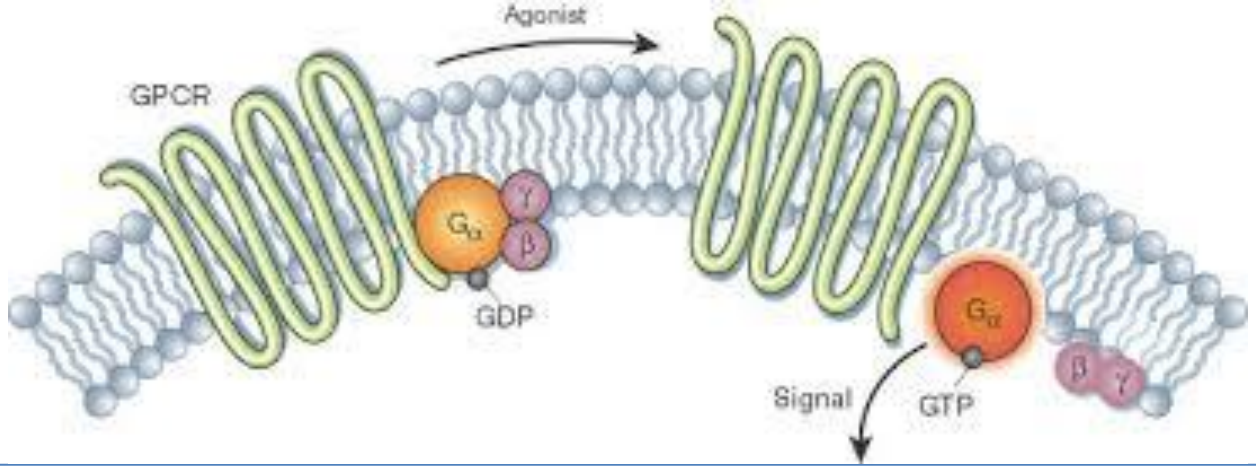
Types of Receptors

- **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.



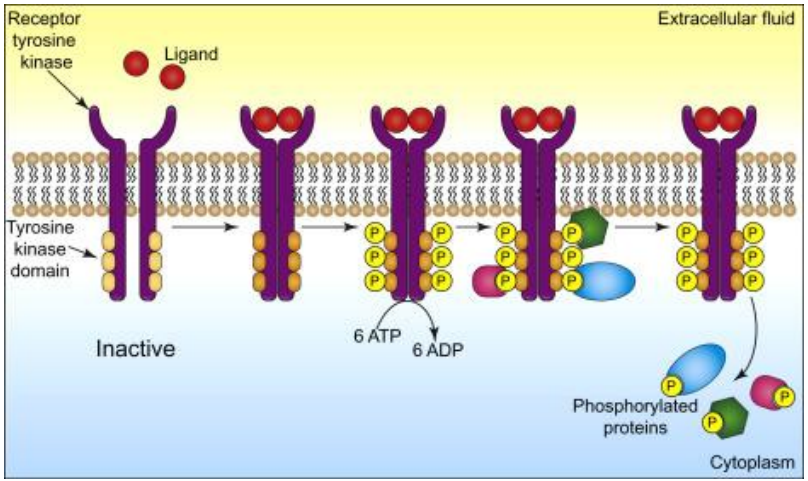
G-protein coupled receptors (GPCRs)

- 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



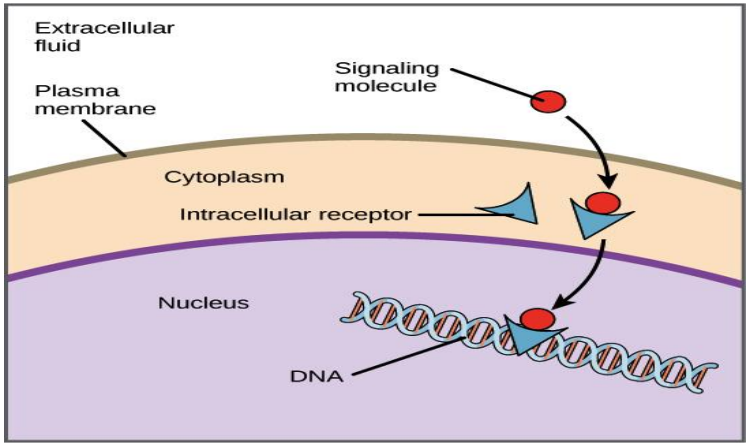
Kinase-linked and related receptors

- 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.).

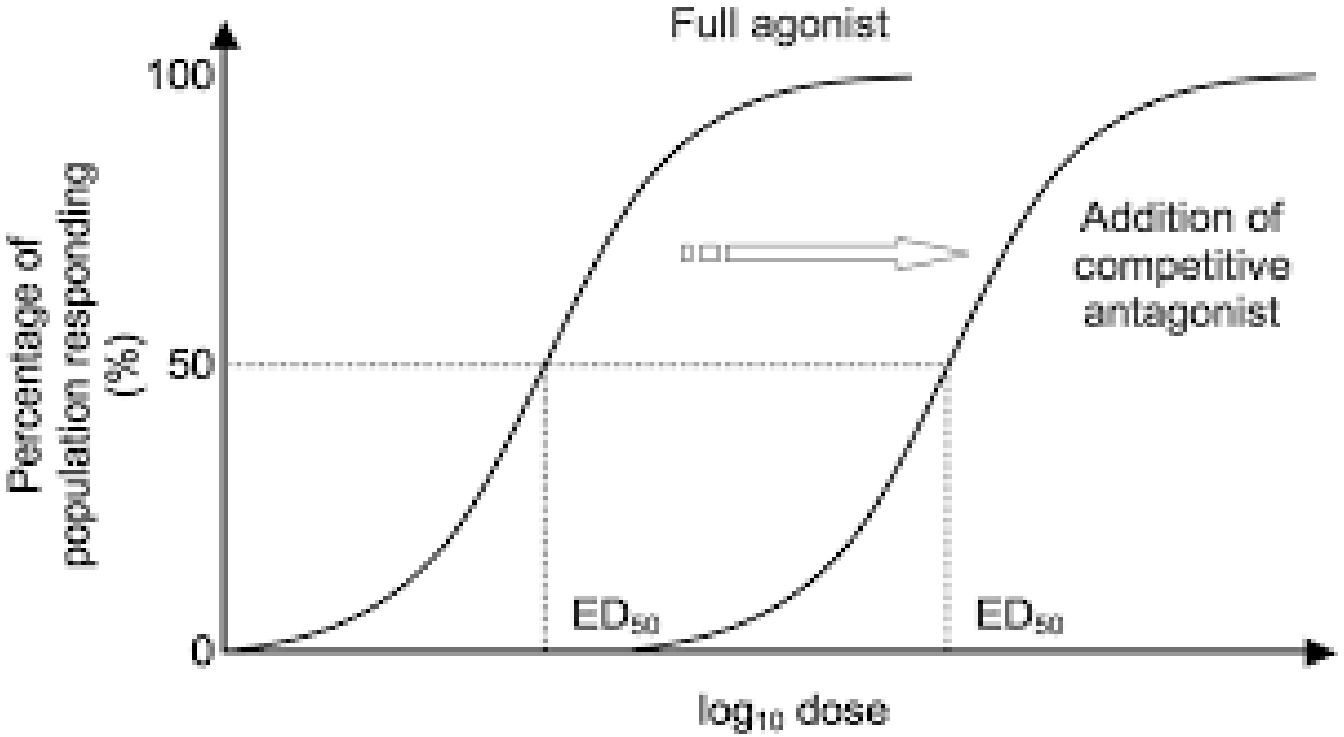
3. Physiological/ Functional antagonism: Two drugs act on different receptors, mechanisms or by different , have opposite overt effects on the same physiological function i.e. pharmacological effects in opposite direction.

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

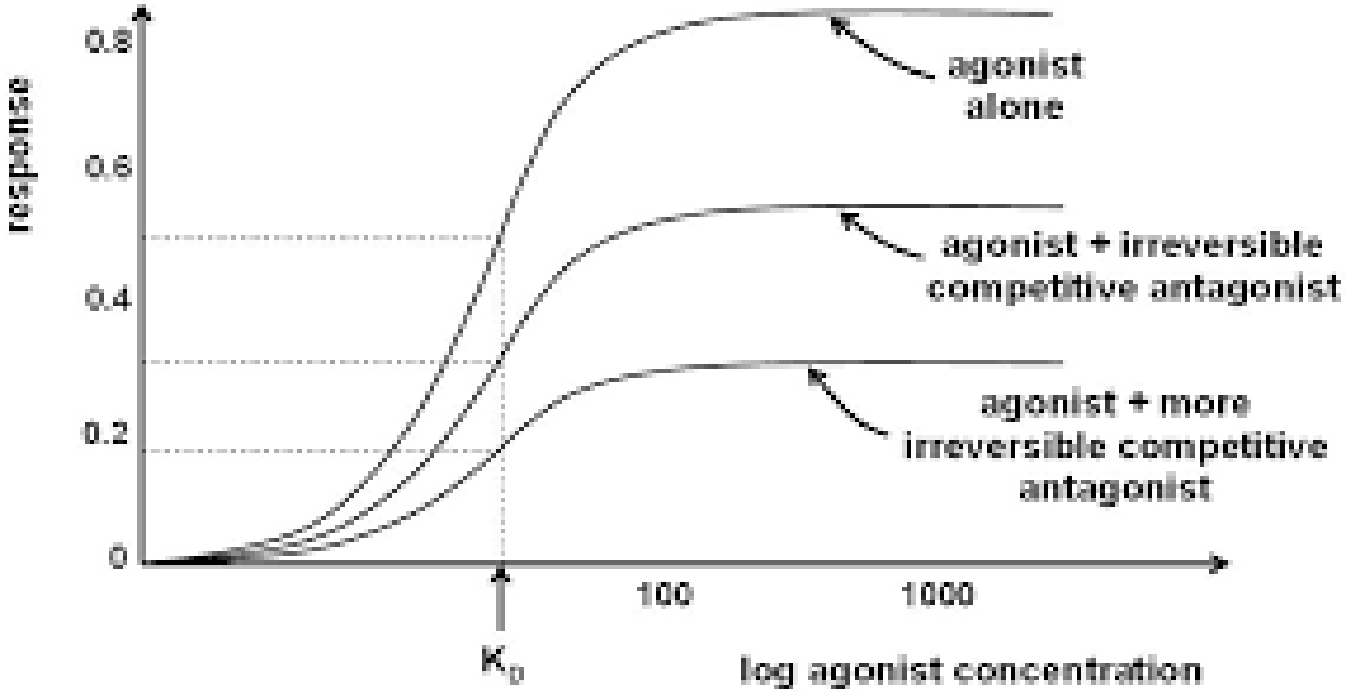
4. Antagonism by Receptor Block: The antagonist interferes with binding of the agonist with its receptor or inhibits the generation of response consequent to such binding.

- 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

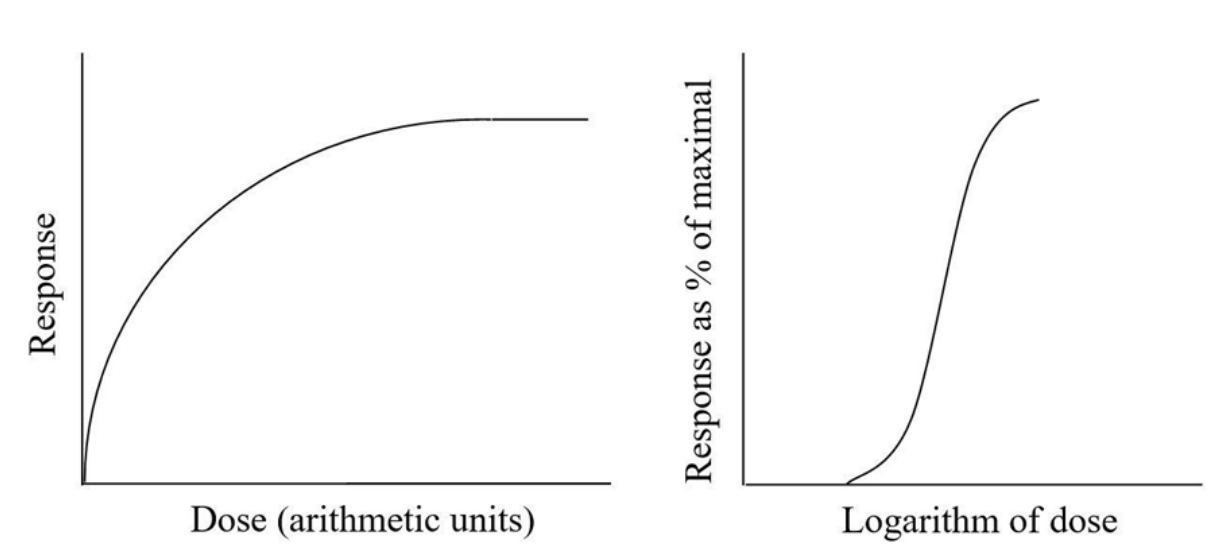
(ii) Quantal dose response curve

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

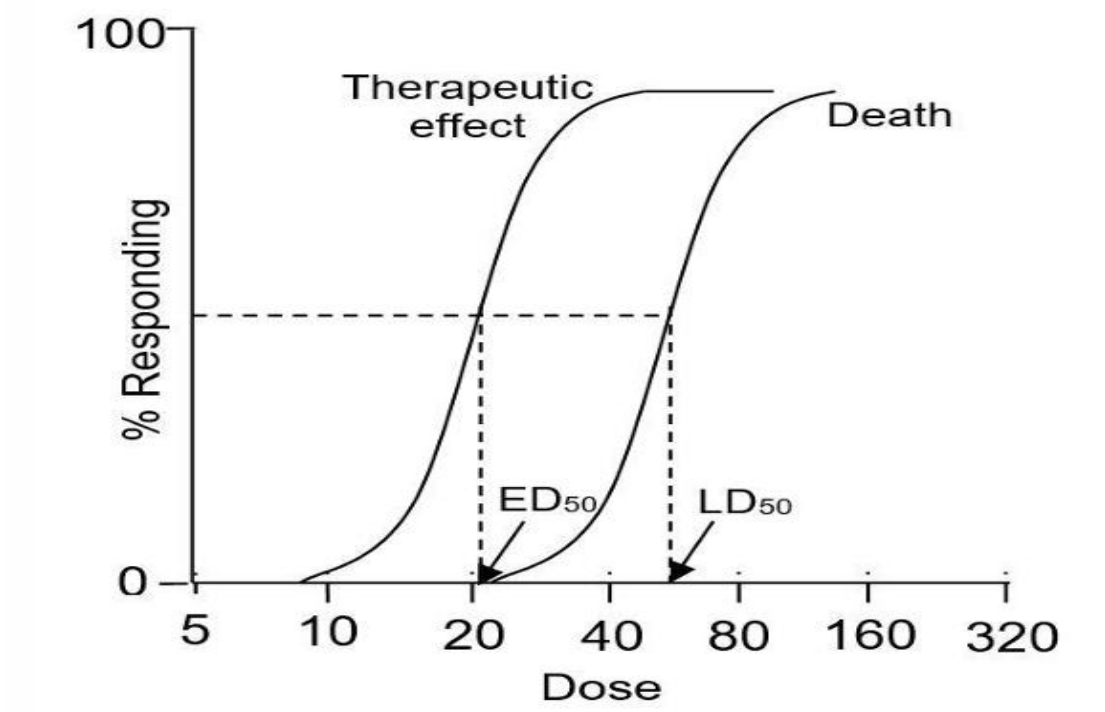
Graded Dose Response Curve



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.

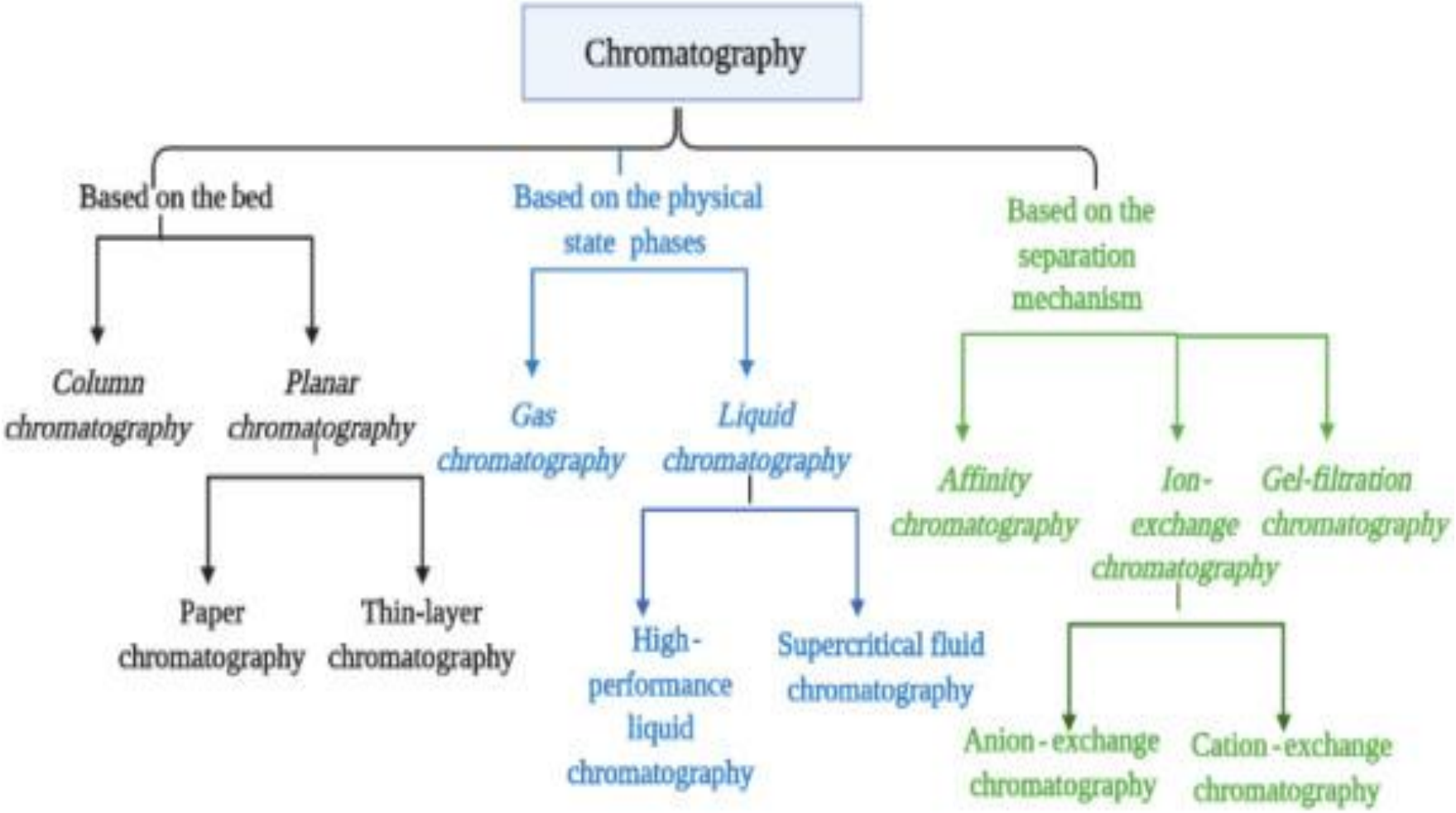
1. Drug interactions may be due to chelation of drugs by nutrients e.g. tetracyclines in presence Ca^{+2} ions.
2. Interactions may be at the level of absorption, distribution (less distribution due to more protein binding). Metabolism (induction of microsomal enzymes), excretion (Penicillin in presence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

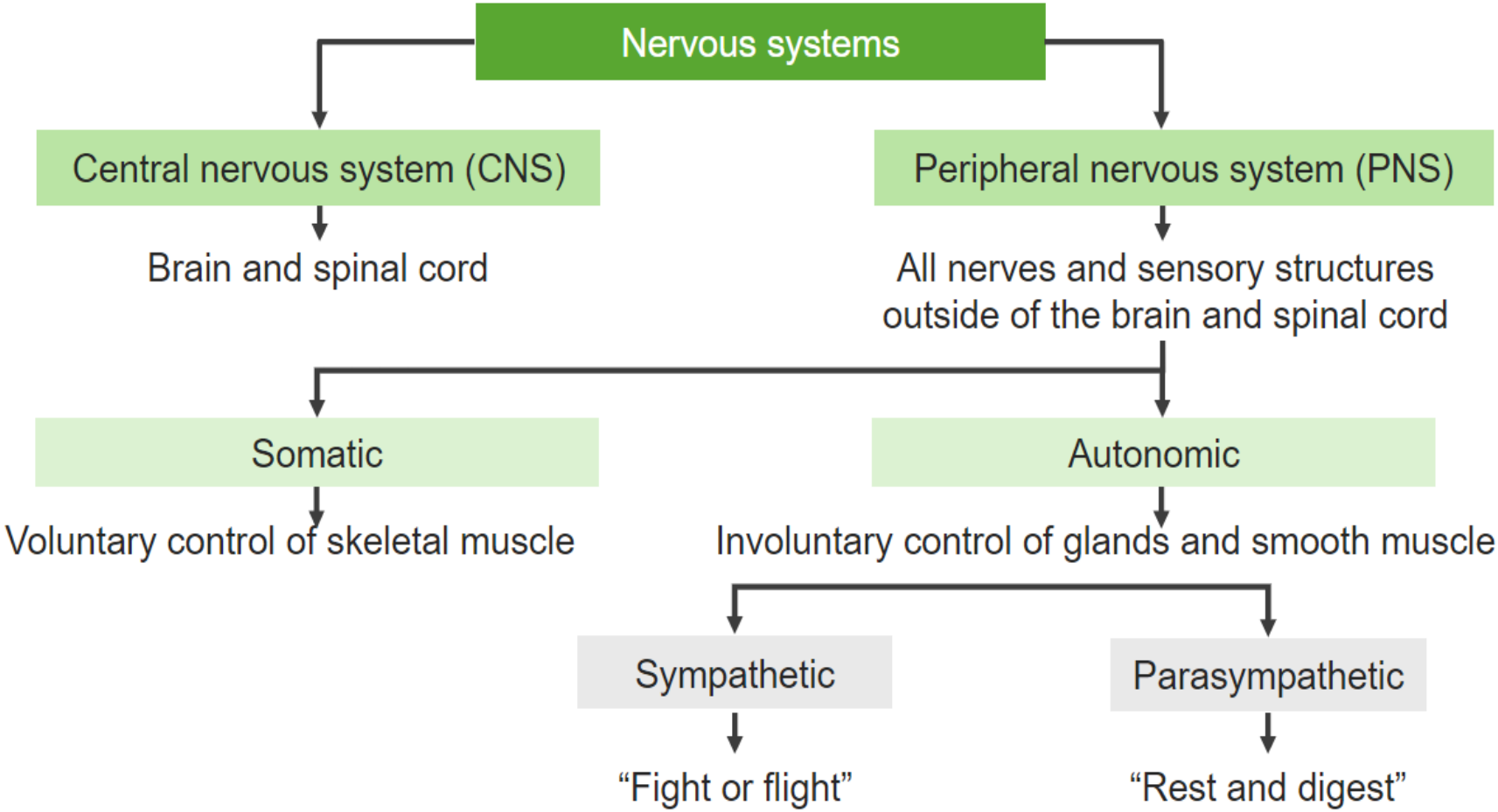
(ii) Warfain toxicity in the presence of Aspirin.

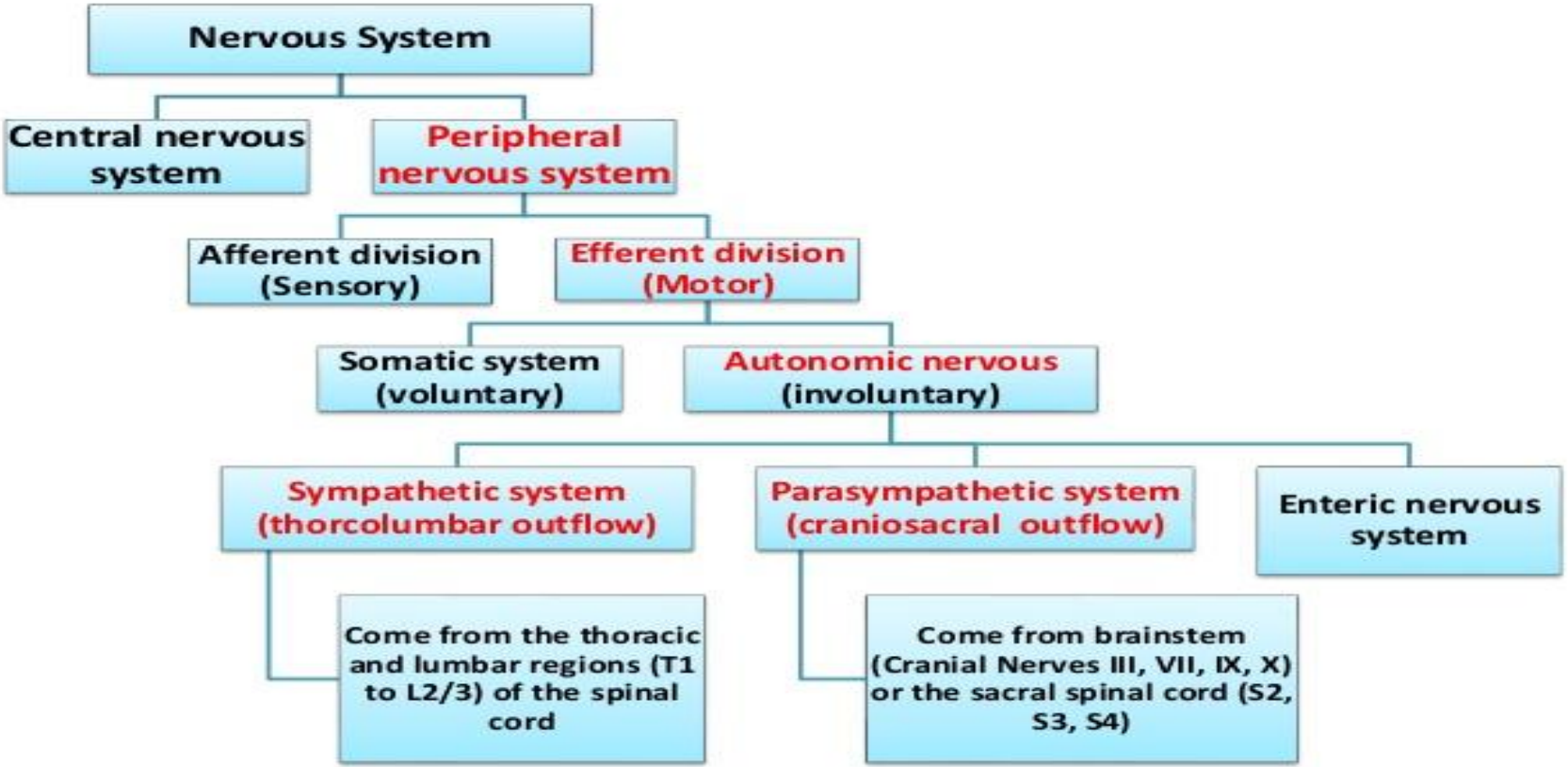
- **Hypersensitivity/ Drug Allergic reactions:**
- These are immunologically mediated untoward drug effects and are unrelated to pharmacodynamic profile of drugs.
  - These reactions are not dose-related and exposure of little amount of drug can lead to severe manifestations. These reactions are generally 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:

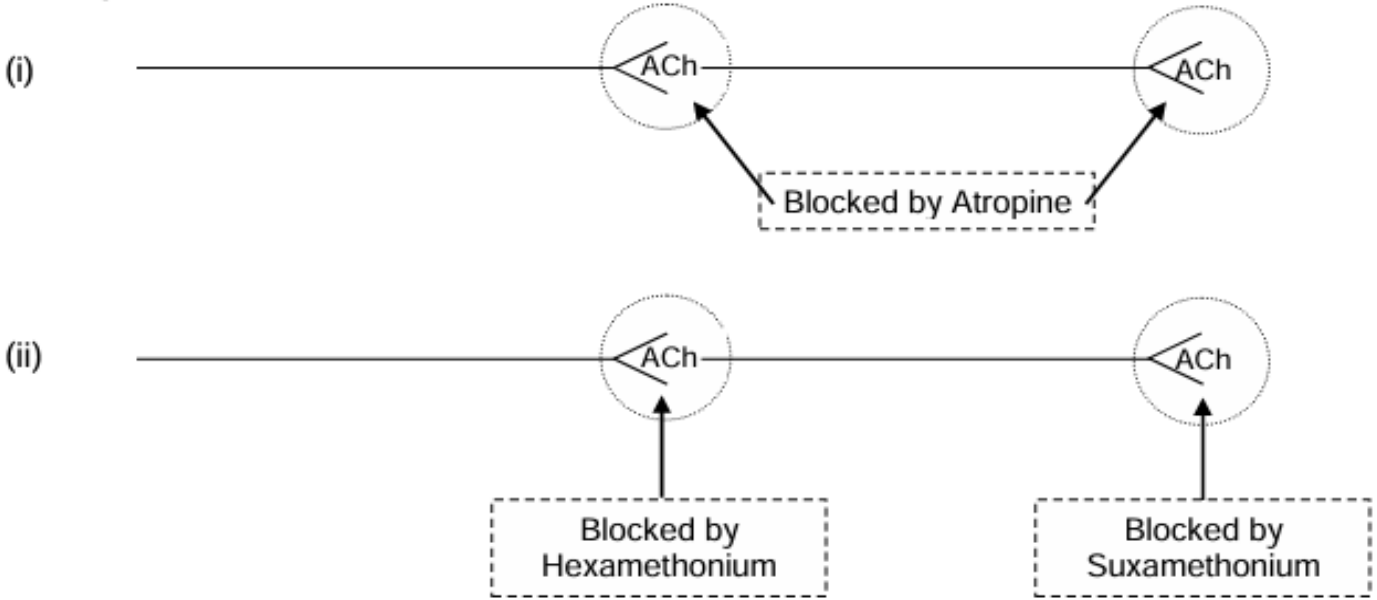
Sympathetic Fibres:

(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.

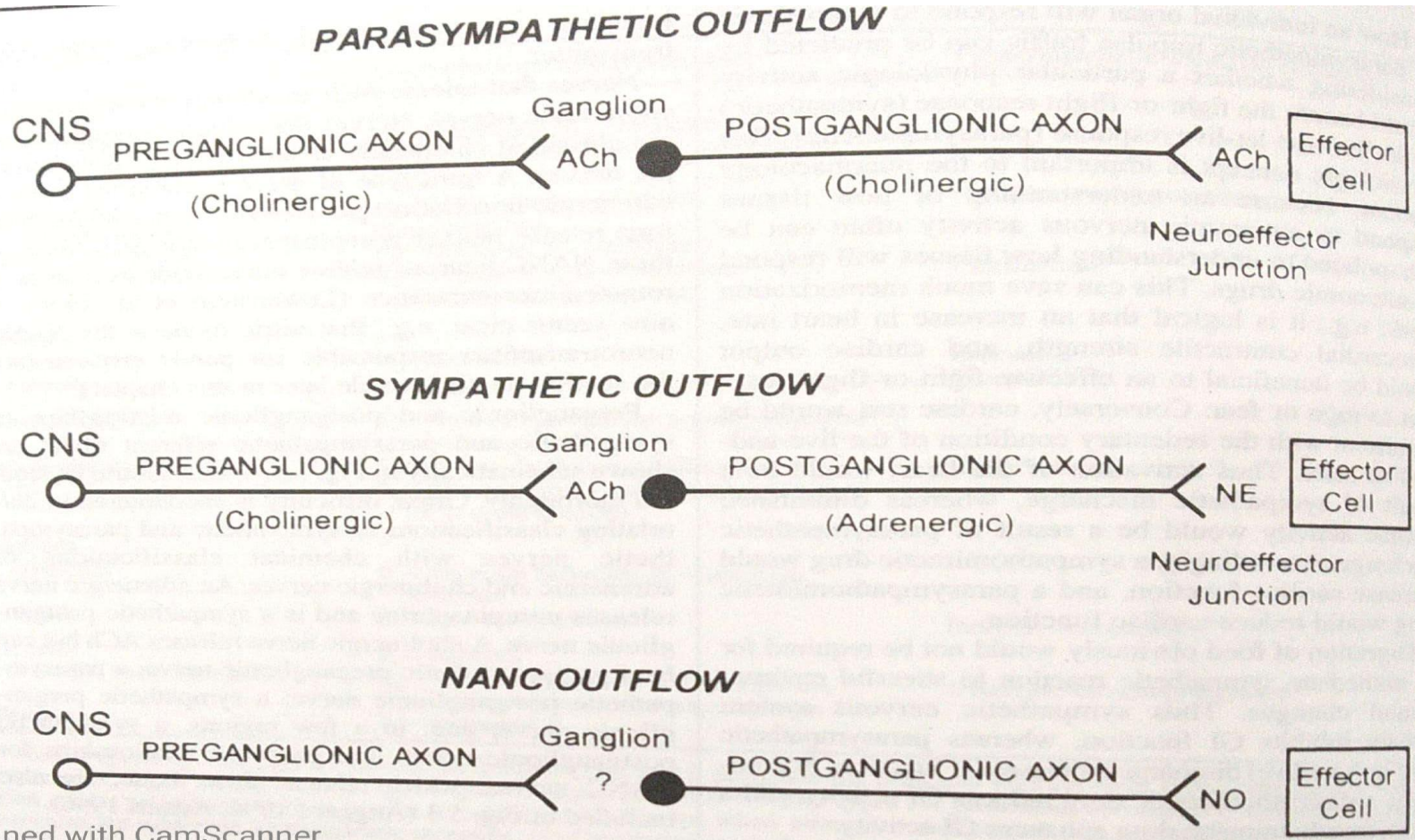


FIG. 5.3—Schematic representation of the preganglionic and

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.

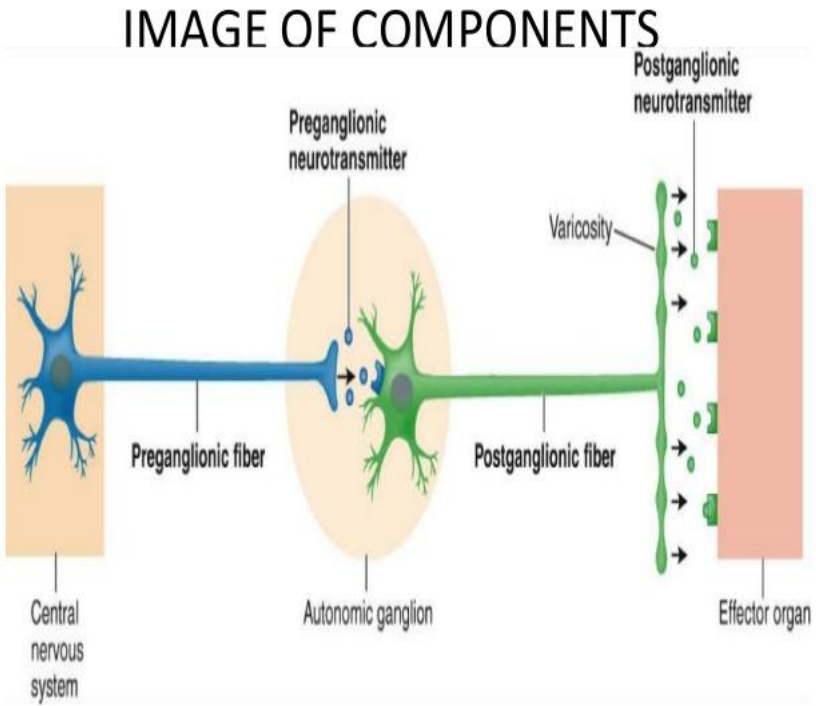
Effector tissues	*Sympathetic-mediated responses*[1]	*Parasympathetic -mediated responses*[2]
Heart	General excitation	General inhibition
Sinoatrial (SA) node	β_1 – increase heart rate	Decrease heart rate
Atria	β_1 – increase contractile force, conduction velocity	Decrease contractile force
Atrioventricular (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

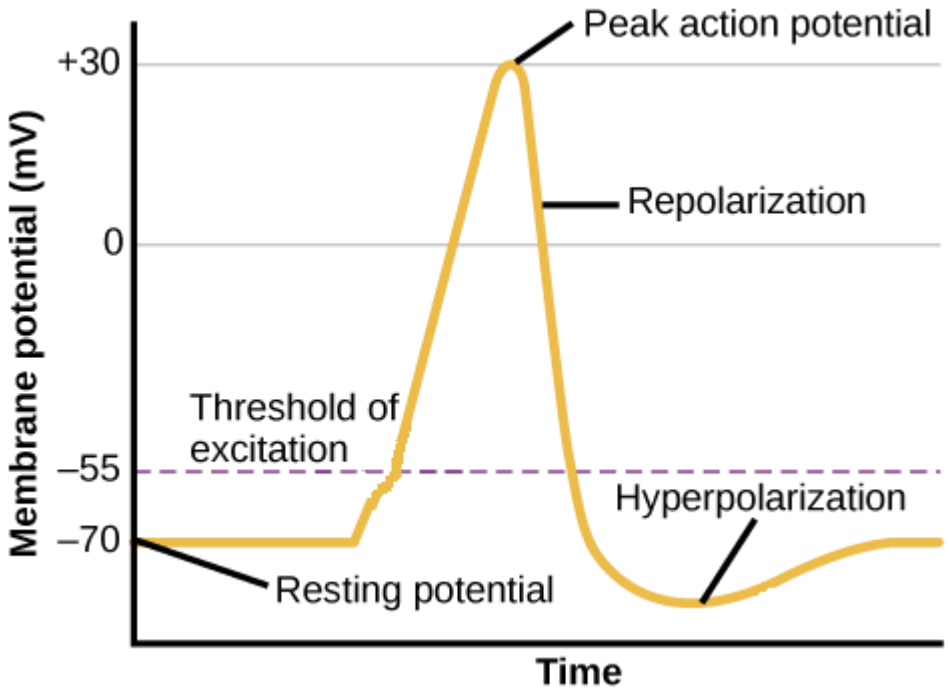
1. Axonal conduction
2. Junctional Transmission

- 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

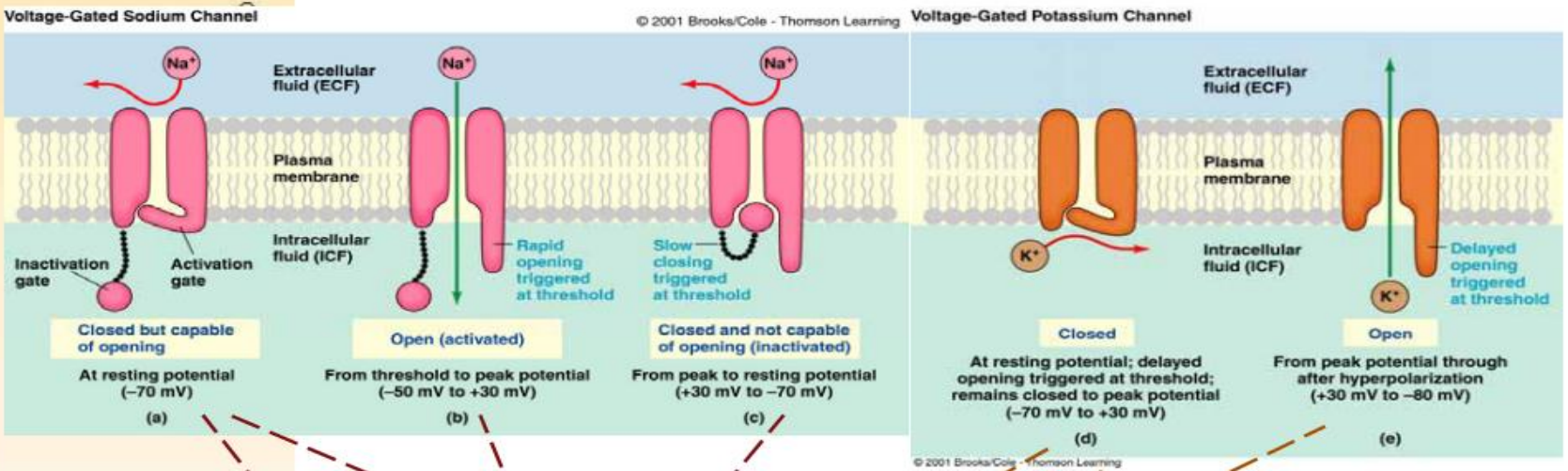
AXONAL CONDUCTION

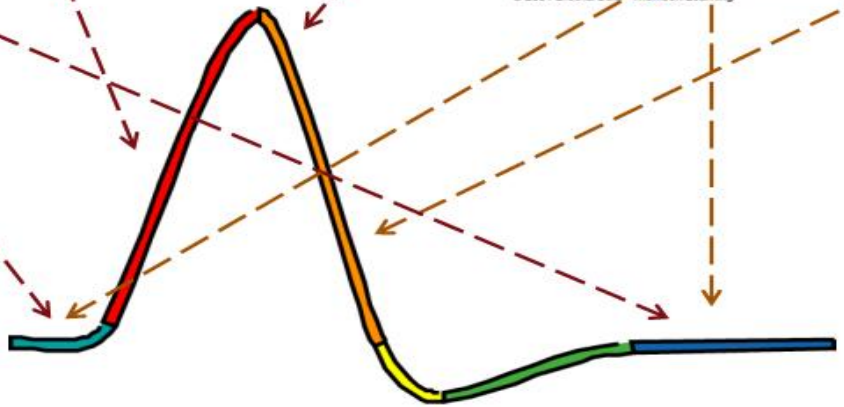
- Axonal conduction: passage of an impulse along a nerve fibre. It is dependent upon selective changes in the permeability of the axonal membrane to electrolytes.
- **Action Potential** or nerve impulse reflects a reversal of polarisation state present at rest (negative- inside and positive-outside) 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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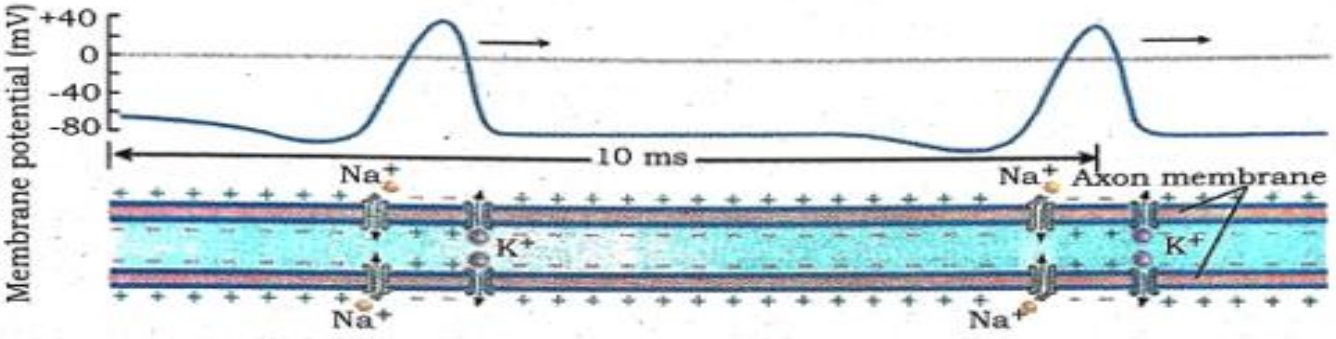
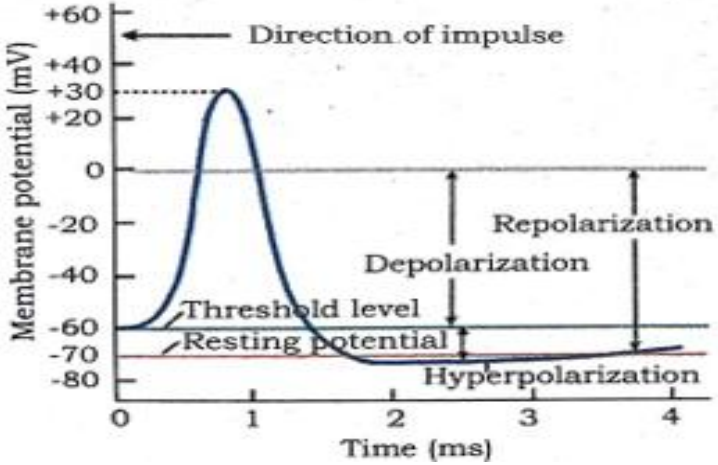
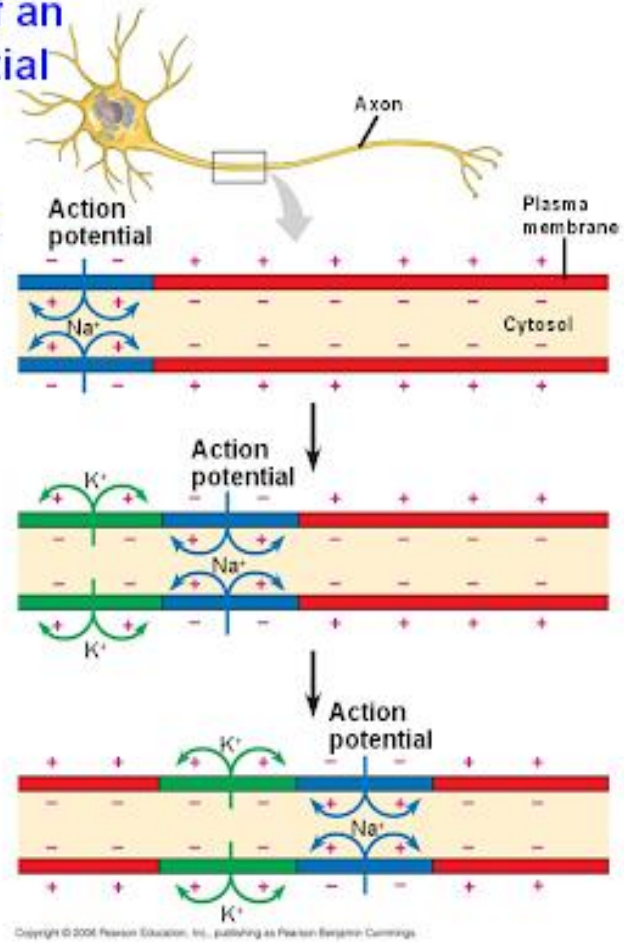

Membrane potential (mV)
+40
0
-40
-80
10 ms
Na+
K+
Axon membrane

(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

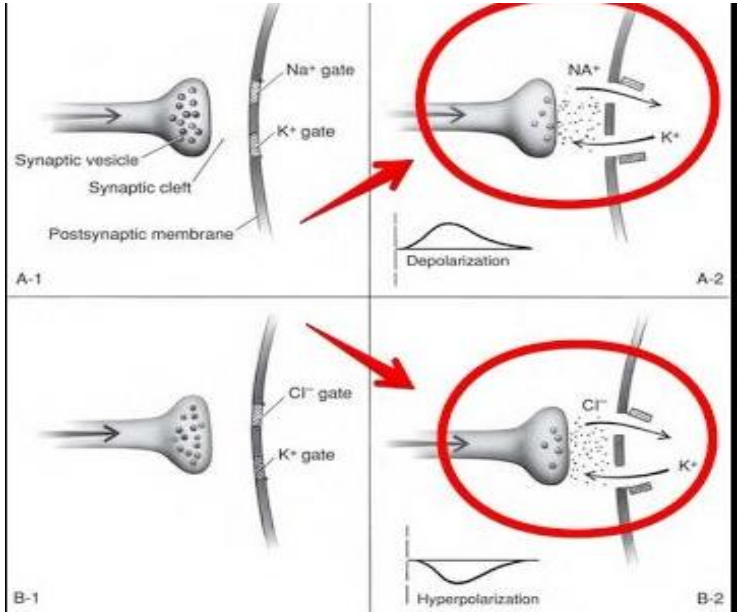
- Transmitter diffuse across the synaptic and junctional cleft
- combine within specialised receptors on post junctional membrane
- this result in localised increase in ionic permeability or conductance of the membrane.
- Following permeability change may occur depending on the type of receptor

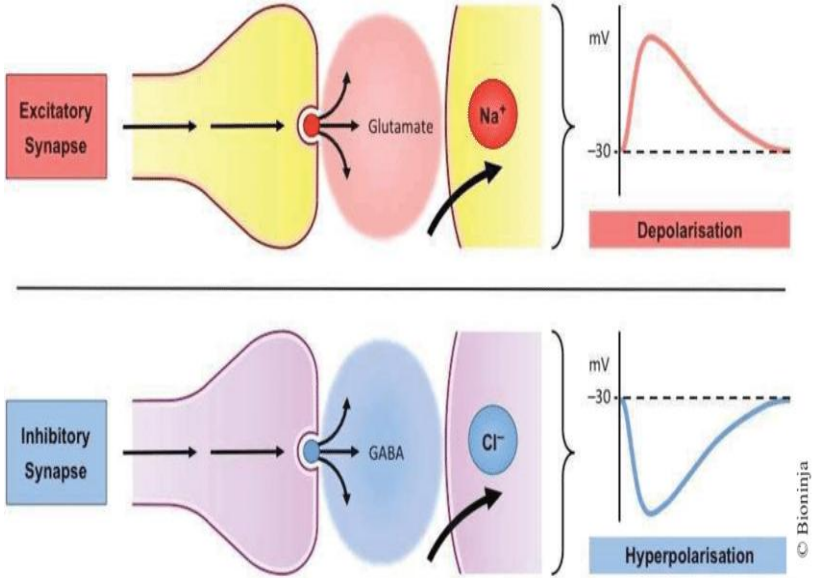
  i) A generalised increase in permeability to cation(notably Na but occasionally Ca++ resulting in localised depolarisation of the membrane(EPSP: Excitatory Post Synaptic Potential)

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

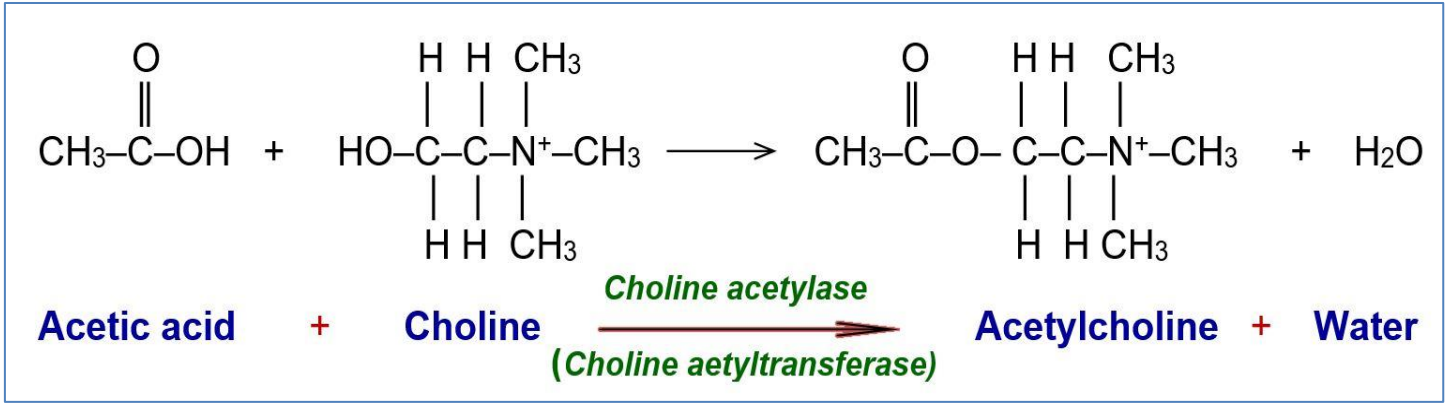

Excitatory Synapse
Glutamate
Na+
mV
-30
Depolarisation
Inhibitory Synapse
GABA
Cl−
mV
-30
Hyperpolarisation
© Bioninja

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

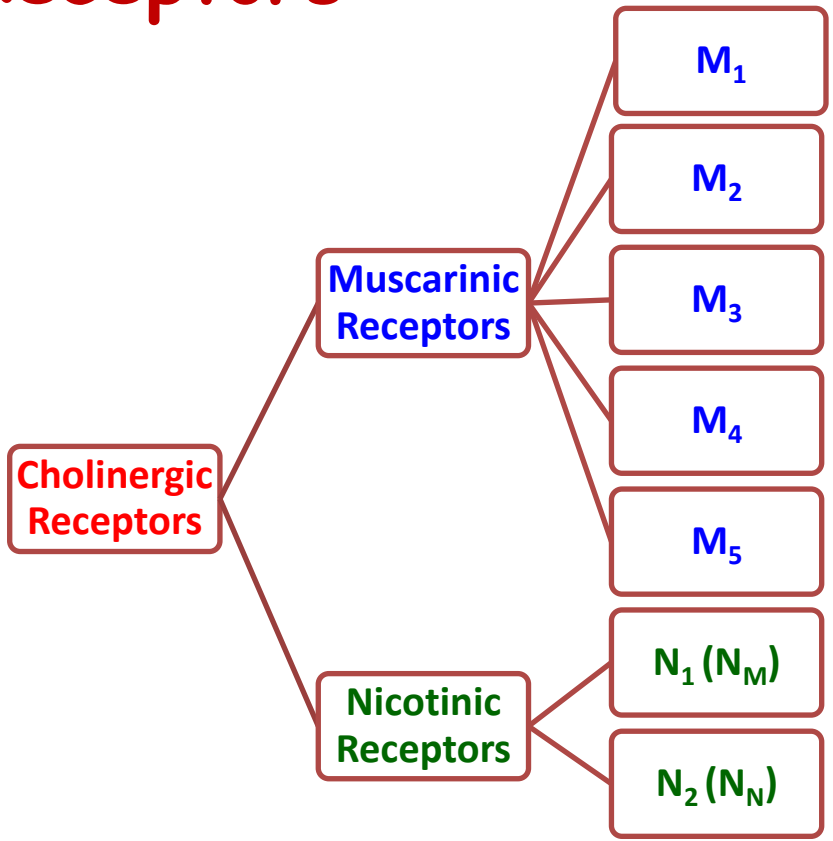
- ✓ After serving the transmitter function, ACh within the junctional space is rapidly inactivated by hydrolysis by a specific enzyme, acetylcholine esterase (AChE).
- ✓ AChE is present in cholinergic nerves, autonomic ganglia and neuromuscular & neuroeffector junctions.

- ✓ 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

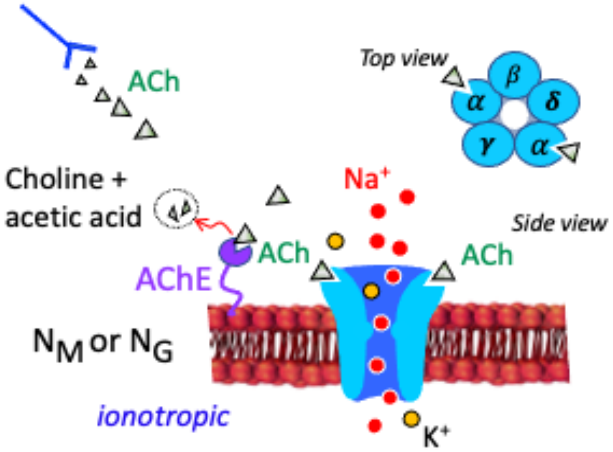
- ✓ **Muscarinic receptors (G-protein coupled receptors)**
- ✓ Selective affinity for alkaloid, muscarine (*Amanita muscaria*) - mimic the activity of ACh at the parasympathetic neuroeffector junctions.

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



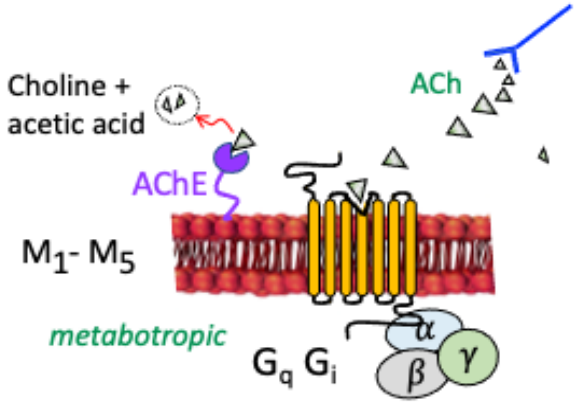
Nicotinic

- 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.

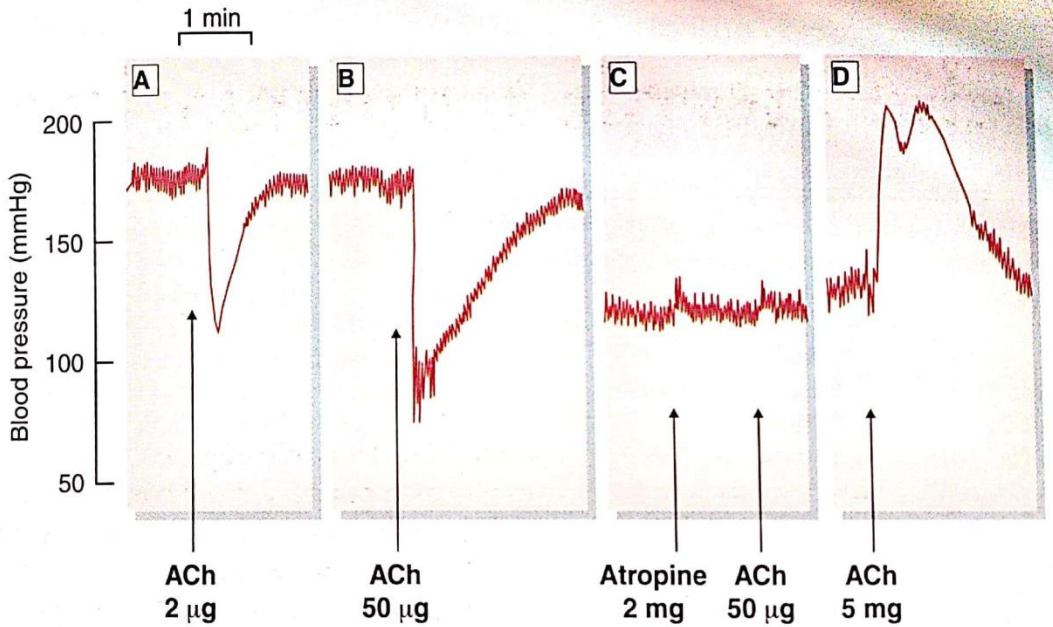
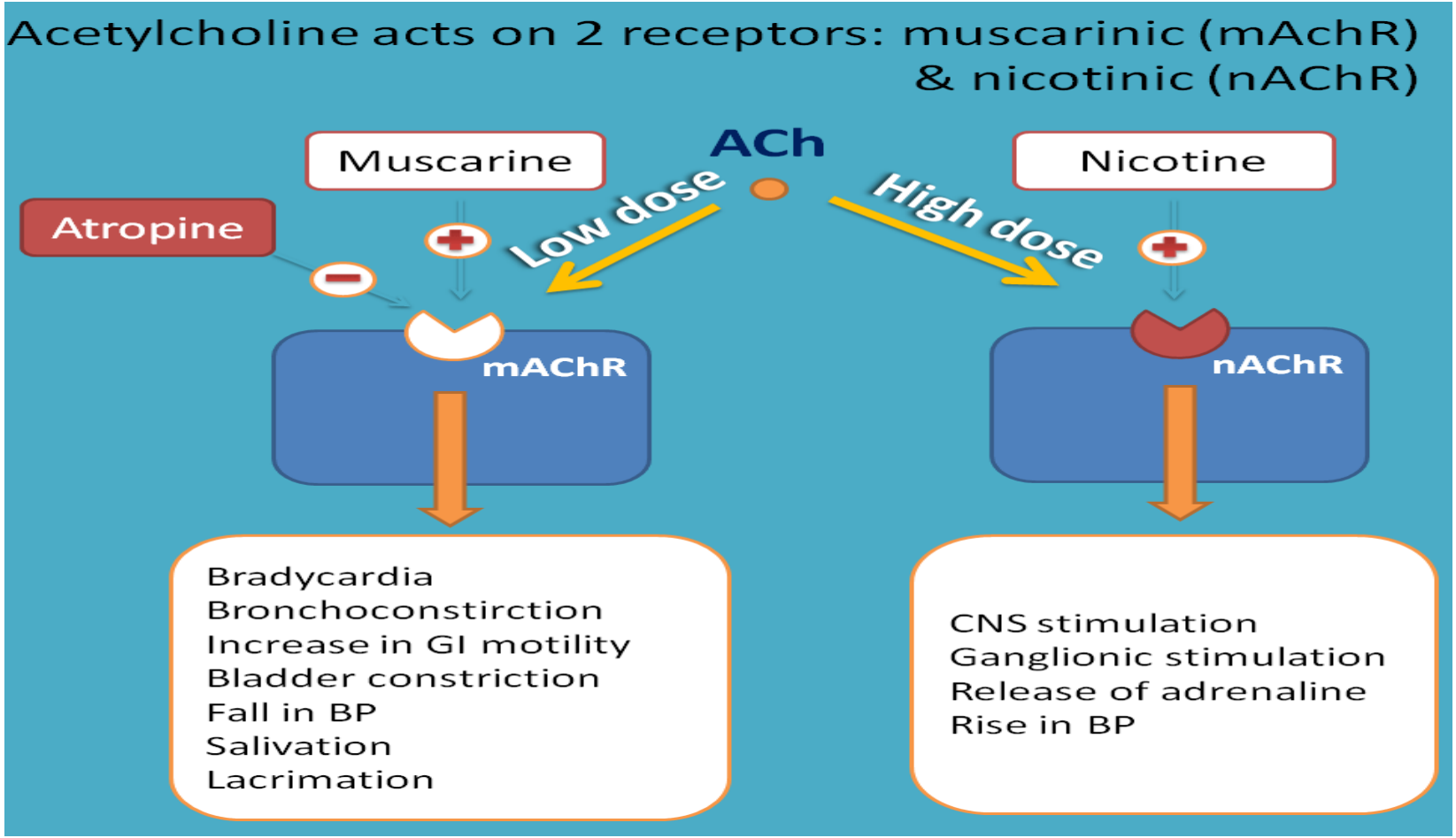
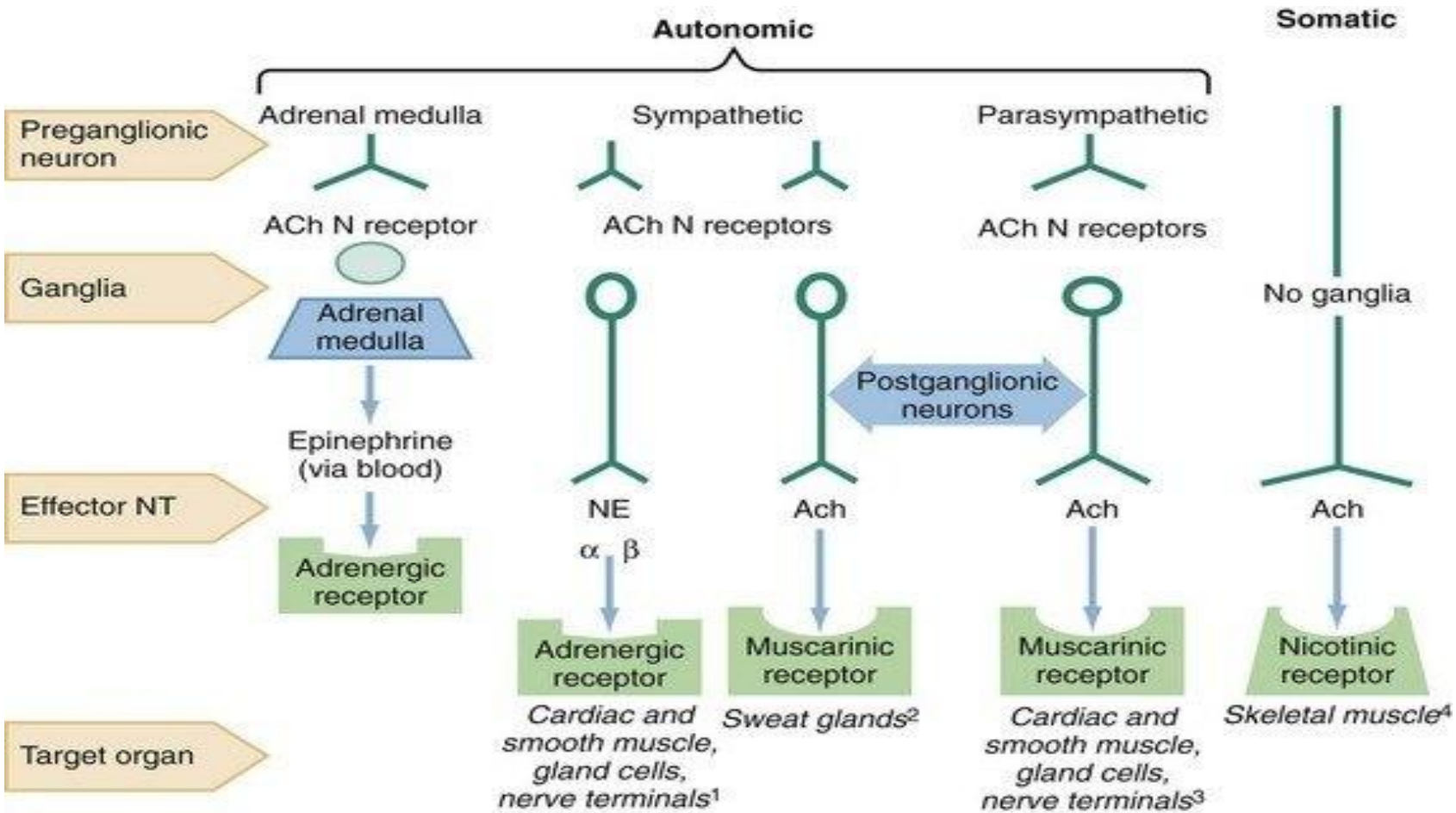


Fig. 10.1 Dale's experiment showing that acetylcholine (ACh) produces two kinds of effect on the cat's blood pressure. Arterial pressure was recorded with a mercury manometer from a spinal cat. A ACh causes a fall in blood pressure owing to vasodilatation. B A larger dose also produces bradycardia. Both 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

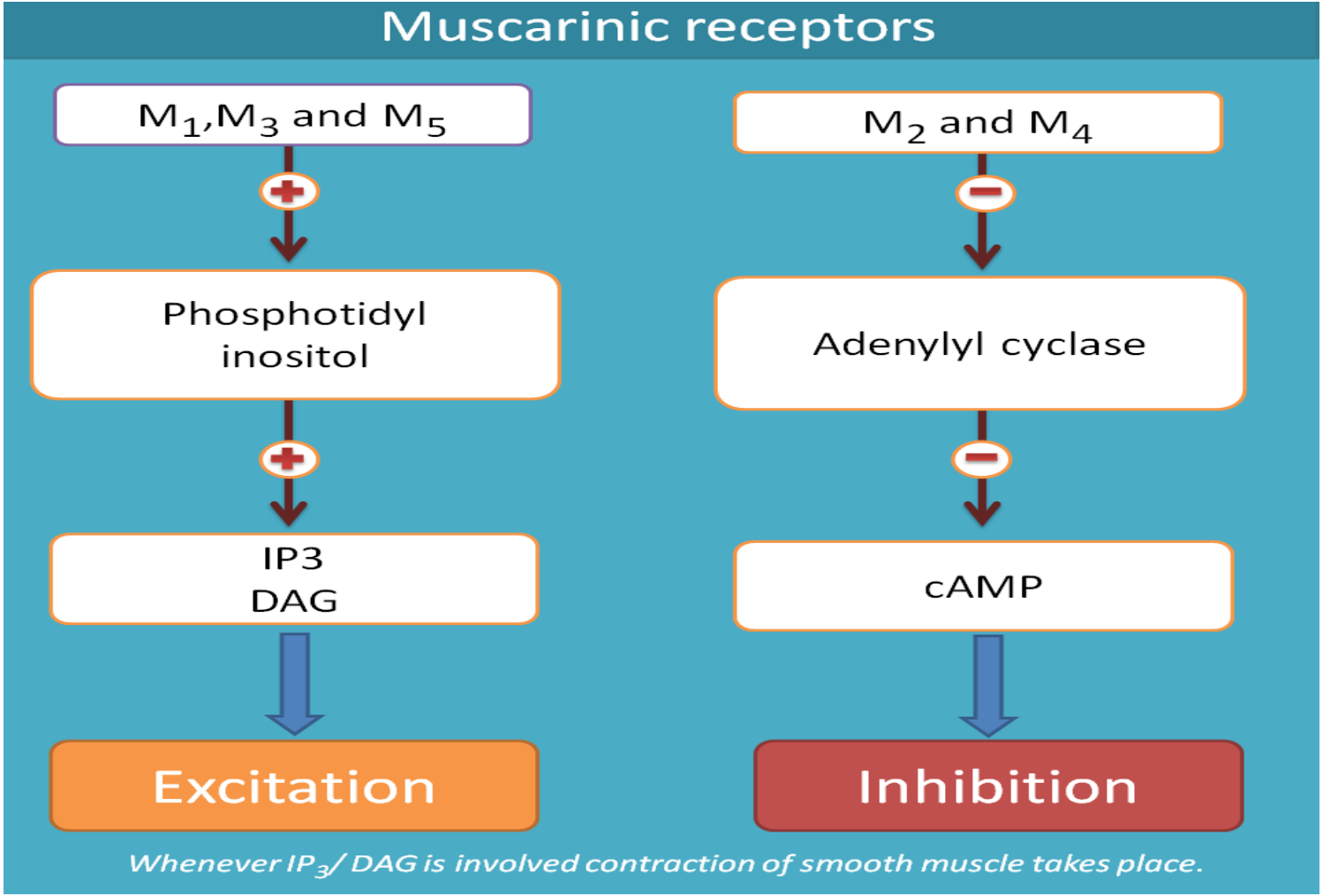
	N_M	N_N
1.Location and function subserved	Neuromuscular junction: Depolarization of muscle end plate ⇨ contraction of skeletal muscle.	Autonomic ganglia: Depolarization ⇨ post-ganglionic impulse. Adrenal medulla: Catecholamine release. CNS: Site specific excitation
2.Transducer mechanism/ membrane response	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

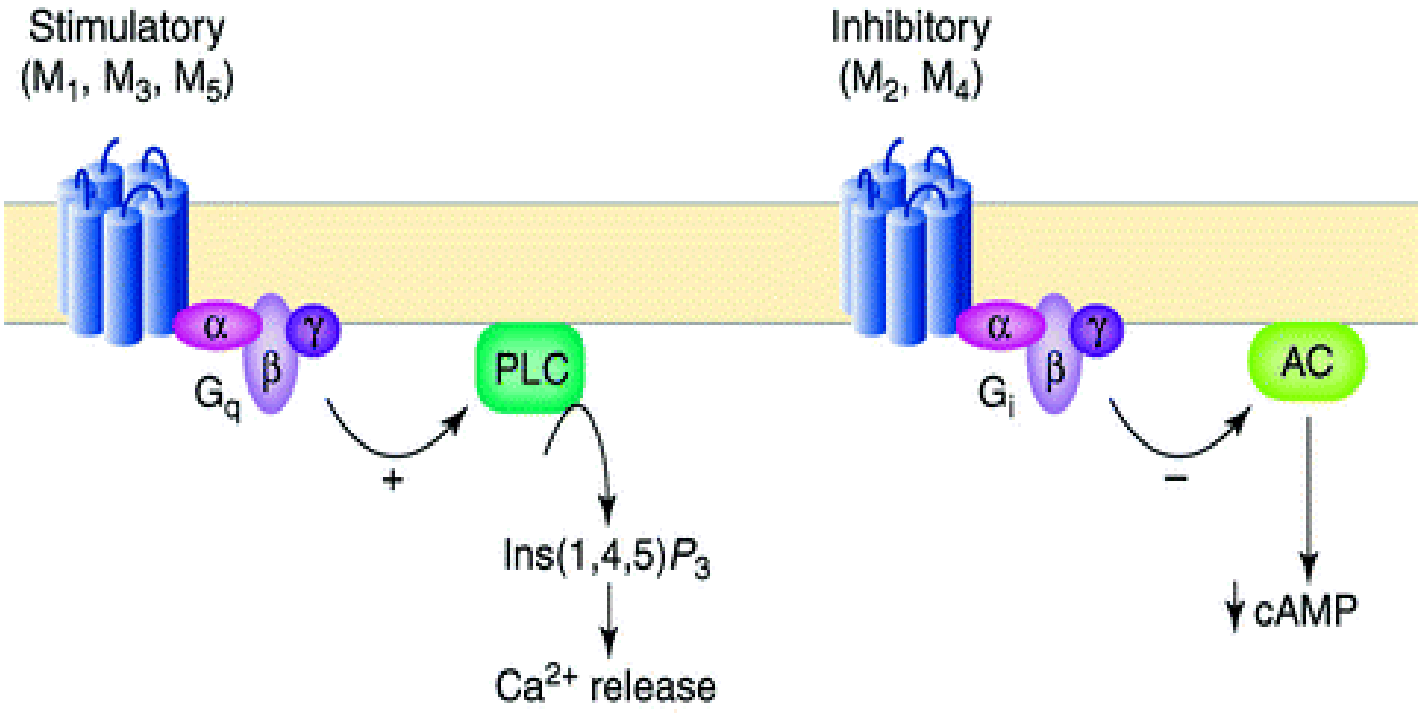
Muscarinic receptor

- 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

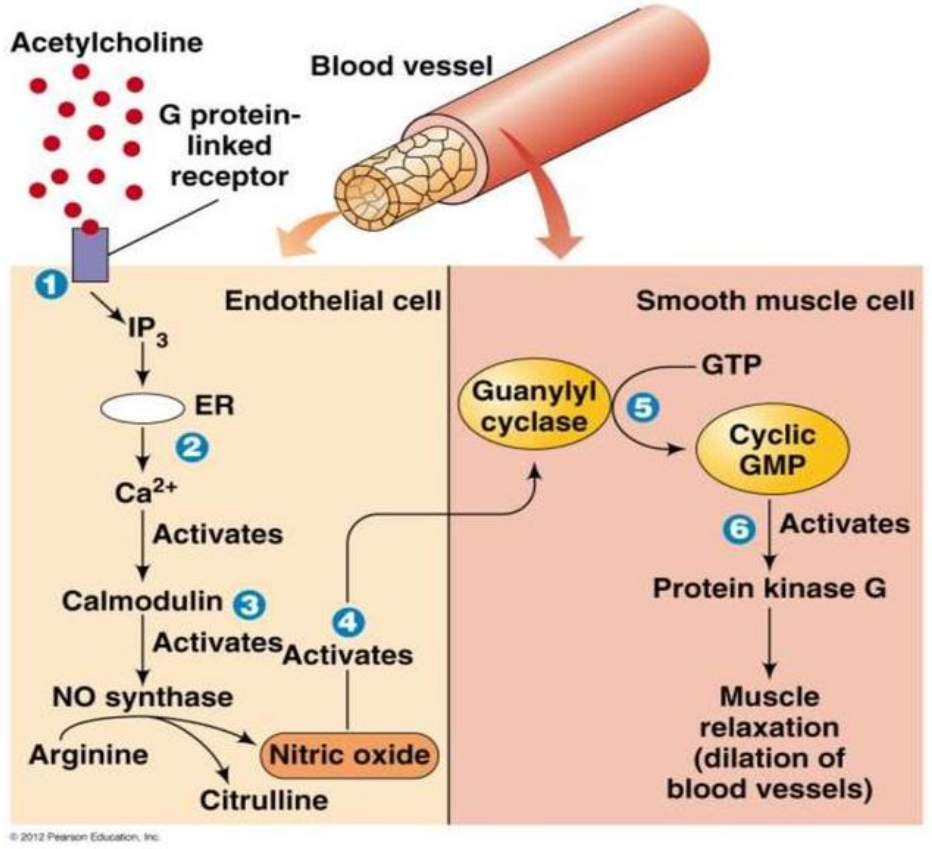
	M_1	M_2	M_3
Transducer mechanism	IP3/DAG-increased cytosolic ca2+ ion, PLA2 stimulation-PG synthesis	K channel opening, decrease in cAMP level	IP3/DAG-increased cytosolic ca2+ ion, PLA2 stimulation-PG synthesis
Agonist	Oxotremorine	Methacholine	Bethanechol
Antagonist	Pirenzepine, Telenzepine	Methoctramine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

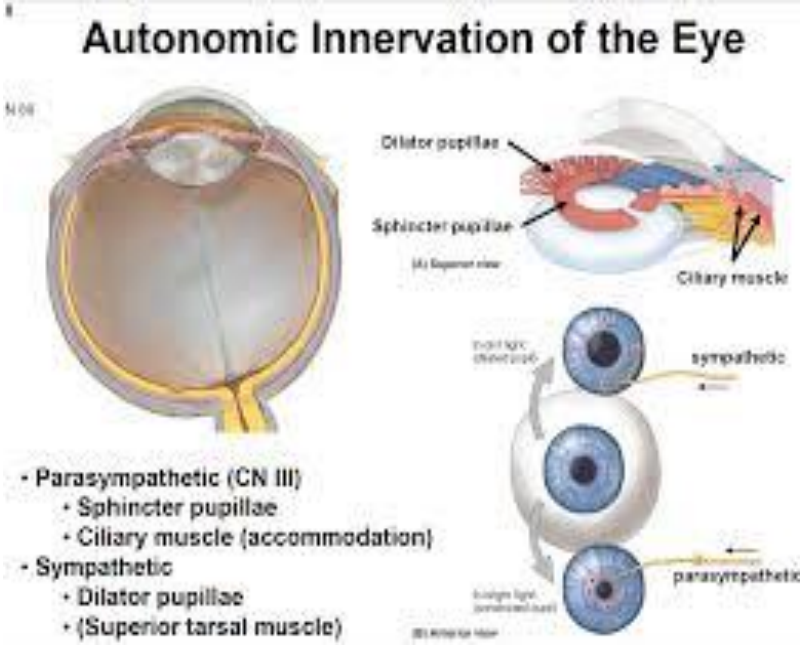

Stimulatory
(M1, M3, M5)
Inhibitory
(M2, M4)
α
β
γ
Gq
Gi
PLC
AC
+
−
Ins(1,4,5)P3
Ca2+ release
cAMP
TRENDS in Pharmacological Sciences

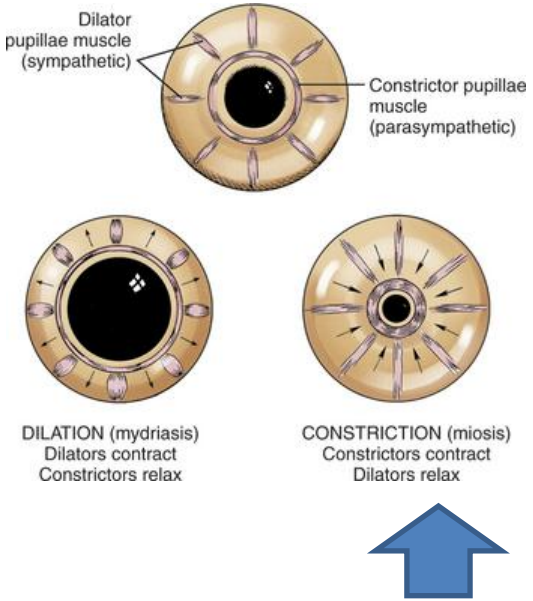
Action of Ach on Blood Vessels

- **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



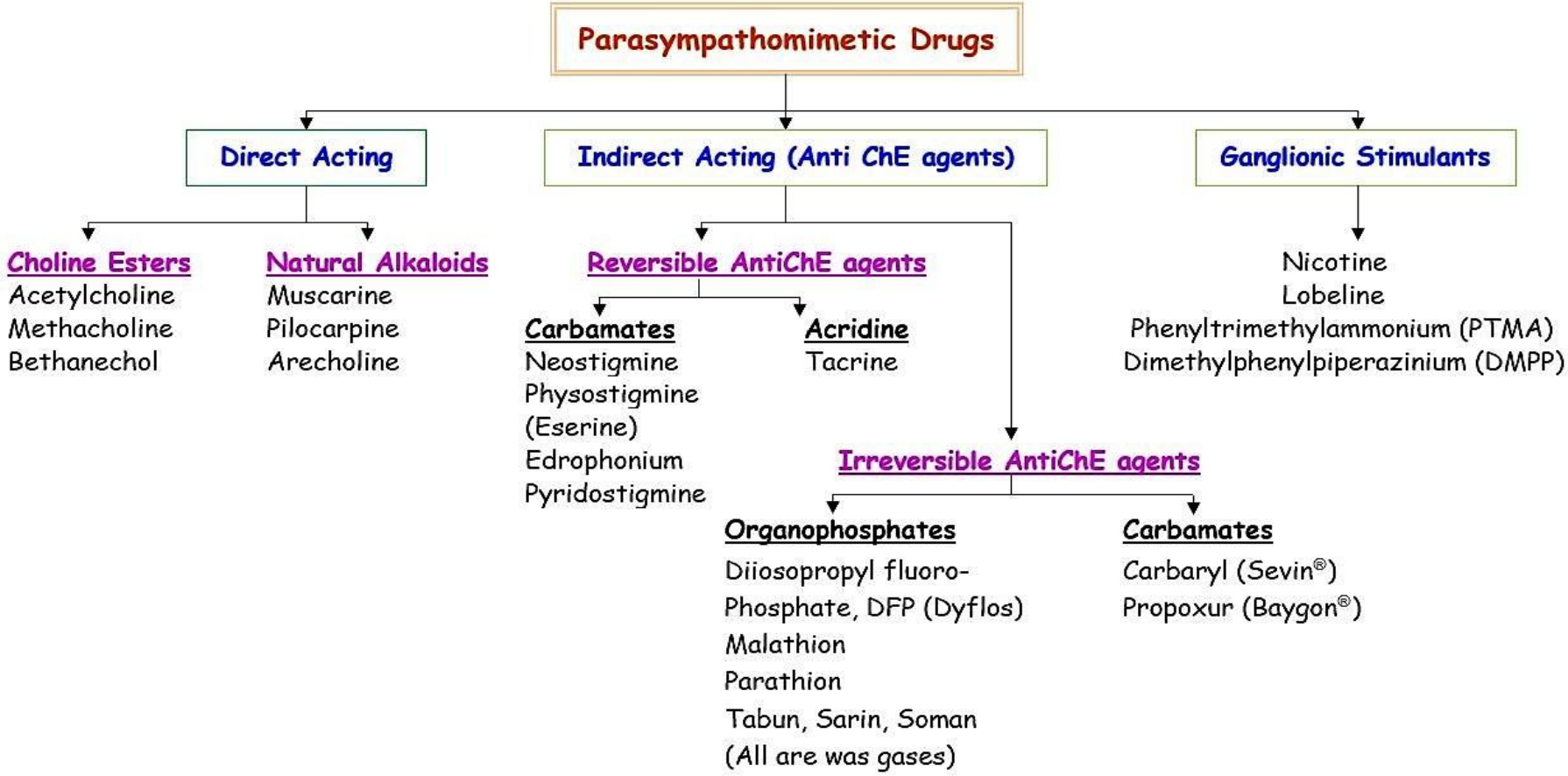
Autonomic innervation of eye and effect of sympathetic and parasympathetic stimulation





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.

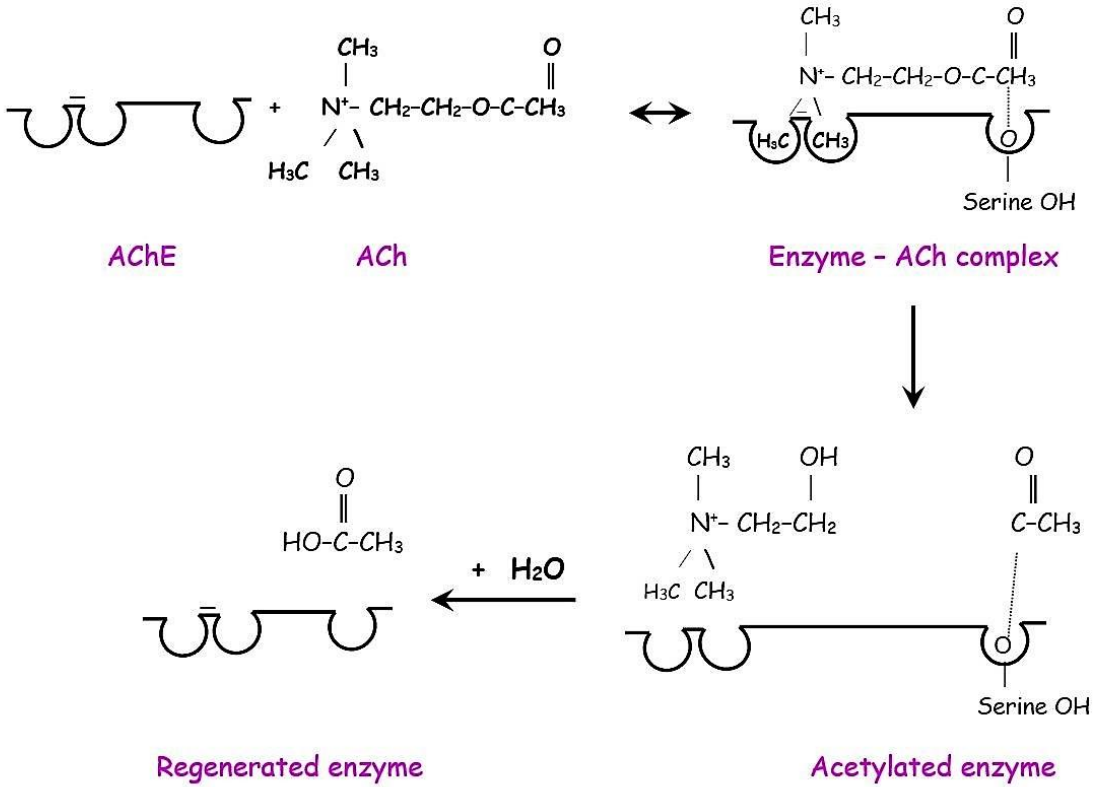
- **Acetylcholinesterase (AChE):**

- **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.

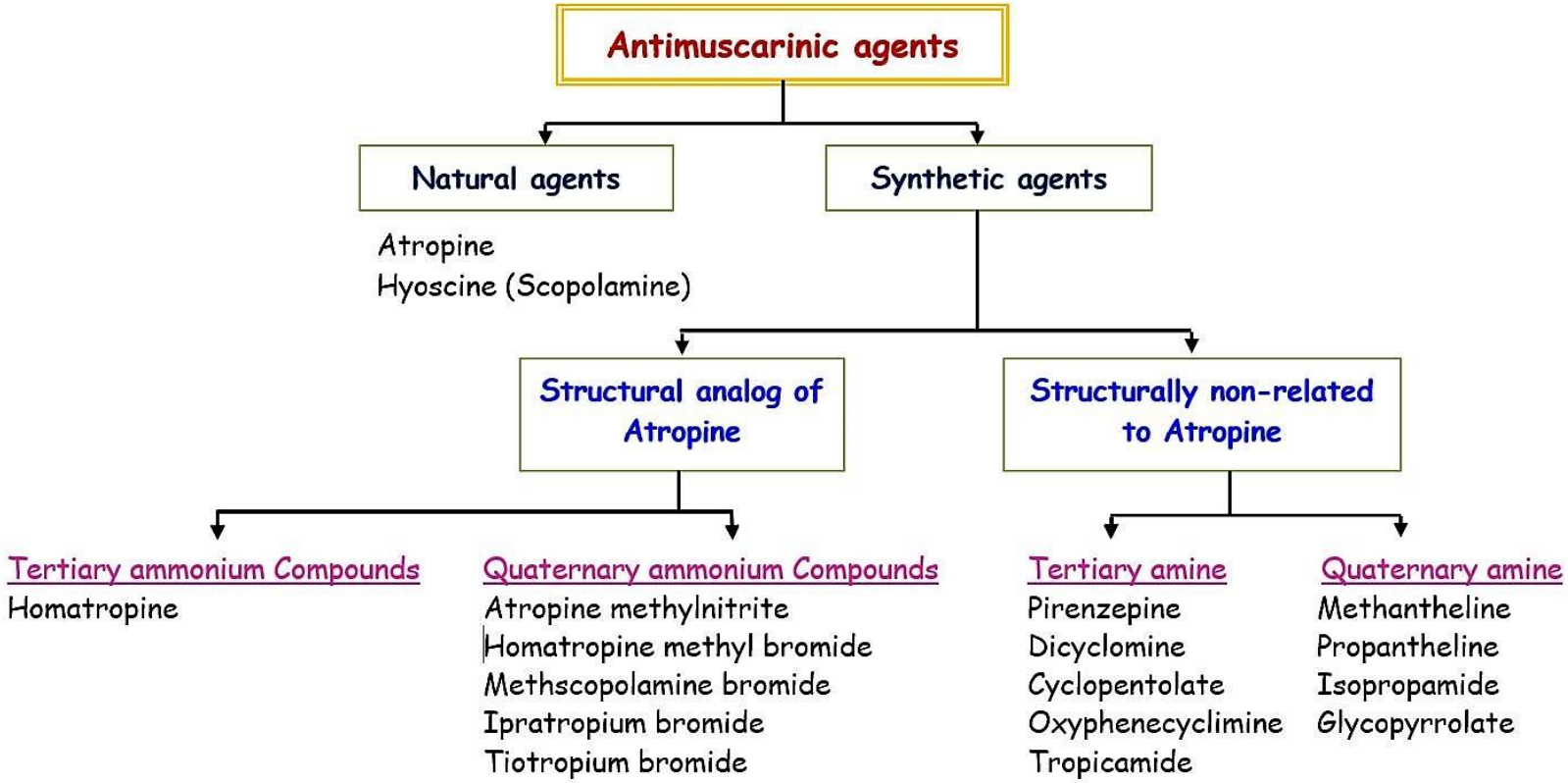
Anticholinergic (Parasympatholytic) Drugs

✓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.

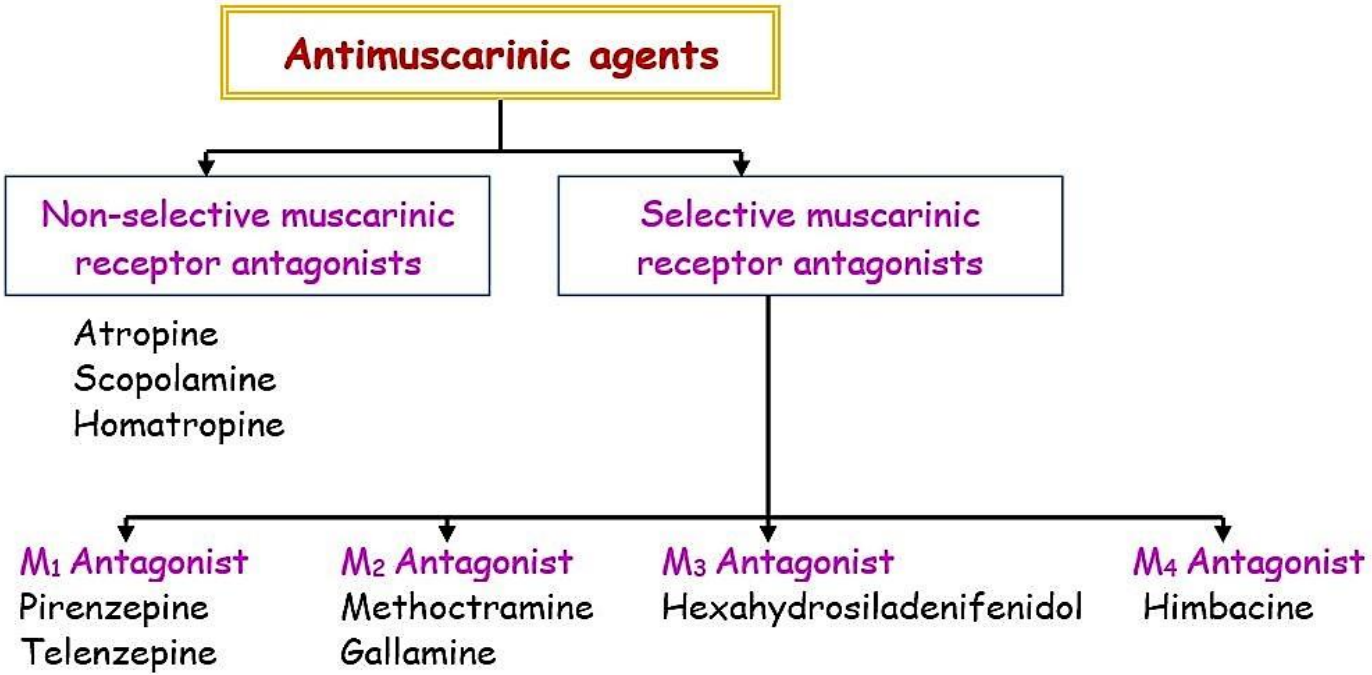
Classification of Parasympatholytic Drugs

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

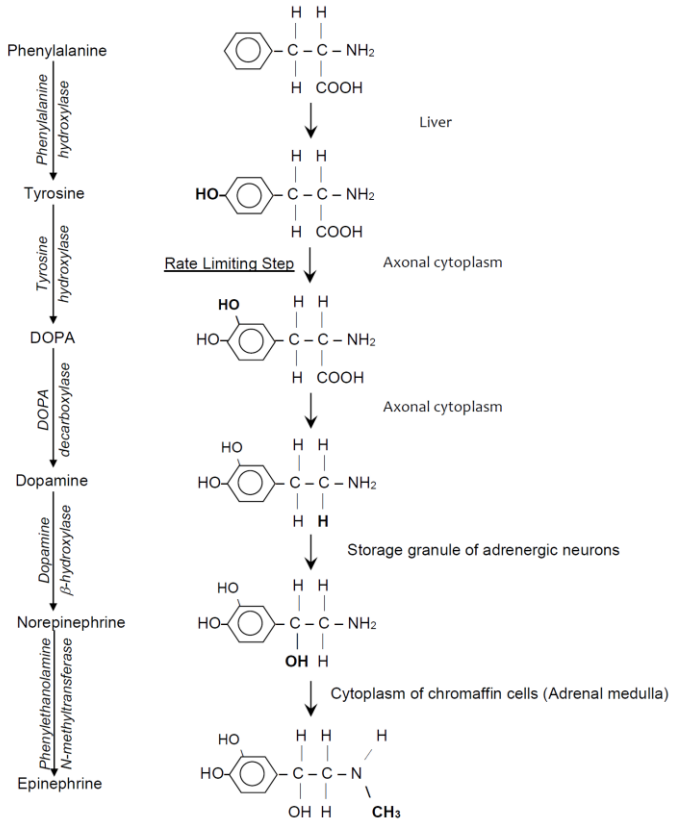


Fig.: Steps involved in the synthesis of catecholamines

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

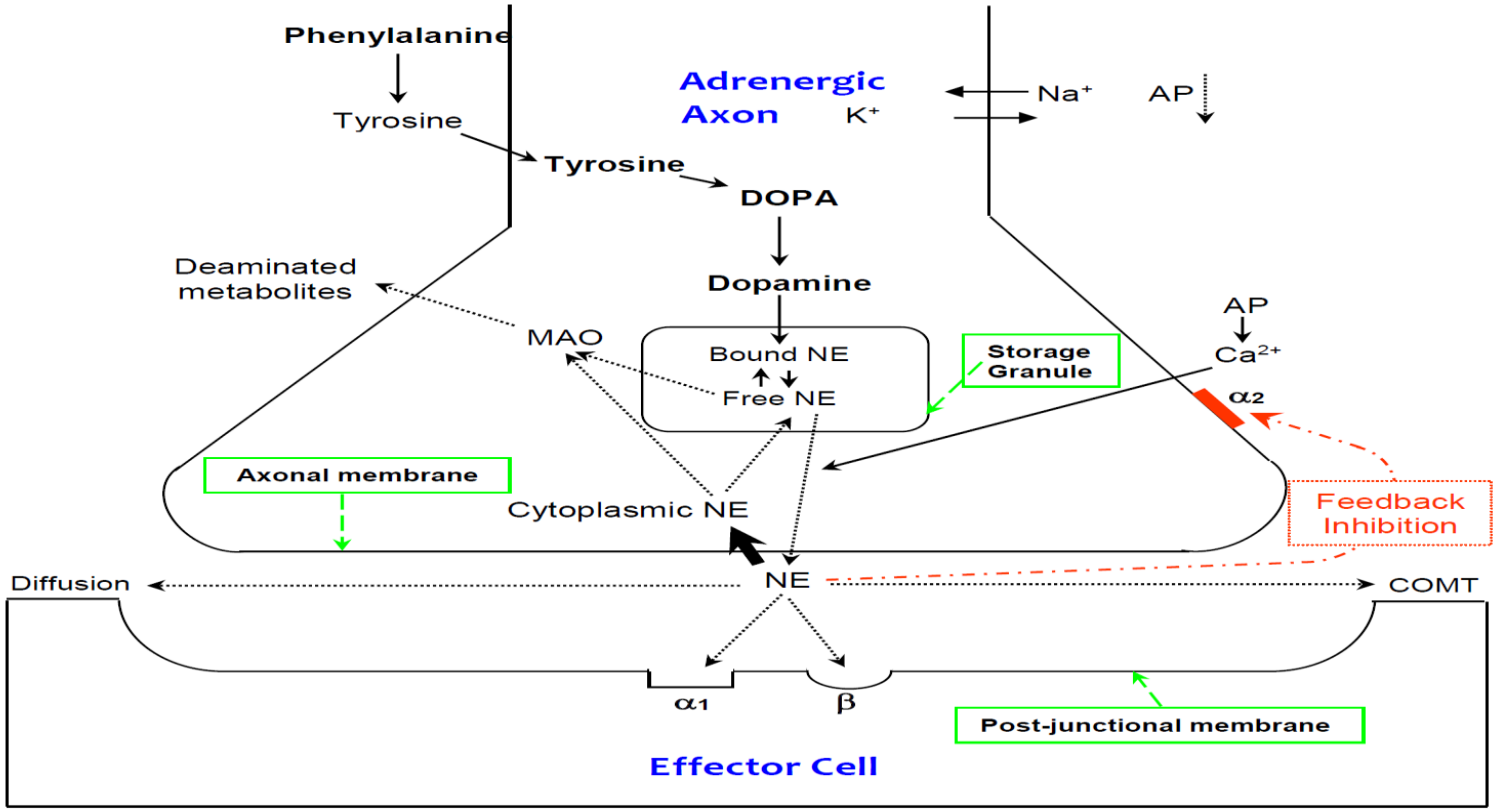


Fig.: Showing neurohumoural transmission at the adrenergic neuroeffector junction

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

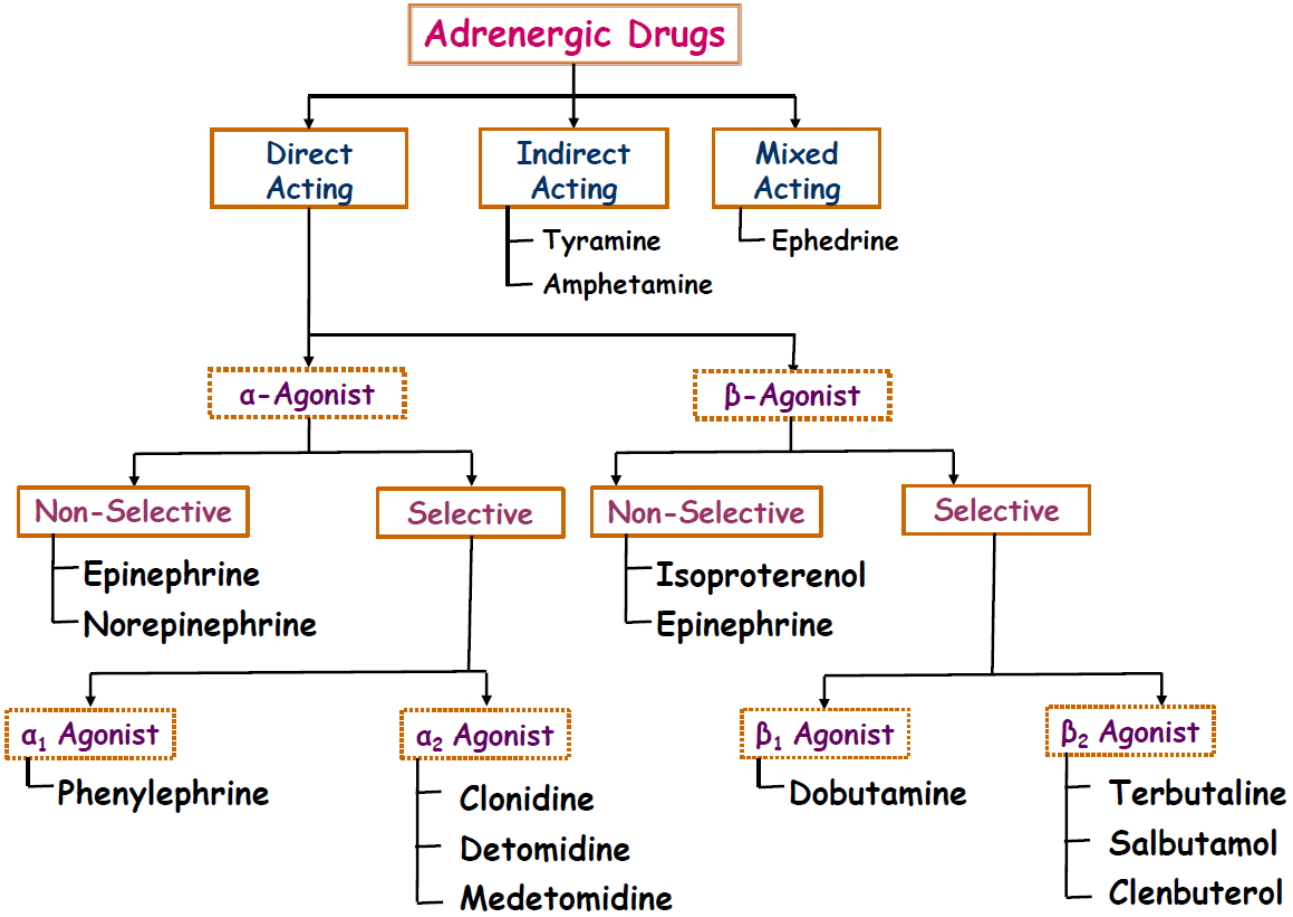


TABLE 5.1—Typical responses of effector tissues to sympathetic and parasympathetic nerve impulses

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

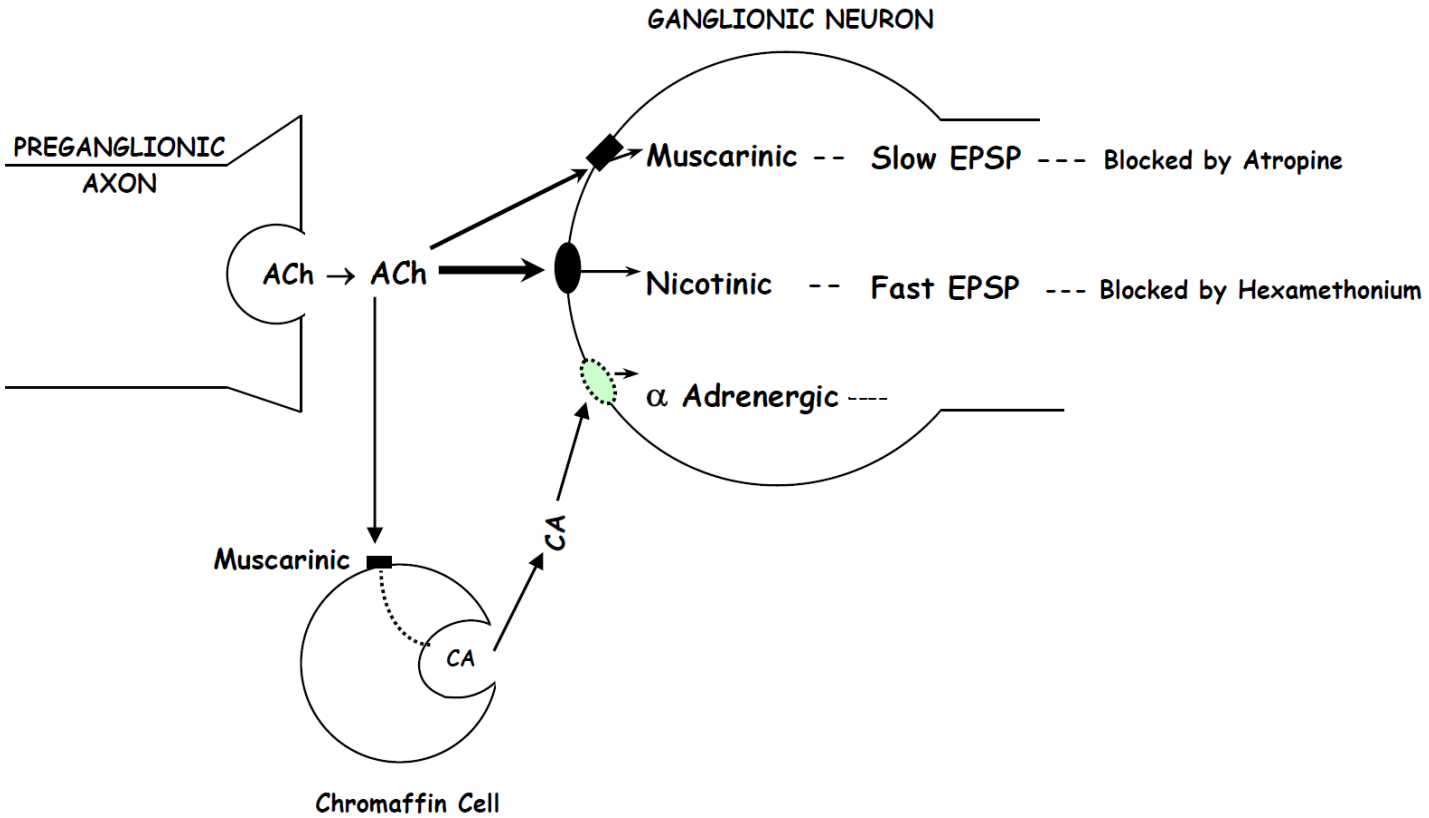


Fig.: Impulse transmission in sympathetic autonomic ganglia.

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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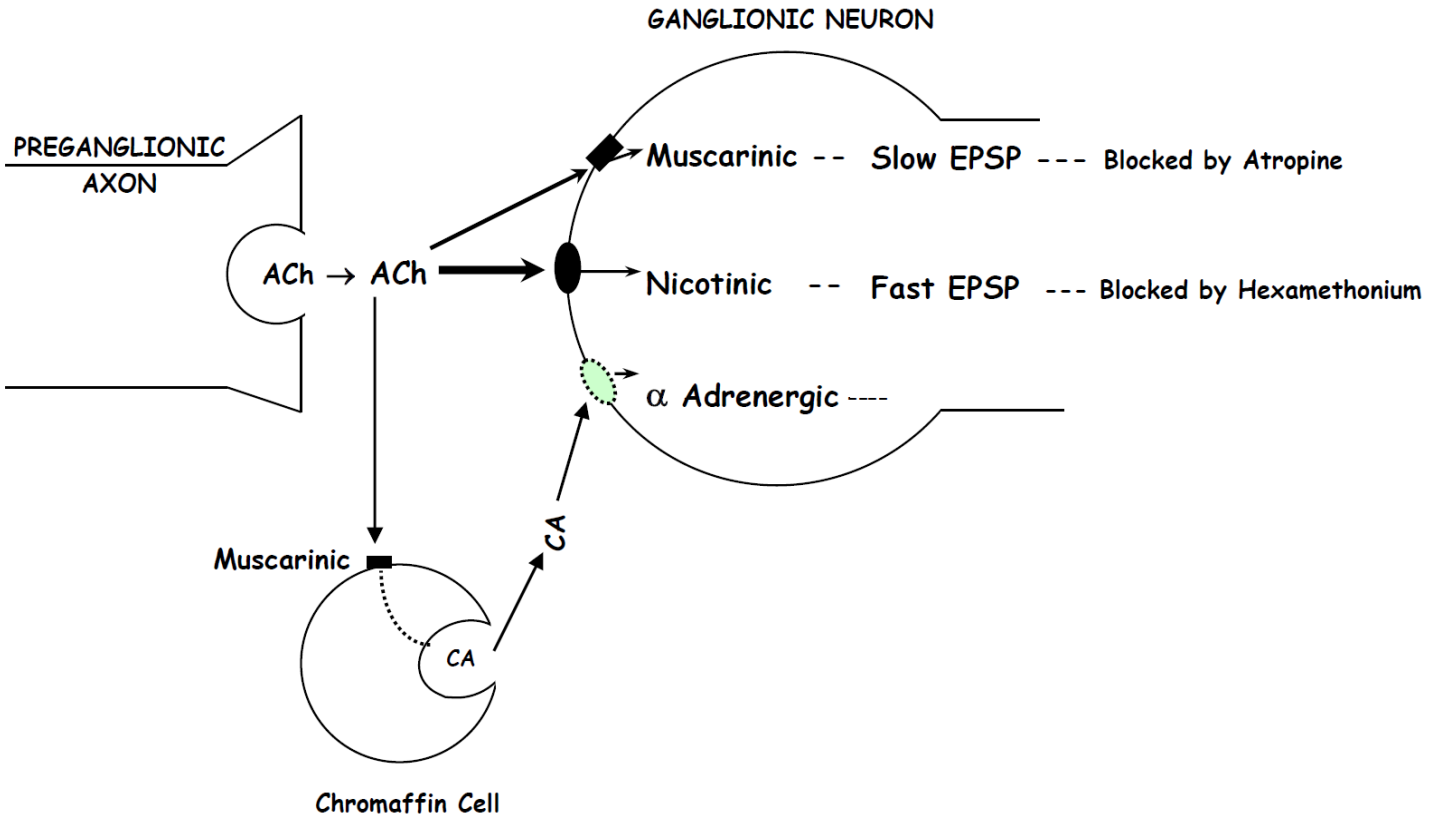

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Autacoids

- ✓‘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

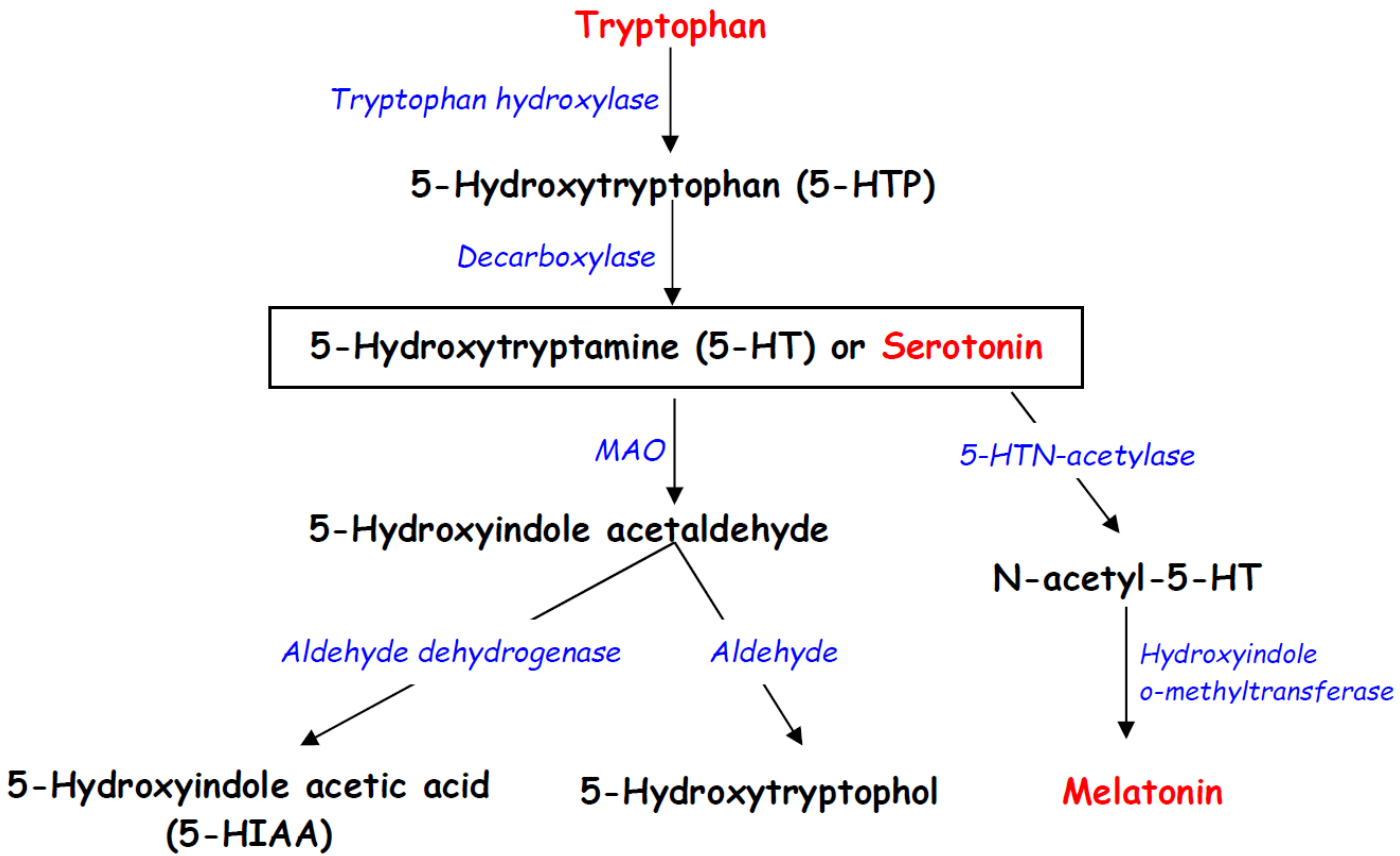

Fig.: Showing synthesis and degradation of 5-HT

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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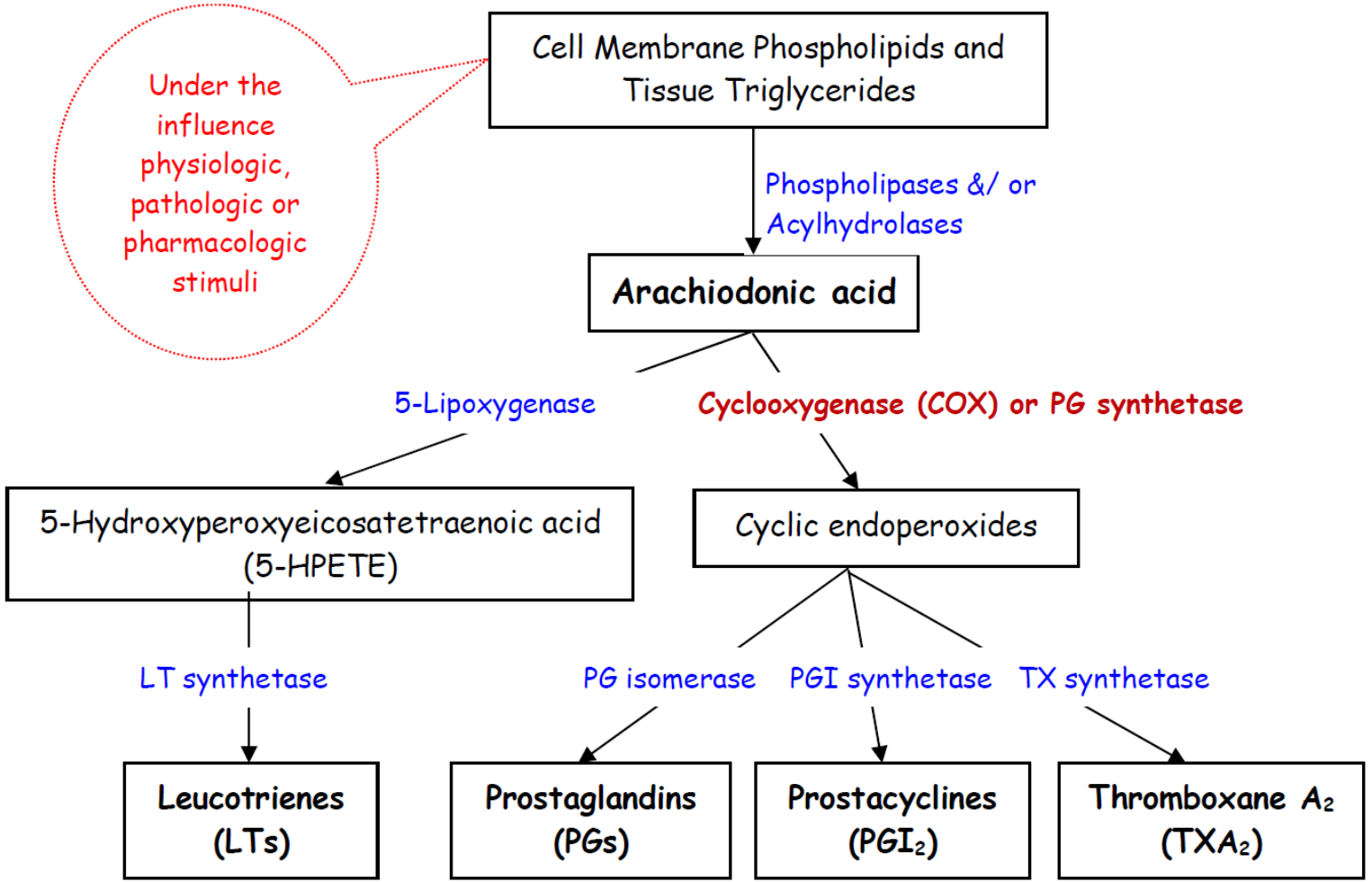
Eicosanoids (PG, PGI, TXA & LT)

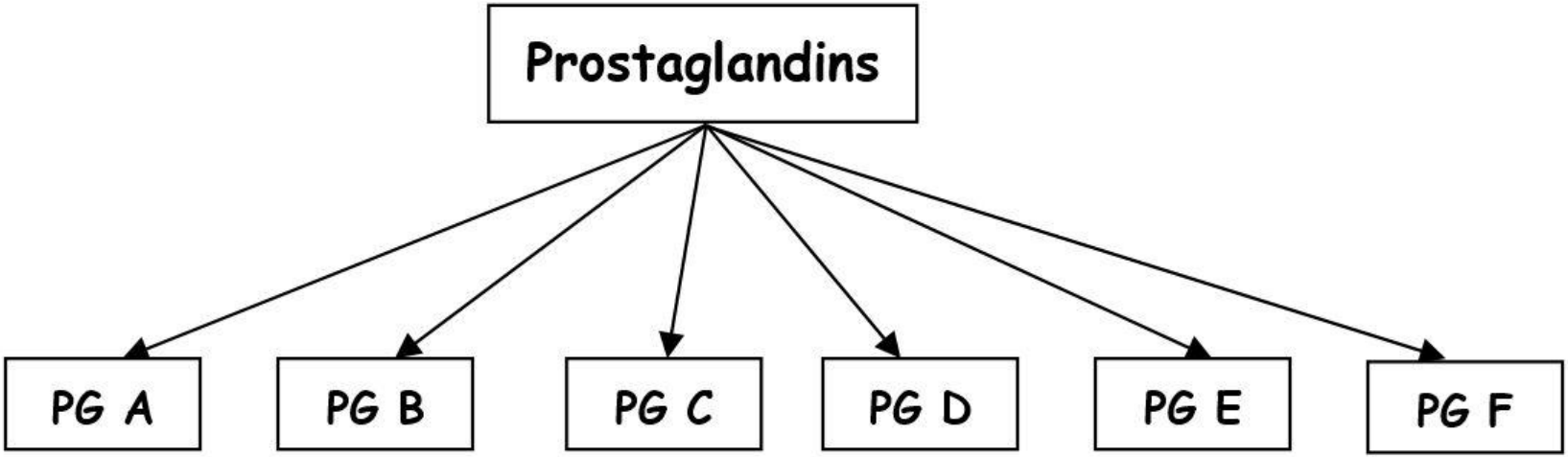
- ✓ The biologically active substances that are derived from **20 carbon polyunsaturated fatty acids** (mainly arachiodonic acid) which share a prefix **'eicosa' (means twenty)** are termed eicosanoids.

- ✓ 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.

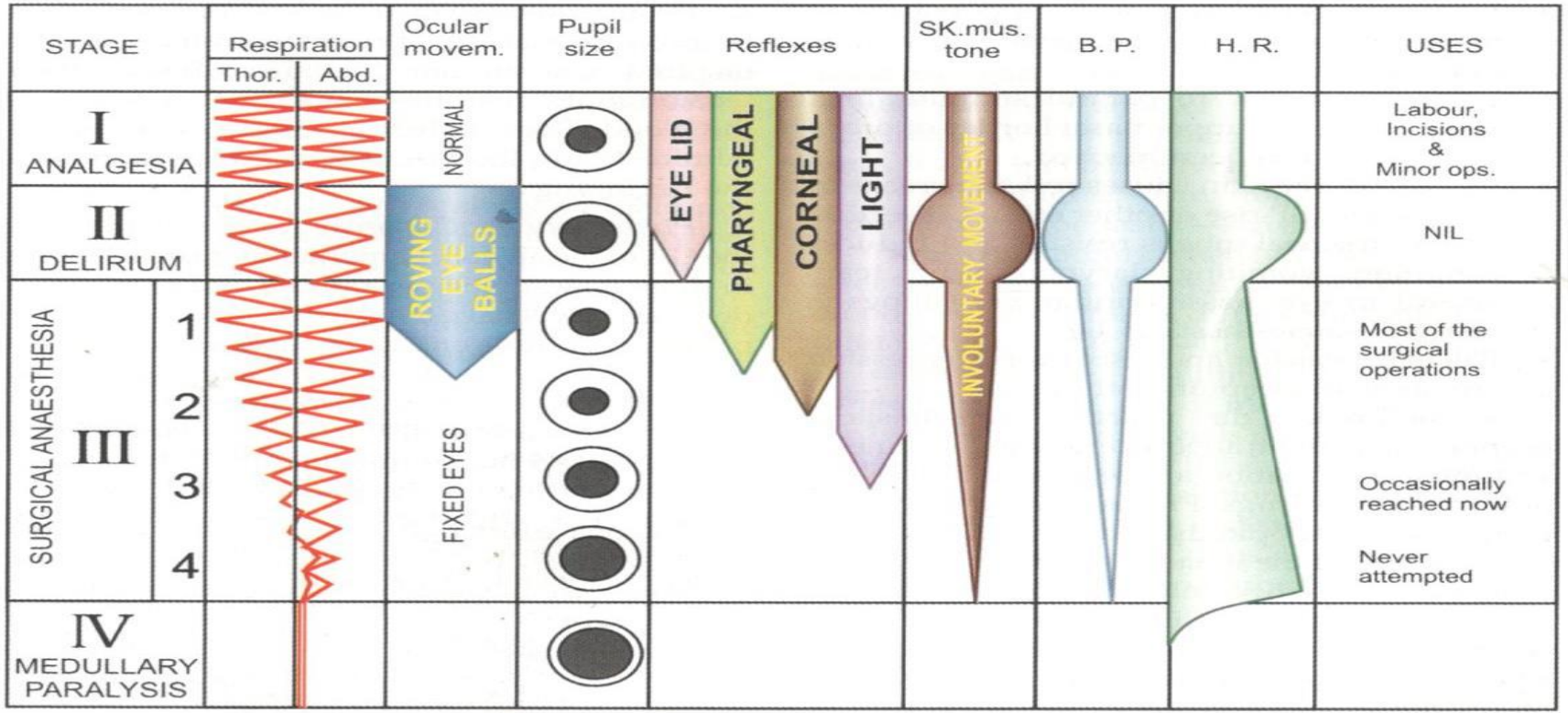
Stages of Anesthesia

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

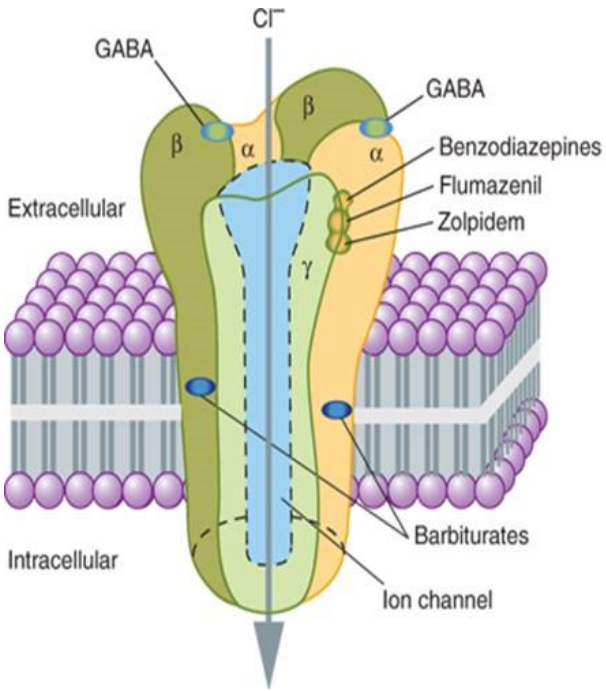


Fig: GABA Receptor chloride channel complex. (linear view)

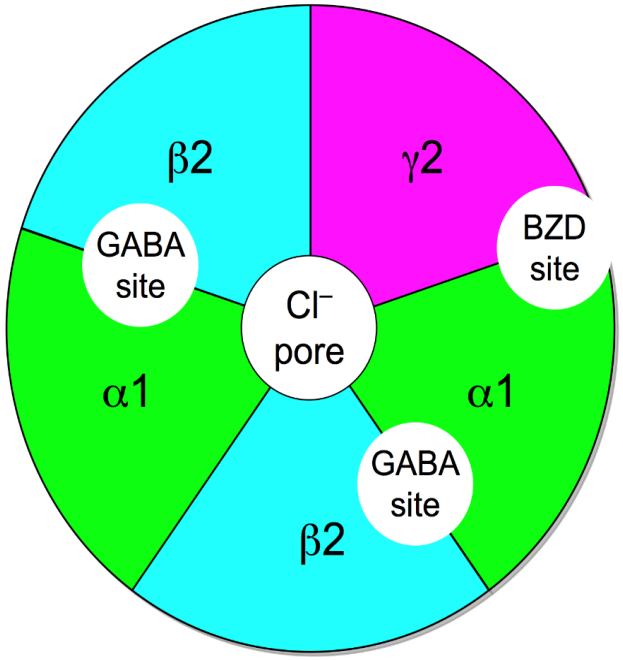


Fig: GABA Receptor (front view)

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

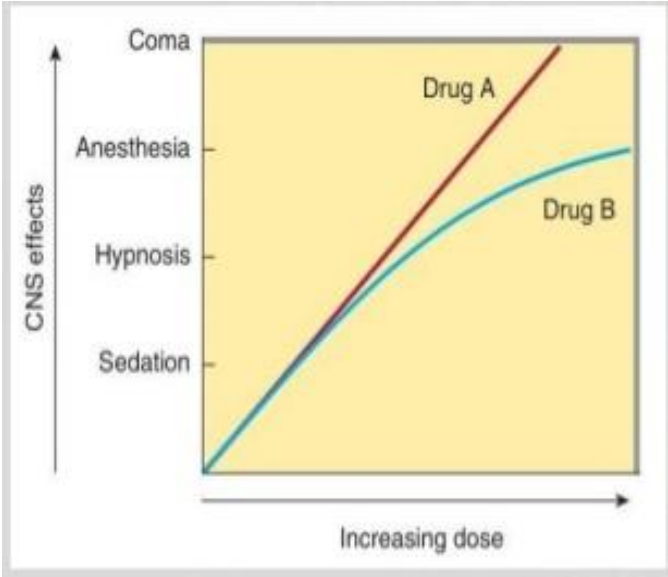
Dose response curve of sedative and hypnotics

- **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.**

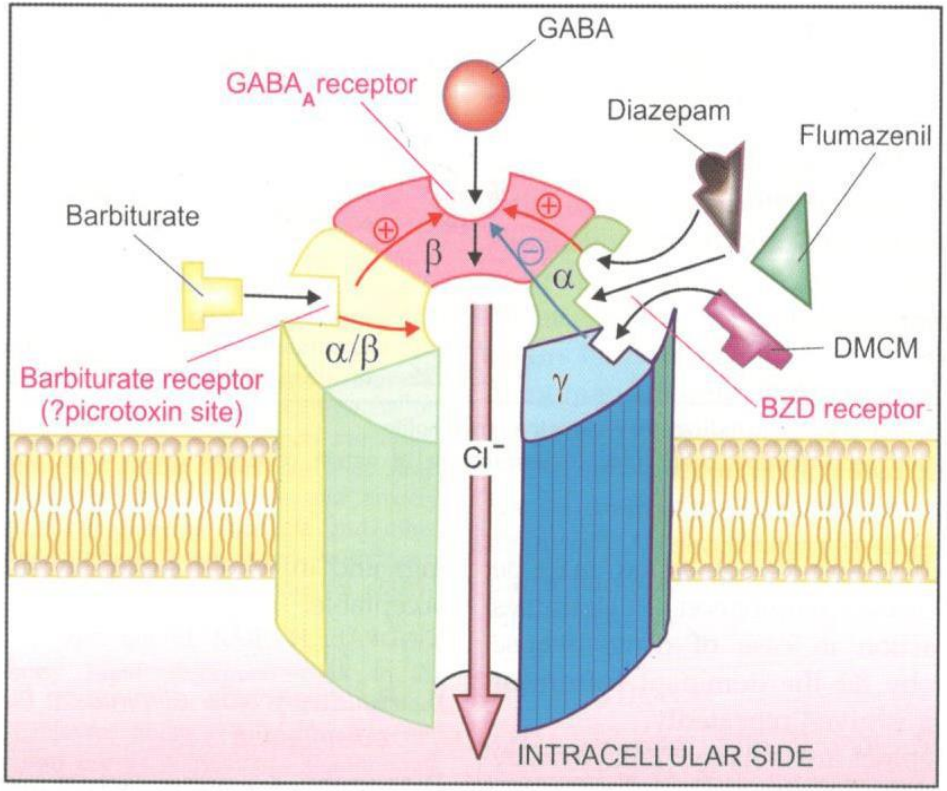
Classification of Benzodiazepines

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)

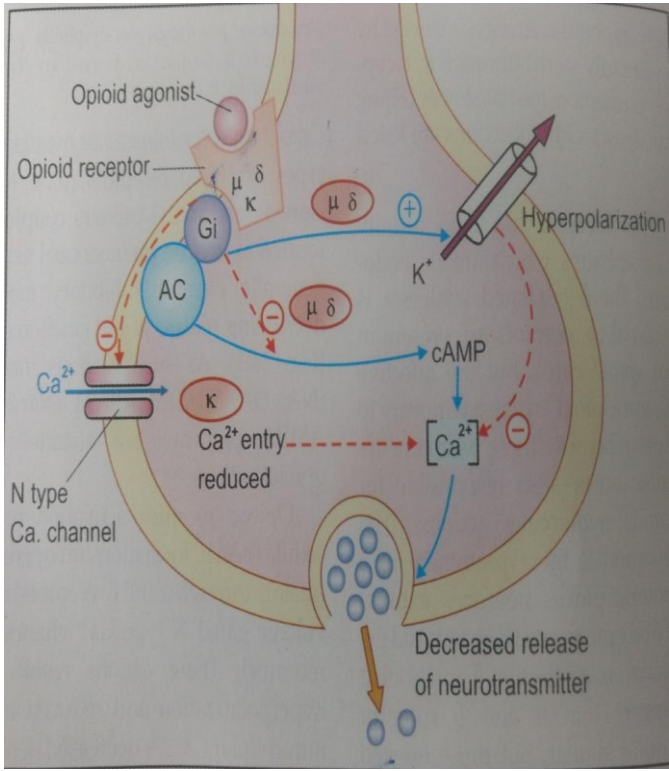
- OPIOIDS: refer to all compounds which act through opioid receptors, drugs derived from juice of opium poppy, *Papaver somniferum*
- Opium contains over 20 different alkaloids and belongs to two distinct chemical classes. Phenanthrenes & benzylisoquinolines.
- PHENANTHRENES: Morphine - Analgesic, CNS 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

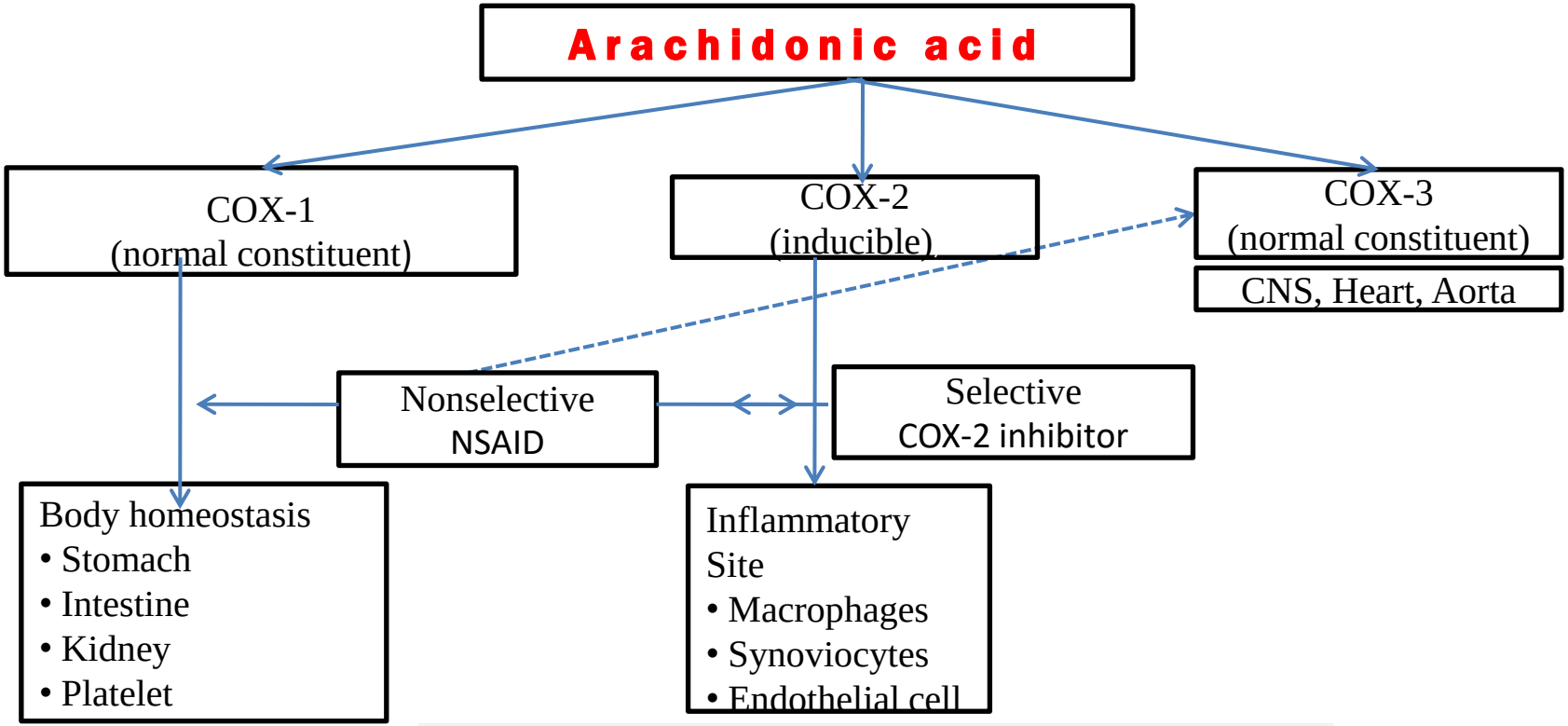
Preferential COX-2 inhibitors	Selective COX-2 inhibitors	Analgesic-antipyretics with poor Antiinflammatory action
Nimesulide, Diclofenac, Aceclofenac, Meloxicam, Etodolac	Celecoxib, Etoricoxib, Parecoxib.	1.Paraaminophenol derivative: Paracetamol(Acetaminophen). 2.Pyrazolone derivatives: Metamizol (Dipyrone),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

MOA

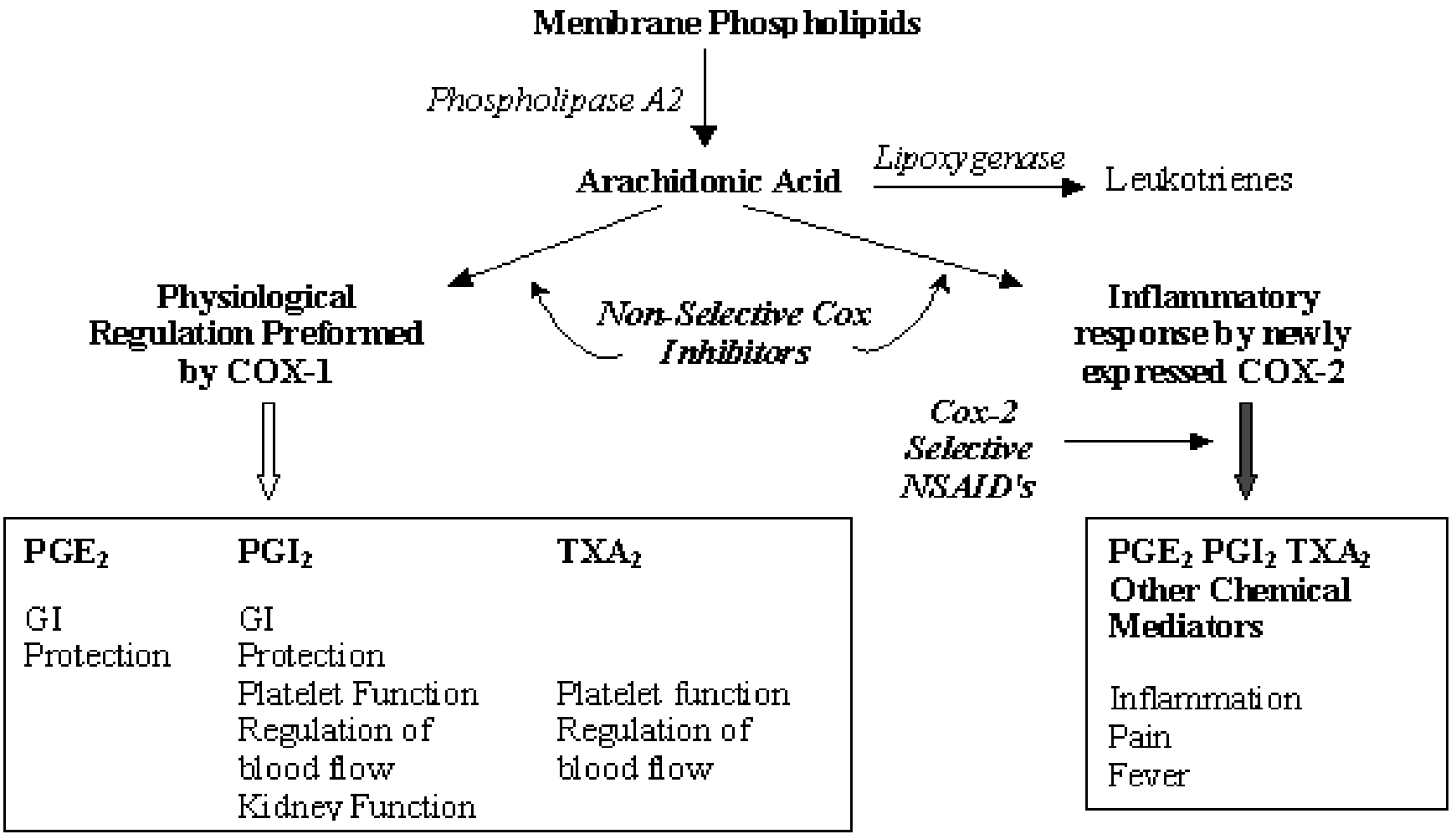
- MOA: These drugs block cyclo-oxygenase enzyme (COX-enzyme) either reversibly or irreversibly (Aspirin) causing inhibition of synthesis of PGs, prostacyclin (PGI_2) and thromboxane A_2 (TXA_2)
- Block of Cox-1 and Cox-2 are Non specific/Non-selective COX Inhibitors
- Blockers of COX-2 are called selective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

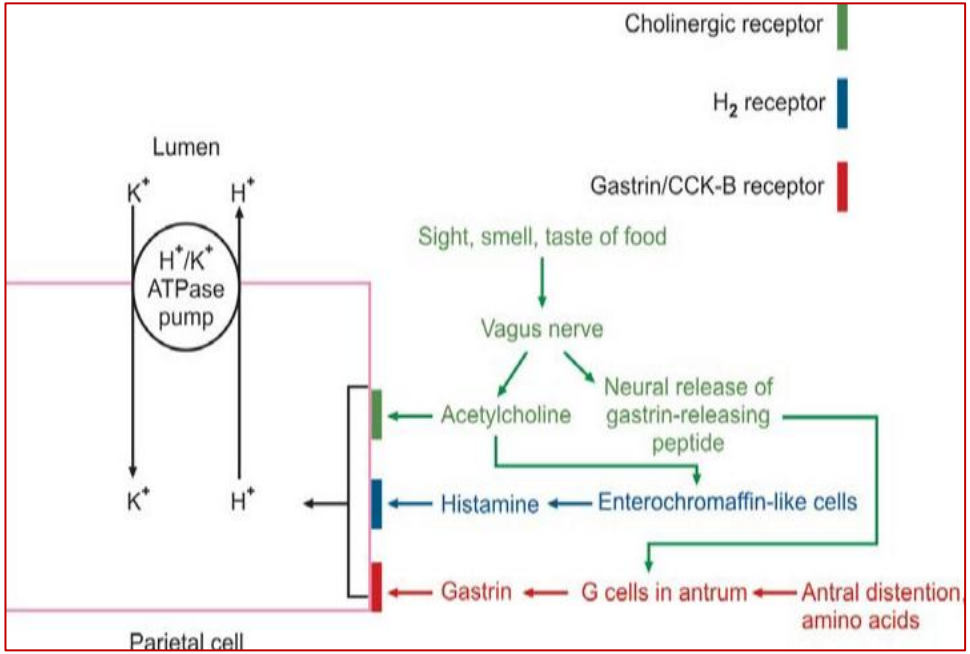
- Eg : Ginger, Nuxvomica.

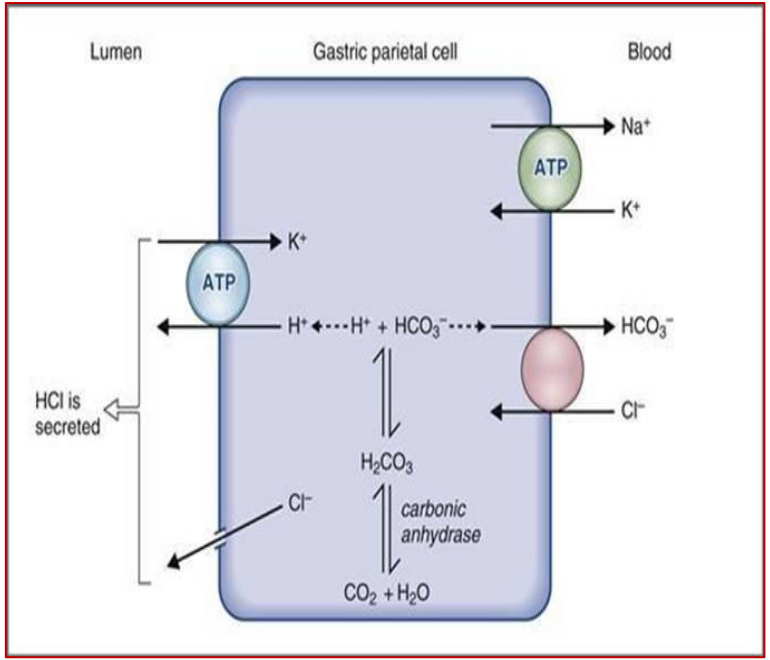
Gastric Acid

- 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.

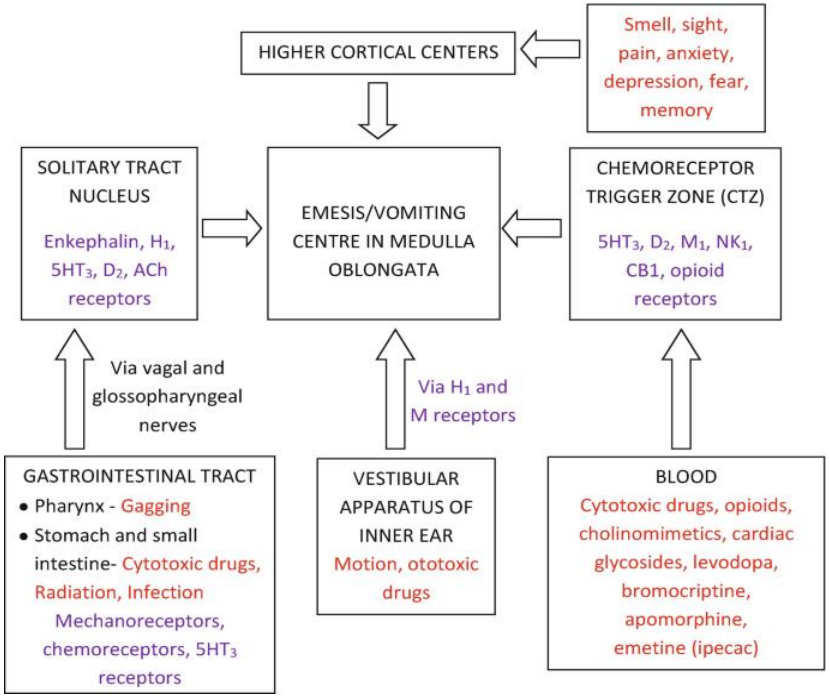
Eg : sodium chloride, sodium carbonate, Hydrogen peroxide etc.

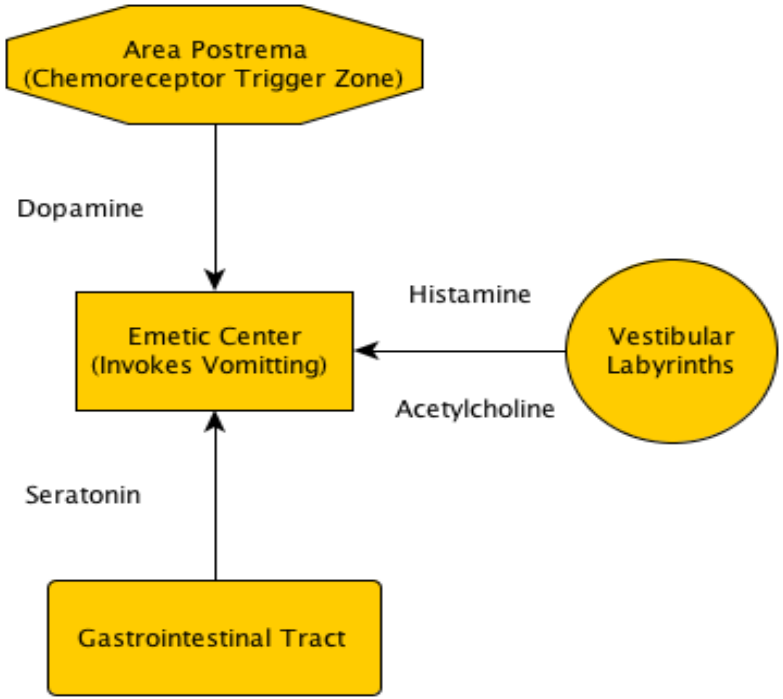
Central emetics : These agent cause vomition by stimulating the medullary emetic centre directly or through CTZ

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

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Gastric Acid

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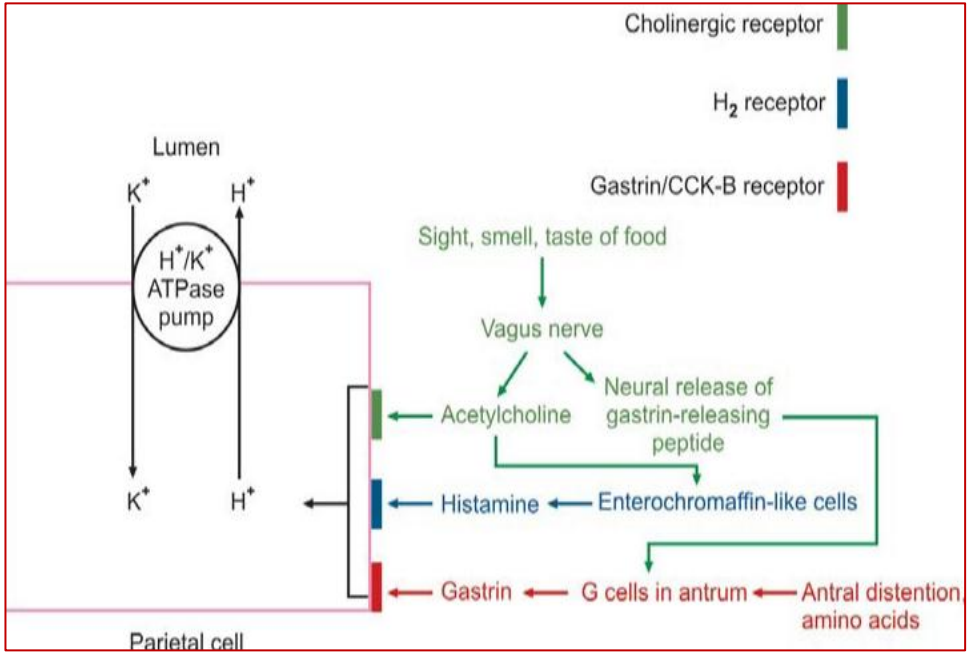
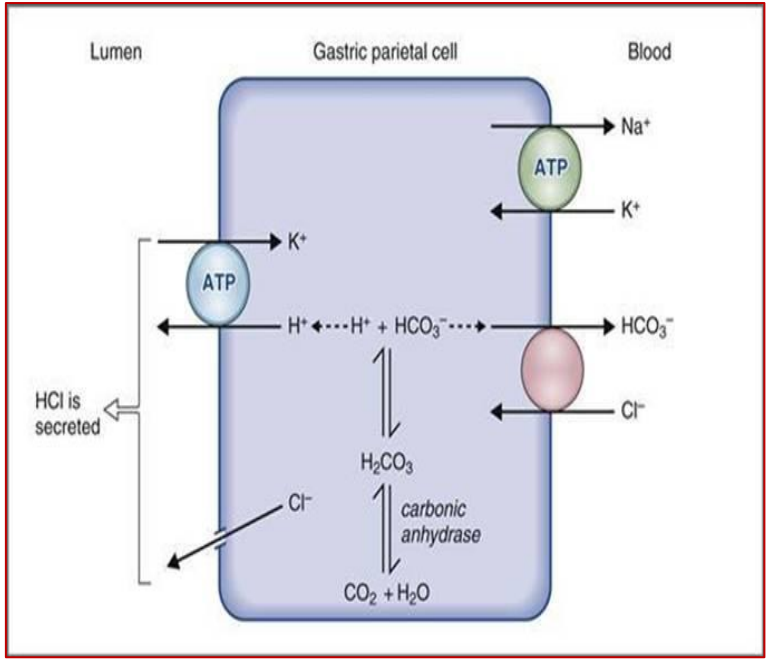
- Naturally secreted by action of

- 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.

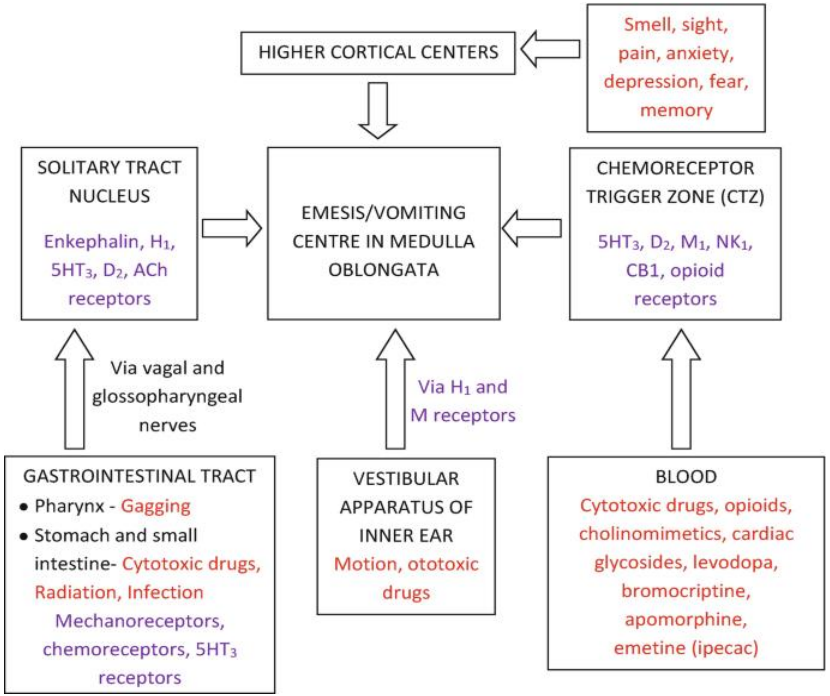
Eg : sodium chloride, sodium carbonate, Hydrogen peroxide etc.

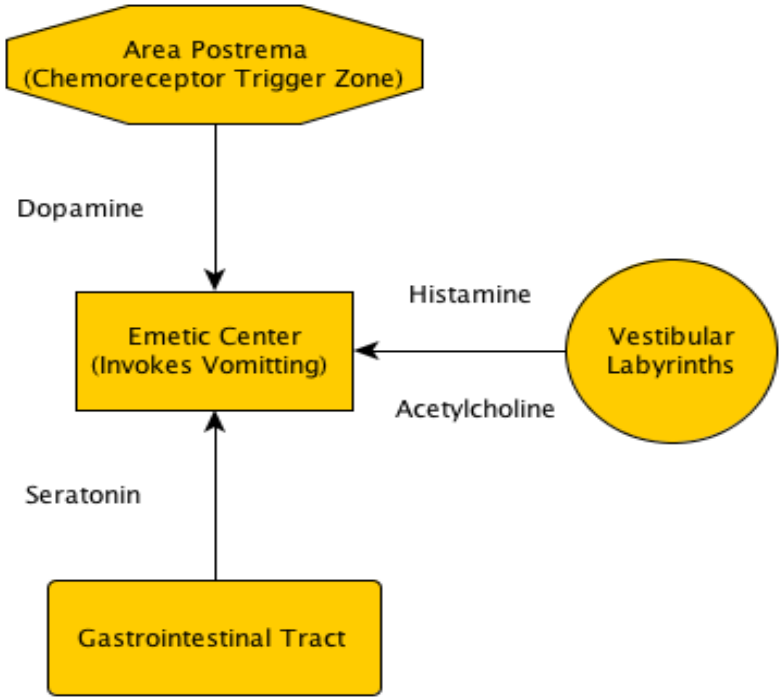
Central emetics : These agent cause vomition by stimulating the medullary emetic centre directly or through CTZ

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 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

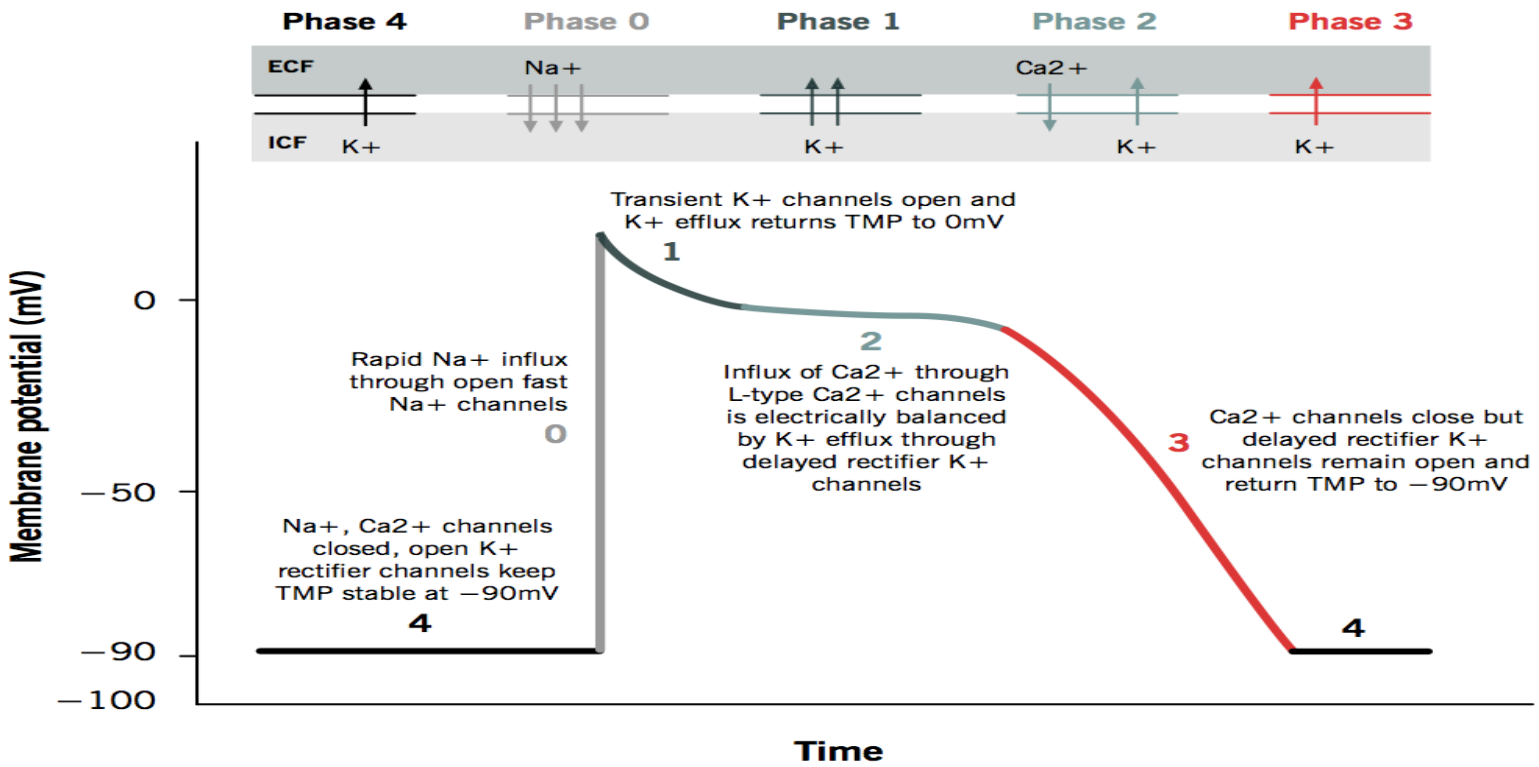
- Used in sinusitis (allergic or viral).
- Histamine receptor (H_1) antagonists e.g. *dimenhydrinate*, *diphenhydramine*, *chlorpheniramine*, *hydroxyzine*, Cetrizine
- Sympathomimetic drugs: α-adrenergic agonists e.g. *ephedrine*, *pseudoephedrine*, *phenylephrine*, *oxymetazoline*, *tramazoline*, *xylometazoline*.
- 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.

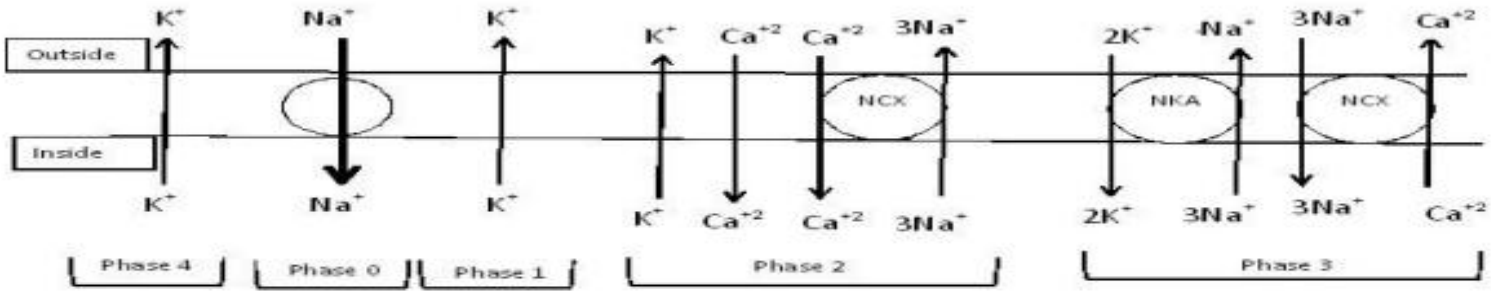
DRUGS ACTING ON CARDIO VASCULAR SYSTEM

* 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

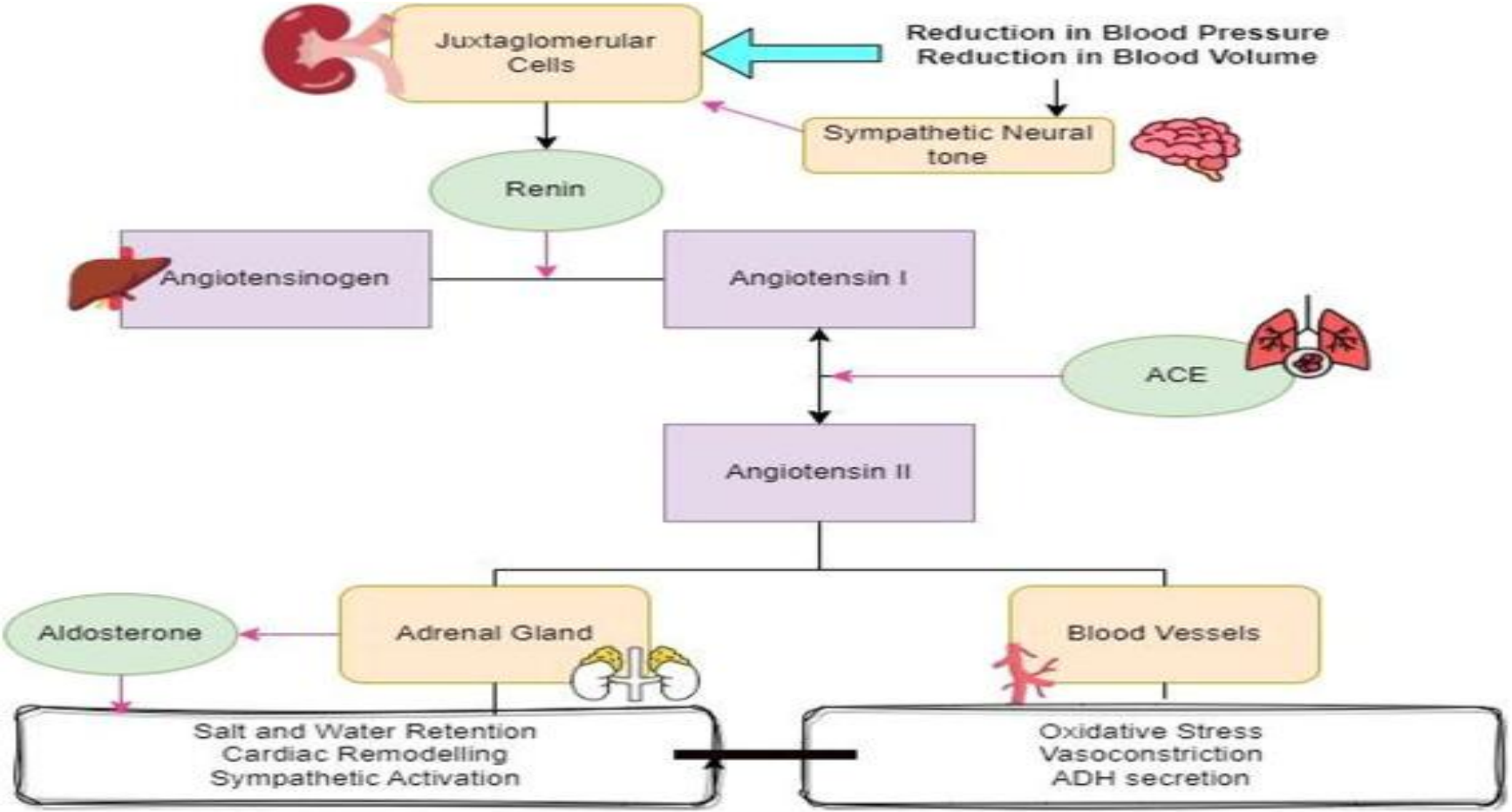
ACE inhibitors

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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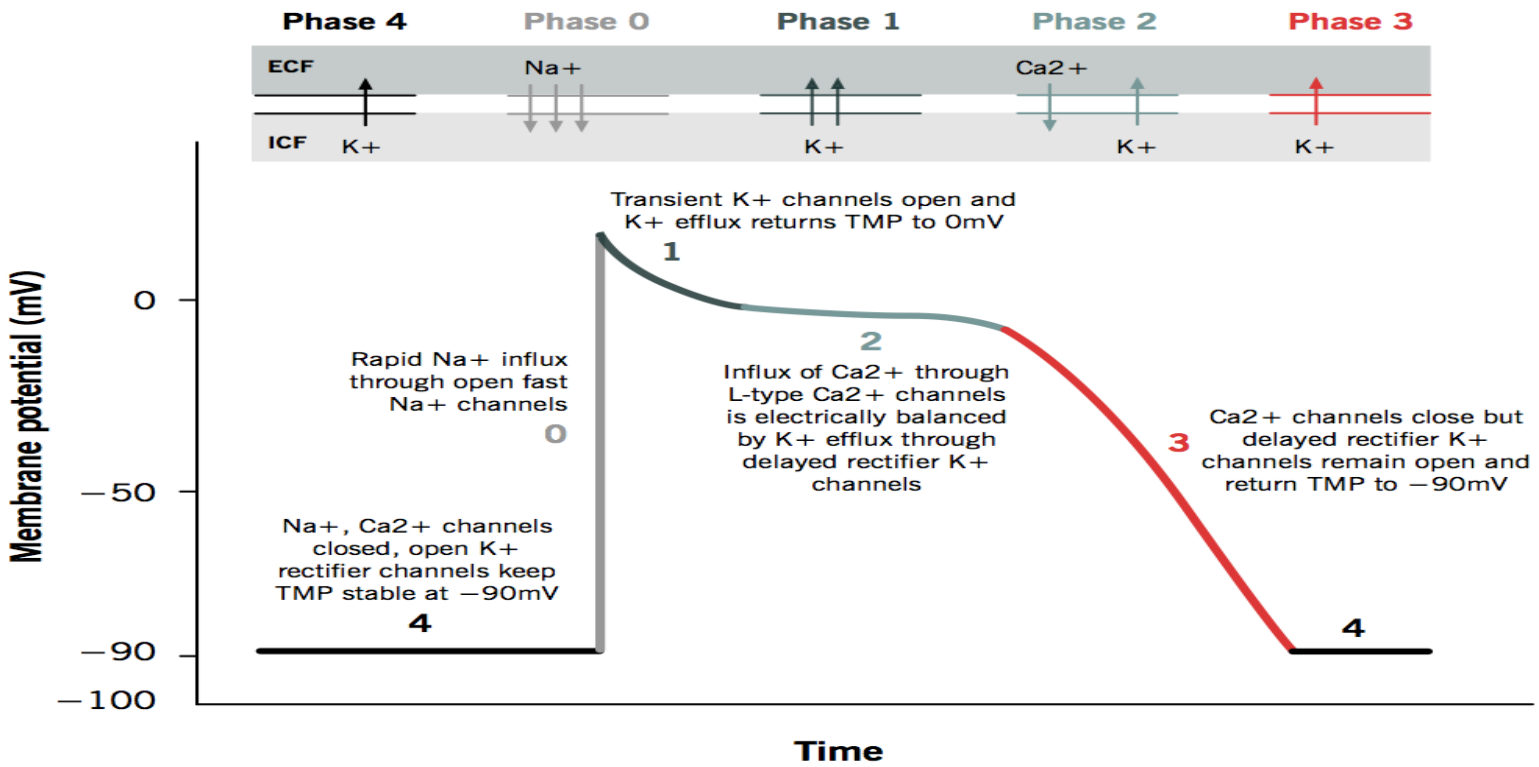
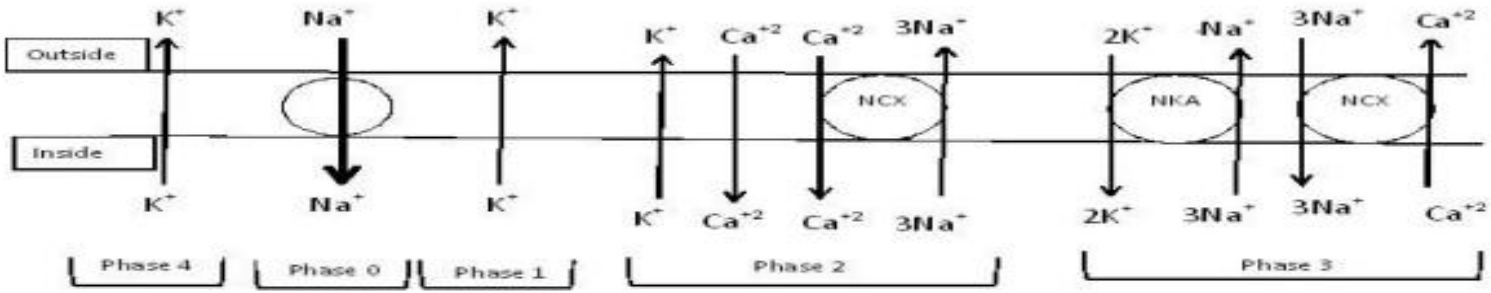
Grigoriy Ikonnikov and Eric Wong





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

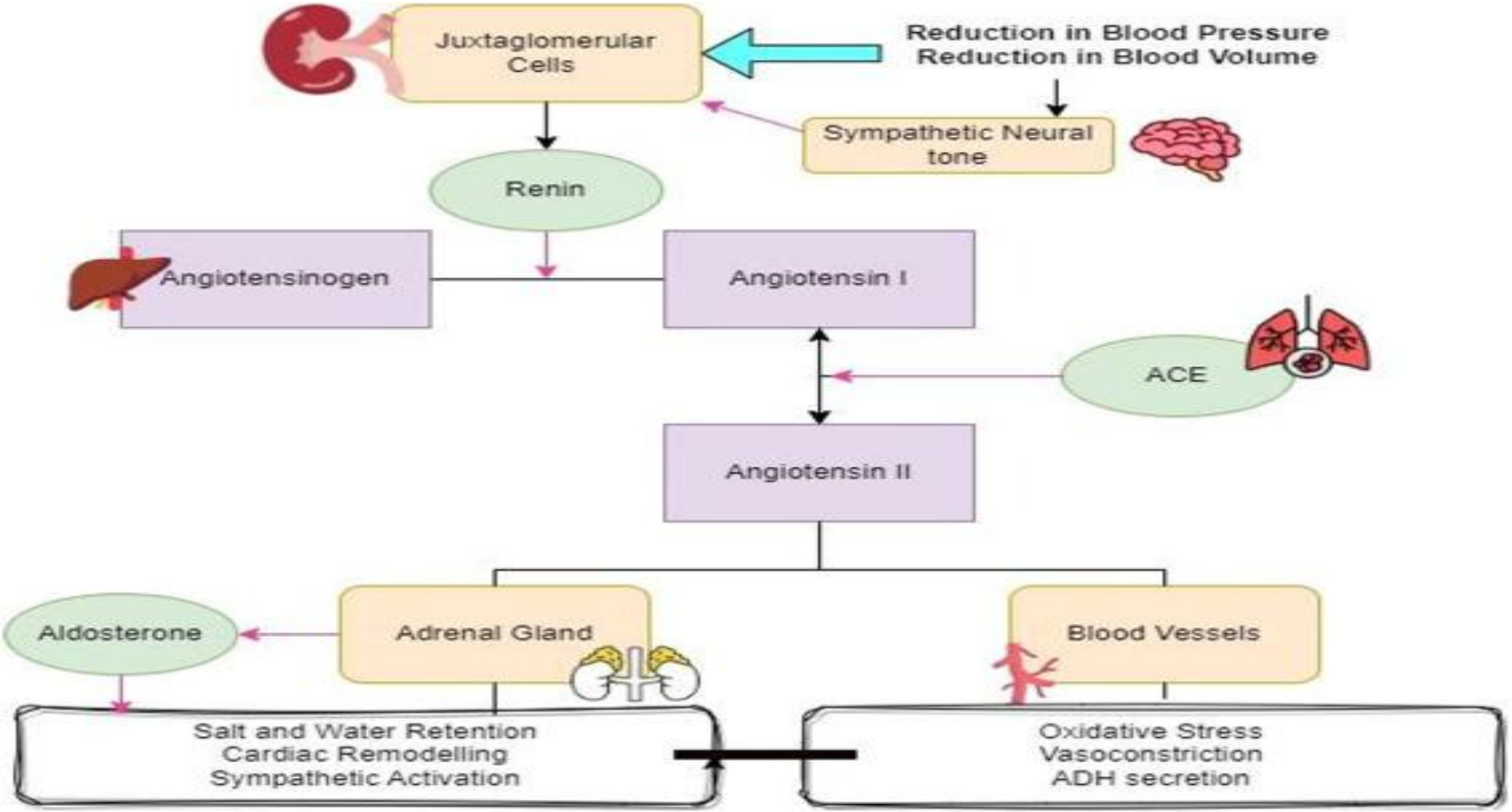
ACE inhibitors

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

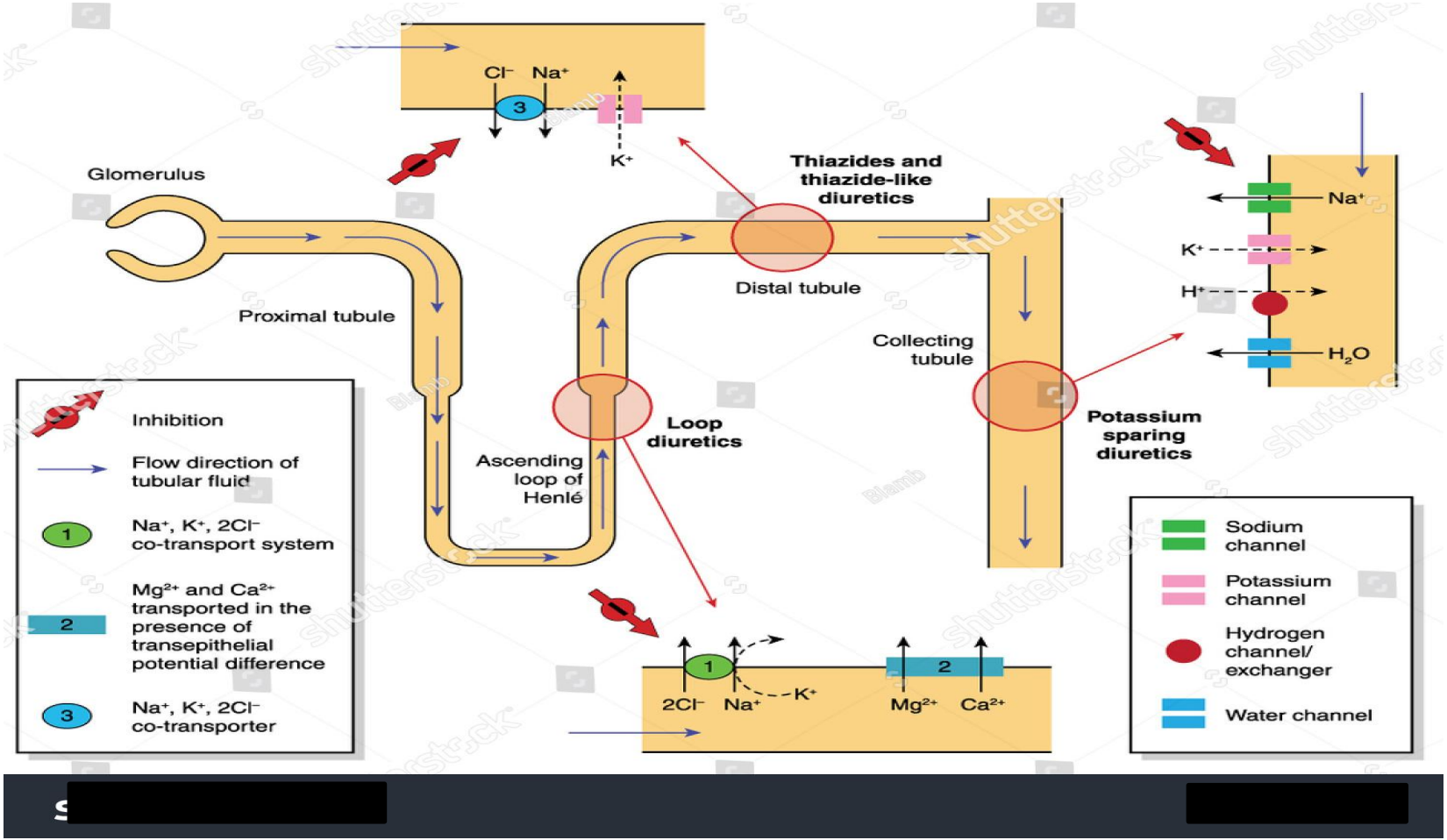
- Thrombolytic/Fibrinolytic agents: cause accelerated conversion of plasminogen to plasmin. E.g. Streptokinase, urokinase
- Antithrombotic / Antiplatelet drugs: Inhibitors of Thromboxane – aspirin, Dipyridamole

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