Nature of drug

The physical nature of drugs

- **Organic ---** proteins, lipids, carbohydrates or
- **Inorganic ---** iron, lithium, Iodine
- Physical nature determine the best **route of administration**
- **Solid** at room temperature – aspirin, atropine
- **Liquid** --- Nicotine, Ethanol
- **Liquid & evaporate** ---- halothane, amyl nitrate
- **Gaseous** --- Nitrous oxide

Size of a drug molecule

- Very small (lithium ion MW 7) to very large (alteplase (t-PA) MW 59050)
- Majority of drugs MW between 100 to 1000
- **Route of administration &**
- **Ability to move within the body from the site of administration to site of action**
  - Very large drugs (usually proteins) directly administered into the compartment of action ---altepase -- I/V

Aqueous & Lipid Solubility

- **Weak bases or weak acids**
- **The aqueous solubility --- degree of ionization or polarity of the molecule.**
  - Water molecules behave as dipoles & are attracted to charged molecules, forming an aqueous shell around them.
- **The lipid solubility of a molecule is inversely proportional to its charge.**

What drugs can do?

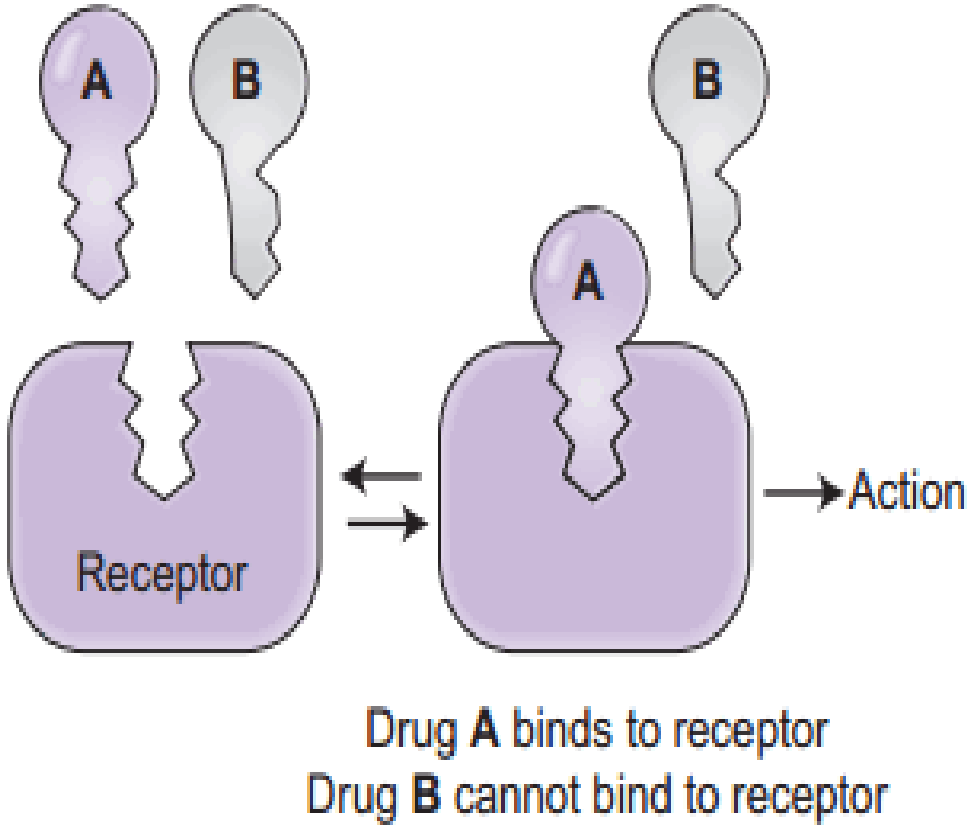
- **Drugs alter** (activate or inhibit) **the normal functions of cells and tissues in the body**
- Drugs cannot confer any new function on them

How drugs act?

- Through Specific **receptors**
- Alteration of the activity of **enzymes**
- Nonspecific **chemical or physical interactions** -- Antacids, osmotic agents, and chelators
- **Antimetabolite action --- Drug act as nonfunctional analogue** of a naturally occurring metabolite

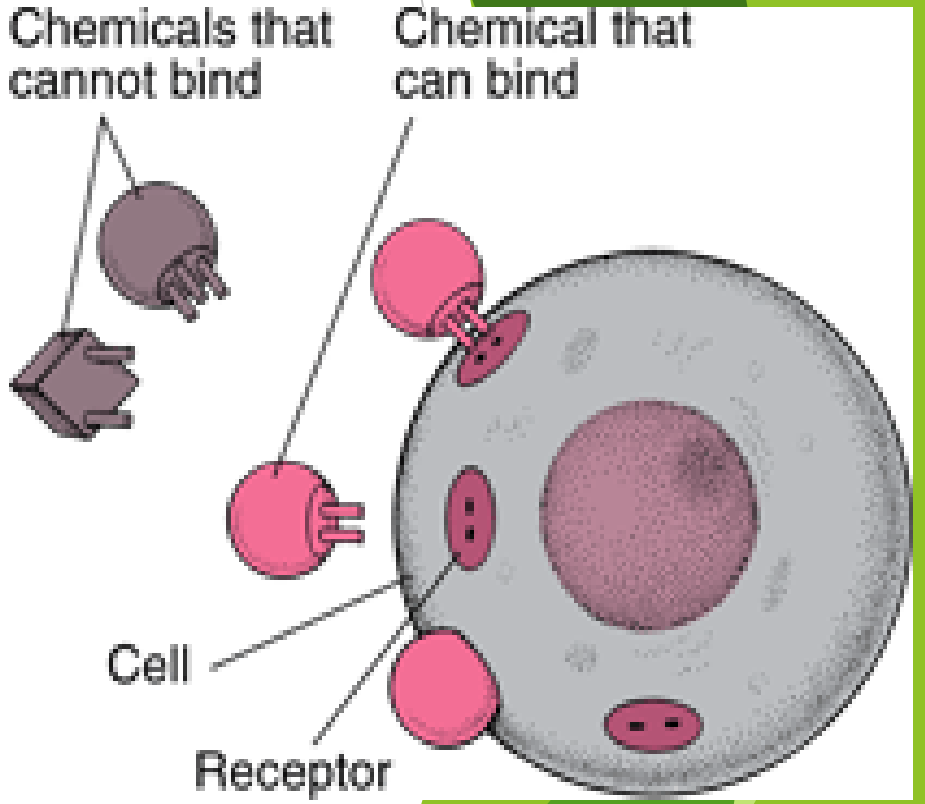
Shape of Drug molecule

- **Shape** --- permit binding to its receptor site
- Drug reacts with a **regulator molecule called as receptor** to show its effects



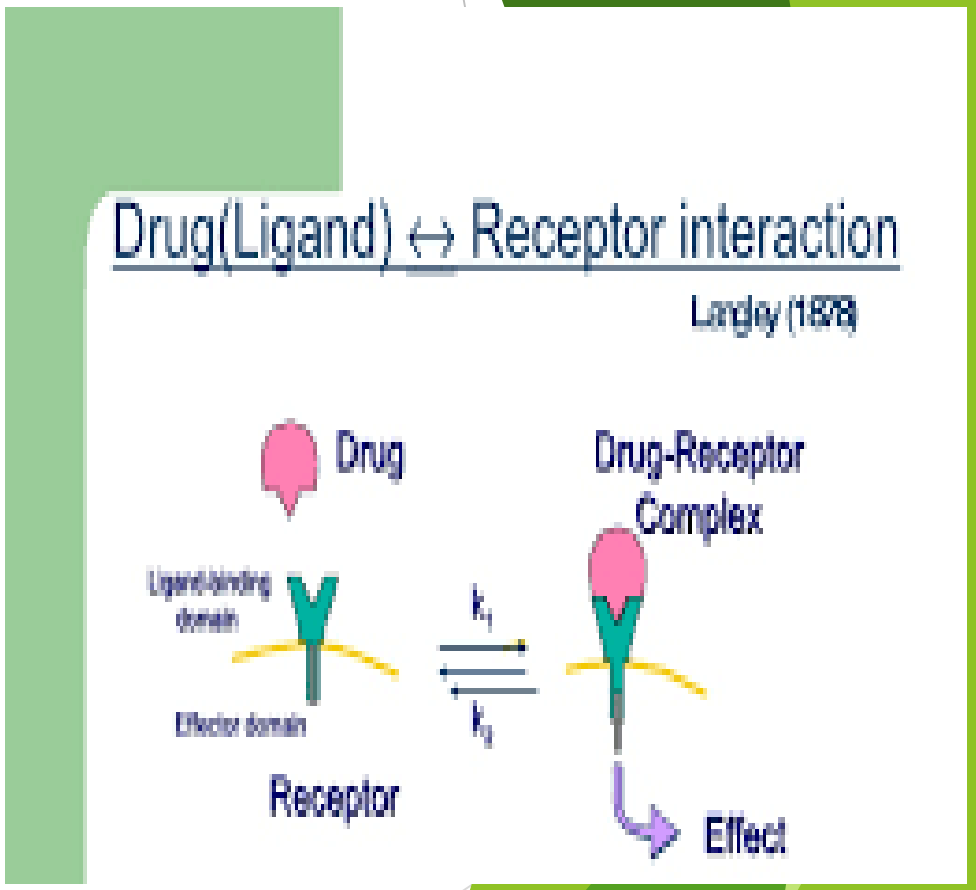
What are receptors?

Receptors are **Protein molecules** whose function is to recognize & respond to endogenous chemical signals



Drug + Receptor ↔ drug-receptor complex → Effector molecule → biological effects

- Other macromolecules with which drugs interact to produce their effects are known as **drug targets**



How drugs bind with the receptors?

- Drugs interact with receptors by means of chemical forces or bonds

- **Covalent**
- **Electrostatic**
- **Hydrophobic**

Covalent
(Very strong , may be irreversible)

- **Phenoxybenzamine & α adrenergic receptors**
- **Aspirin** whose acetyl group forms covalent bond **with cyclo-oxygenase of platelets.**
- **DNA-alkylating agents** in cancer chemotherapy

Electrostatic & Hydrophobic bonds

- **Electrostatic**
  - **Weaker & more common** than covalent bonding
  - Due to linkages between ionic molecules & hydrogen bonds
  - Force varies from relatively strong linkage to very weak Van der Waal forces
- **Hydrophobic**
  - Quiet weak, between **highly lipid soluble drugs with the lipids of cell membrane**
  - Due to interaction of the drug with the internal walls of the receptor pockets

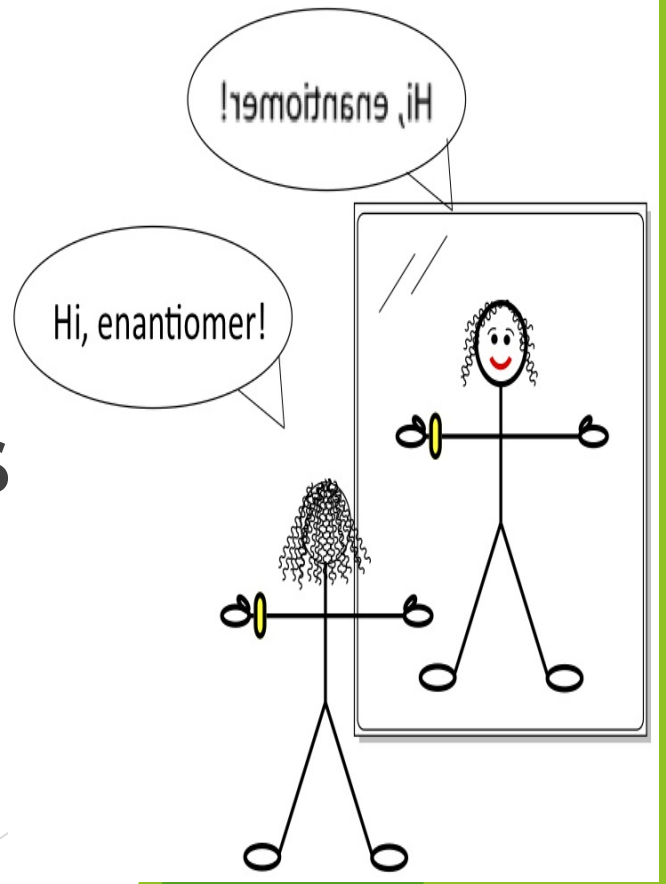
Chirality (stereoisomerism)

What is the role of the shape of the drug molecule?

- It permit binding to its receptor site
- Drug's shape is complimentary to the receptor site like a key is complimentary to a lock
- **Shape and charge to 'fit' to only one type of receptors**

Chirality (stereoisomerism)

- A single chiral molecule --- two enantiomers
  - > than ½ of all useful drugs are **chiral molecules** ----They exist as **enantiomeric pairs**
- Drugs with **two asymmetric centers** have **four diastereomers**
  - **Ephedrine**, a sympathomimetic drug
  - **Labetalol**, an α & ß receptor blocking drug



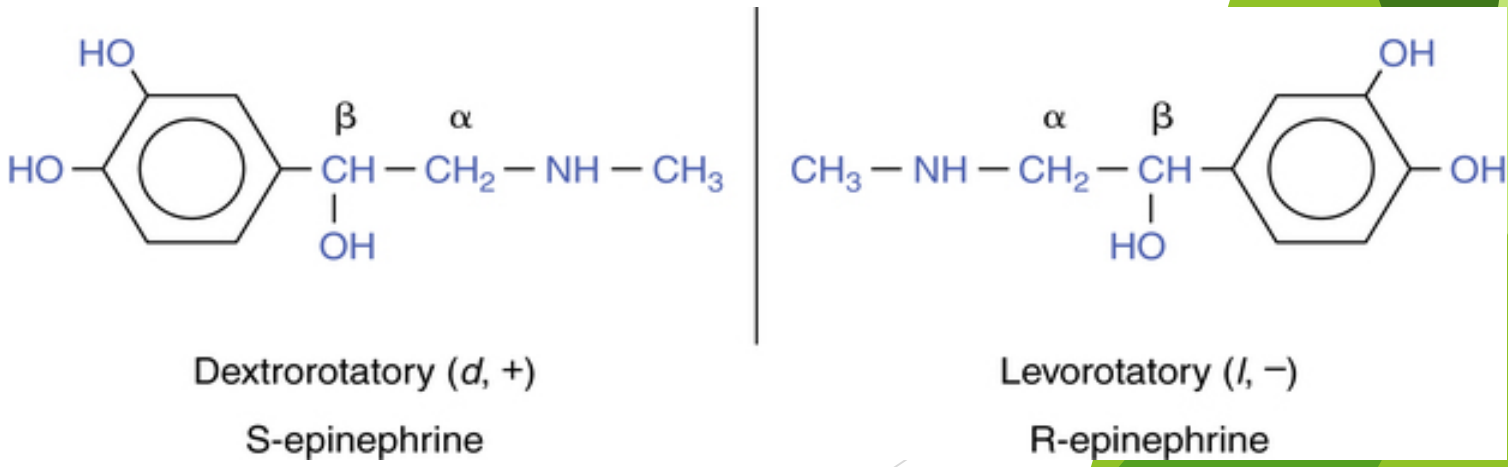
- Active isomers ---- About 45% of the chiral drugs used clinically are active isomers
- **Racemic mixture ---** The rest are available only as racemic mixtures
  - More active enantiomer
  - Inactive

What qualities of the drugs are affected by Chirality (stereoisomerism)?

- **Potency**
  - One of the enantiomers may be much **more effective** than its mirror image enantiomer, reflecting a **better fit to the receptor site**
- **Side effects &**
- **Duration of action**

Examples -- A single chiral molecule --- two enantiomers

- The **levoisomer *s* (-)of adrenaline/epinehrine** is **ten** times more potent than its dextroisomer
- S(+) enantiomer of **methacholine**, a parasympathomimetic drug, is over **250 times more potent** than its mirror image enantiomer.



Examples -- A single chiral molecule --- two enantiomers

- **Carvedilol --**
  - S(-) isomer is a potent ß receptor blocker
  - R(+) isomer is 100 fold weaker at ß receptor
  - Equipotent as α receptor blockers
- **Ketamine**
  - The (+) enantiomer is a potent anesthetic & is less toxic than the (-) enantiomer

Stereoisomerism and receptor binding

Receptor site is like a glove into which the **hand (the drug molecule)** fits to bring its effects

If receptor site is to be like a glove. "left oriented" drug will be more effective in binding to a left-hand receptor than will be its "right oriented" enantiomer