MECHANISM OF DRUG ACTION

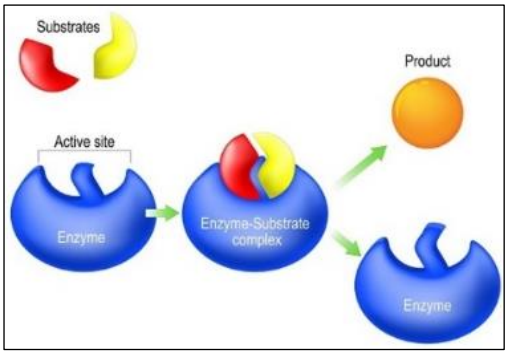
- Drugs (except those gene based) do not impart new functions to any system, organ or cell they only alter the pace of ongoing activity.
- The basic types of drug action can be broadly classed as:
  - i) **Stimulation**
    - It refers to selective enhancement of the level of activity of specialized cells, e,g. adrenaline stimulates heart.
  - ii) **Depression**
    - It means selective diminution of activity of specialized cells, e.g. barbiturates depress CNS, quinidine depresses heart, omeprazole depresses gastric acid secretion.
    - Certain drugs stimulate one type of cells but depress the other, e.g. acetylcholine stimulates intestinal smooth muscle but depresses SA node in heart.
    - Thus, most drugs cannot be simply classed as stimulants or depressants.
  - iii) **Irritation**
    - This is a nonselective, often noxious effect and is particularly applied to less specialized cells (epithelium, connective tissue).
    - Strong irritation results in inflammation, corrosion, necrosis and morphological damage. This may result in diminution or loss of function.
  - iv) **Replacement**
    - This refers to the use of natural metabolites, hormones or their congeners(जन्मदाता) in deficiency states, e.g. levodopa in parkinsonism, insulin in diabetes mellitus, iron in anaemia.
  - v) **Cytotoxic action**
    - Selective cytotoxic action on invading parasites or cancer cells, attenuating them without significantly affecting the host cells is utilized for cure of infections and neoplasms, e.g. penicillin, chloroquine etc.

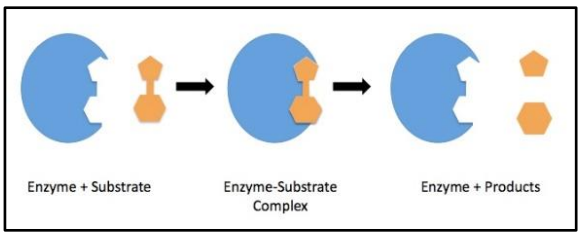
❖ **MECHANISM OF DRUG ACTION**

1. **By physical or chemical property** -Only a handful of drugs act by virtue of their simple physical or chemical property examples are:
   - Bulk laxatives (ispaghula)-physical mass
   - Dimethicone, petroleum jelly-physical form,opacity
   - Activated charcoal-adsorptive property
   - Mannitol, mag. sulfate-osmotic activity
   - Antacids-neutralization of gastric HCl
   - Pot. permanganate-oxidizing property
   - Chelating agents (EDTA, dimercaprol)-chelation of heavy metals.

2. Biological interaction

- Majority of drugs produce their effects by interacting with a target biomolecules(generally a protein)
- This mechanism create selectivity to the action of drug.
- Proteins that are targets of drug action can be grouped into *four* major categories, *viz.*
  - a) Enzymes,
  - b) Ion Channels,
  - c) Transporters And
  - d) Receptors
- However, a few drugs do act on other proteins (e.g. colchicine, vinca alkaloids, taxanes bind to the structural protein tubulin) or on nucleic acids (alkylating agents).

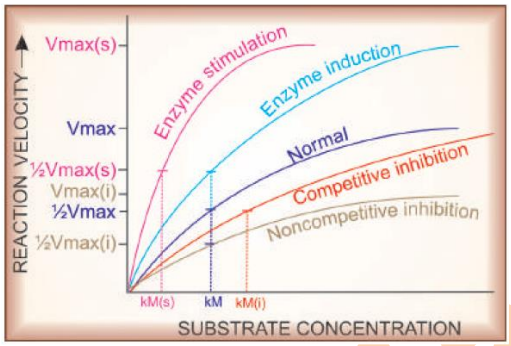




A. Enzyme-

- Mechanism of enzyme (lock and key hypothesis):-

- Almost all biological reactions are carried out by biocatalyst(enzymes).
- Drugs can either increase or decrease the rate of enzymatically mediated reactions.
- Stimulation of an enzyme increases its affinity for the substrate so that rate constant (*kM=substrate concentration*) of the reaction is lowered
- Increase in enzyme activity can also occur by *enzyme induction,* i.e. synthesis of more enzyme protein. This cannot be called stimulation because the *kM* does not change



➢ **Enzyme inhibition**

- Some chemicals (heavy metal salts, strong acids and alkalies, formaldehyde, phenol, etc.) denature proteins and inhibit all enzymes nonselectively.
- They have limited medicinal value restricted to external application only.
- However, selective inhibition of a particular enzyme is a common mode of drug action. Such inhibition is either competitive or noncompetitive.

(i) Competitive inhibition:-

Equilibrium type-

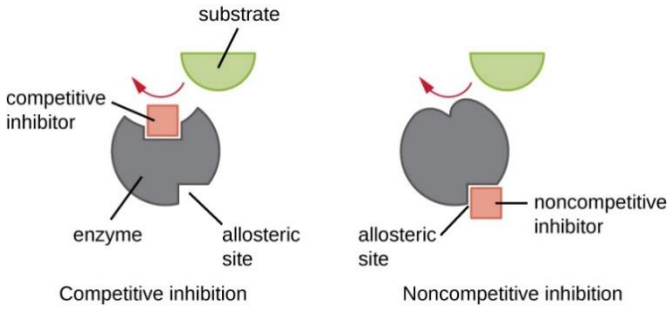
- The drug being structurally similar to substrate
- It competes with the normal substrate for the catalytic binding site of the enzyme so that the product is not formed or a nonfunctional product is formed, and a new equilibrium is achieved in the presence of the drug.
- Such inhibitors increase the *kM* but the *Vmax* remains unchanged
- If substrate concentration is sufficiently increased, then it can displace the inhibitor(drug)

Non-eqilibrium type

- In *nonequilibrium type* of enzyme inhibition drugs react with the same catalytic site of the enzyme but either form strong covalent bonds or have such high affinity for the enzyme that the normal substrate is not able to displace the inhibitor.
- In these situations, *kM* is increased and *Vmax* is reduced

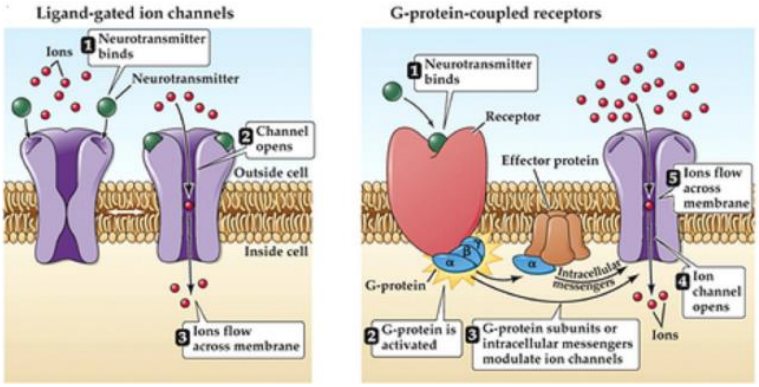
(ii) Non-competitive inhibiton

- The inhibitor reacts with an adjacent site and not with the catalytic site, but alters the enzyme in such a way that it loses its catalytic property.
- Thus, *kM* is unchanged but *Vmax* is reduced.



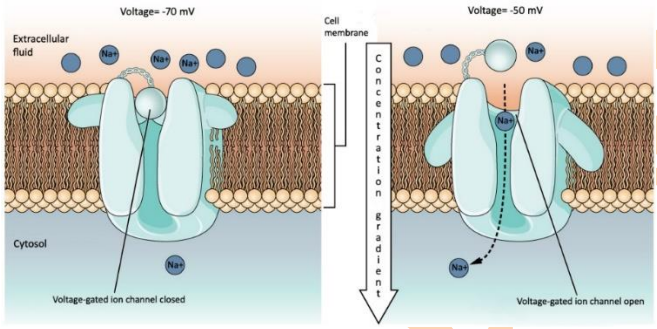
B. Ion channel

- Proteins which act as ion selective channels participate in transmembrane signaling and regulate intracellular ionic composition
- Ion channel can be categorise into 4 types-
  - i) **Ligand gated channel**- Some ion channels are operated by specific signal molecules directly and are called *ligand gated channels*
  - ii) G-protein regulated channel- Some ion channels are operated by specific signal molecules through G-proteins and are termed *G-protein regulated channels*



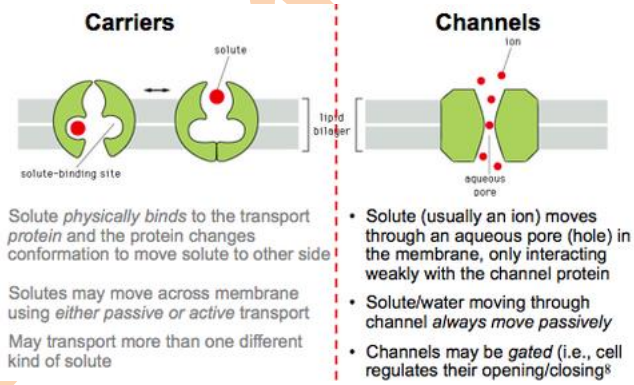
iii) voltage gated channel and iv) stretch sensitive channels

- Drugs can also act on *voltage operated* and *stretch sensitive* channels by directly binding to the channel and affecting ion movement through it, e.g. local anaesthetics which obstruct voltage sensitive Na^+ channels



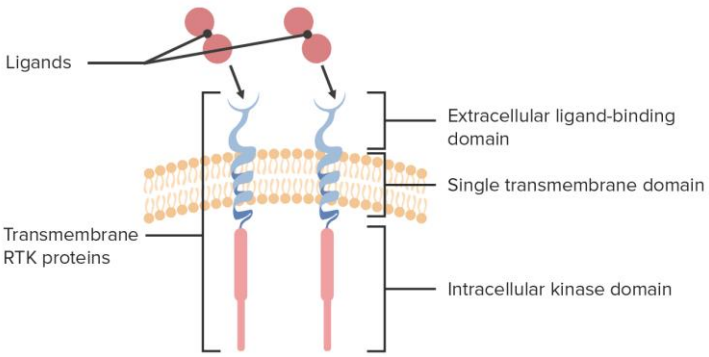
C. Transporters(carriers)

- Several substrates are translocated across membranes by binding to specific transporters (carriers) which either facilitate diffusion in the direction of the concentration gradient or pump the metabolite/ion against the concentration gradient using metabolic energy



D. Receptors

- The largest number of drugs do not bind directly to the effectors, *viz.* enzymes, channels, transporters etc. but act through specific regulatory macromolecules which control the above listed effectors.
- **Definition**- It is defined as a 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.
- Receptors are mostly proteins, though nucleic acids may also serve as receptors



- The following terms are used in describing drug-receptor interaction:
  i) *Agonist* An agent which activates a receptor to produce an effect.
  ii) *Inverse agonist* An agent which activates a receptor to produce an effect in the opposite direction to that of the agonist.
  iii) *Antagonist* An agent which prevents the action of an agonist on a receptor.
  iv) *Partial agonist* An agent which activates a receptor to produce submaximal effect but antagonizes the action of a full agonist.
  v) *Ligand* (Latin: *ligare*—to bind) Any molecule which attaches selectively to particular receptors or sites.

➢ **Receptor occupation theory of drug action**

- Clark (1937) propose a theory of drug action based on occupation of receptors by specific drugs(ligands) and that the pace of a cellular function can be altered by interaction of these receptors with drugs.
- The ability of drug to bind with the receptor is called *affinity,* and the capacity to induce a functional change in the receptor is called *intrinsic activity (IA)* or *efficacy* which could vary from 0 to 1 (nil to maximal).
- Higher affinity implies that the same number of drug-receptor association (DRs) will be formed at lower concentrations of the drug, compared to another drug which has lower affinity.
- *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.
- *Partial agonists* have affinity and submaximal intrinsic activity (IA between 0 and 1), e.g. dichloroisoproterenol (on β adrenergic receptor), buspirone on 5-HT1A receptor.
- *Inverse agonists* have affinity but intrinsic activity with a minus sign (IA between 0 and –1). Inverse agonism is manifest only in case of some receptors which show certain degree of *Constitutive activation*, i.e. they are partially active even in the basal state (complete absence of any agonist). In other words they are tonically active.

➢ **ACTION-EFFECT SEQUENCE**

- 'Drug action' and 'drug effect' are often loosely used interchangeably, but are not synonymous.
- *Drug action*- It is the initial combination of the drug with its receptor resulting in a conformational change in the receptor in case of agonists, or prevention of conformational change in case of antagonists.
- *Drug effect* It is the ultimate change in biological function brought about as a consequence of drug action.
- Receptors has two essential functions, *viz*, *recognition* of the specific ligand molecule and *transduction* of the signal into a response.

❖ **DRUG SYNERGISM AND ANTAGONISM**

- When two or more drugs are given simultaneously or in quick succession, they may be either indifferent to each other or exhibit *synergism* or *antagonism*.

i) Synergism- When the action of one drug is facilitated or increased by the other, they are said to be synergistic. And the effect is called synergistic effect

(a) *Additive*
→ The effect of the two drugs is in the same direction and simply adds up
→ effect of drugs A + B = effect of drug A + effect of drug B

(b) *Supraadditive (potentiation)*
→ The effect of combination is greater than the individual effects of the components
→ effect of drug A + B > effect of drug A + effect of drug B

ii) Antagonism-

- When one drug decreases or abolishes the action of another, they are said to be antagonistic:
- effect of drugs A + B < effect of drug A + effect of drug B

❖ **Therapeutic efficacy**

- The 'therapeutic efficacy' or 'clinical effectiveness' is a composite attribute of a drug
- It is often expressed in terms of
  (a) degree of benefit/relief afforded by the drug (in the recommended dose range)
  (b) success rate in achieving a defined therapeutic end point
- The gap between the therapeutic effect dose-response curve (DRC) and the adverse effect DRC defines the *safety margin* or the *therapeutic index* of a drug

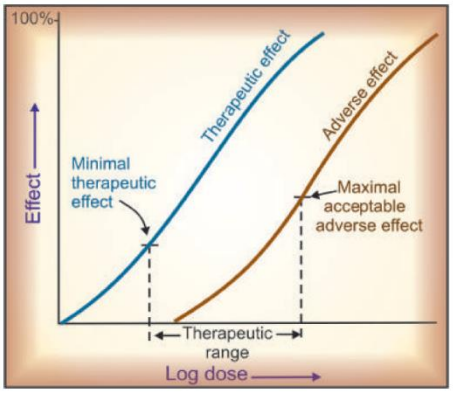


Figure: Illustrative dose-response curves for therapeutic effect and adverse effect of the same drug

$$\text{Therapeutic index} = \frac{\text{median lethal dose}}{\text{median effective dose}} = \frac{LD_{50}}{ED_{50}}$$

❖ **Factors modifying Drug action**

- Variation in response to the same dose of a drug between different patients and even in the same patient on different occasions is a rule rather than exception.
- following categories of differences among individuals are responsible for the variations in drug response:
  i) Individuals differ in pharmacokinetic handling of drugs: attain varying plasma/target site concentration of the drug.
  ii) Variations in number or state of receptors, coupling proteins or other components of response effectuation.
  iii) Variations in neurogenic/hormonal concentrations of specific constituents
- The various factors modifying drug action are:

1. Body size

- It influences the concentration of the drug attained at the site of action. The average adult dose refers to individuals of medium built.
- For exceptionally obese or lean individuals and for children dose may be calculated on body weight (BW) basis:

$$\text{Individual dose} = \frac{\text{BW (kg)}}{70} \times \text{average adult dose}$$

- It has been argued that body surface area (BSA) provides a more accurate basis for dose calculation, because total body water, extracellular fluid volume and metabolic activity are better paralleled by BSA.

$$\text{Individual dose} = \frac{\text{BSA } (m^2)}{1.7} \times \text{average adult dose}$$

- The BSA of an individual can be calculated from

DuBois Formula:

$$BSA = 0.007184 \times W^{0.425} \times H^{0.725}$$

Mosteller Formula:

$$\text{BSA } (m^2) = \sqrt{\frac{\text{Ht (Cm) x Wt (kg)}}{3600}}$$

2. Age

- The dose of a drug for *children* is often calculated from the adult dose.
- Child dose is better calculated more accurately on BW basis.
- For many drugs, manufacturers give dosage recommendations on mg/kg basis.
- The *newborn* has low g.f.r. and tubular transport is immature. Therefore t½ of drugs excreted by glomerular filtration (gentamicin) and tubular secretion (penicillin) is prolonged by 3 to 5 times.
- Similarly, hepatic drug metabolizing system is inadequate in newborns —chloramphenicol can produce *gray baby syndrome.* Blood-brain barrier is more permeable—drugs attain higher concentration in the CNS (easy entry of unconjugated bilirubin in brain causes *kernicterus*).
- In the elderly, renal function progressively declines (intact nephron loss) so that g.f.r. is ~ 75% at 50 years and ~ 50% at 75 years age compared to young adults.
- Other affected aspects of drug handling due to age are:
  i) Slower absorption due to reduced gut motility as well as blood flow to intestines,
  ii) Lesser plasma protein binding due to lower plasma albumin,
  iii) Increased or decreased volume of distribution of lipophilic and hydrophilic drugs respectively.

3. Sex-

- Females have smaller body size and require doses that are on the lower side of the range.
- A number of antihypertensives have potential to interfere with sexual function in males but not in females.
- Gynaecomastia is a side effect that can occur only in men.
- Ketoconazole causes loss of libido in men but not in women.
- Obviously androgens are unacceptable to women and estrogens to men
- There are marked and progressive physiological changes during pregnancy, especially in the third trimester, which can alter drug disposition.
  (i) Gastrointestinal motility is reduced → delayed absorption of orally administered drug.
  (ii) Plasma and extracellular fluid volume expands—volume of drug distribution may increase.
  (iii) While plasma albumin level falls, that of α1 acid glycoprotein increases—the unbound fraction of acidic drugs increases but that of basic drugs decreases.
  (iv) Renal blood flow increases markedly—polar drugs are eliminated faster.
  (v) Hepatic microsomal enzymes undergo induction—many drugs are metabolized faster.

4. Species and race-

- Rabbits are resistant to atropine, rats and mice are resistant to digitalis and rat is more sensitive to curare than cat.
- Among human beings some racial differences have been observed :-
  i) Blacks require higher and mongols require lower concentrations of atropine and ephedrine to dilate their pupil.
  ii) β-blockers are less effective as antihypertensive in Afro-Caribbeans.
  iii) Considering the widespread use of chloramphenicol in India and Hong Kong between 1950–1980, relatively few cases of aplastic anaemia have been reported compared to its incidence in the west.
  iv) Similarly, quiniodochlor related cases of subacute myelooptic neuropathy (SMON) occurred in epidemic proportion in Japan, but there is no confirmed report of its occurrence in India despite extensive use

5. **Genetics-**
   - All key determinants of drug response, *viz.* transporters, metabolizing enzymes, ion channels, receptors are controlled genetically.
   - *Pharmacogenetics*- The study of genetic basis for variability in drug response is called *'Pharmacogenetics'*.It deals with genetic influences on drug action as well as on drug handling by the body.
   - *Pharmacogenomics is the use of genetic information to guide the choice of drug and dose on an individual basis.*

6. **Route of administration:-**
   - Route of administration governs the speed and intensity of drug response
   - Parenteral administration is often resorted to for more rapid, more pronounced and more predictable drug action.
   - A drug may have entirely different uses through different routes, e.g. magnesium sulfate given orally causes purgation, applied on sprained joints it decreases swelling, while intravenously it produces CNS depression and hypotension.

7. **Environmental factors and time of administration**
   - Exposure to insecticides, carcinogens, tobacco smoke and consumption of charcoal broiled meat are well known to induce drug metabolism.
   - Food interferes with absorption of ampicillin, but a fatty meal enhances absorption of griseofulvin and lumefantrine.
   - Subjective effects of a drug may be markedly influenced by the setup in which it is taken. E.g Hypnotics taken at night and in quiet, familiar surroundings may work more easily.
   - Statins cause greater inhibition of cholesterol synthesis when taken in the late evening

8. **Psychological factor:**
   - Efficacy of a drug can be affected by the patient's beliefs, attitudes and expectations.
   - This is particularly applicable to centrally acting drugs, e.g. a nervous and anxious patient requires more general anaesthetic
   - **Placebo-**This is an inert substance which is given in the garb(भेष) of a medicine. It works by psychodynamic rather than pharmacodynamic means and often produces responses equivalent to the active drug. Some individuals are more suggestible and easily respond to a placebo and are called 'placebo reactors'. e.g. they can release endorphins in brain—causing analgesia

9. **Pathological state**-

Several diseases can influence drug disposition and drug action:-

i) ***Gastrointestinal (g.i.) diseases*** Certain g.i. diseases can alter absorption of orally administered drugs.

ii) ***Liver disease*** -Liver disease (especially cirrhosis) can influence drug disposition in several ways:
   - Bioavailability of drugs having high first pass metabolism is increased due to loss of hepatocellular function.
   - Serum albumin is reduced—protein binding of acidic drugs (diclofenac, warfarin, etc.) is reduced and more drug is present in the free form.
   - Metabolism and elimination of some drugs (morphine, lidocaine, propranolol) is decreased—their dose should be reduced.
   - Prodrugs needing hepatic metabolism for activation, e.g. bacampicillin are less effective and should be avoided.

iii) **Kidney disease** It markedly affects the pharmacokinetics of many drugs. Clearance of drugs that are primarily excreted unchanged (aminoglycosides, digoxin, phenobarbitone) is reduced parallel to decrease in creatinine clearance

iv) **Congestive heart failure** It can alter drug kinetics by—
- Decreasing drug absorption from g.i.t. due to mucosal edema.
- Altering volume of distribution which can increase for some drugs due to expansion of
- extracellular fluid volume
- Retarding drug elimination as a result of decreased perfusion and congestion of liver, reduced glomerular filtration rate and increased tubular reabsorption

v) **Thyroid disease** The hypothyroid patients are more sensitive to digoxin, morphine and CNS depressants.

10. **Other drugs**
Drugs can modify the response to each other by pharmacokinetic or pharmacodynamic interaction between them.

11. Cumulation
Any drug will cumulate in the body if rate of administration is more than the rate of elimination. However, slowly eliminated drugs are particularly liable to cause cumulative toxicity.

12. Tolerance-
- It refers to the requirement of higher dose of a drug to produce a given response.
- Loss of therapeutic efficacy after prolonged/intensive use of a drug is generally called *'refractoriness*