PHARMACODYNAMICS

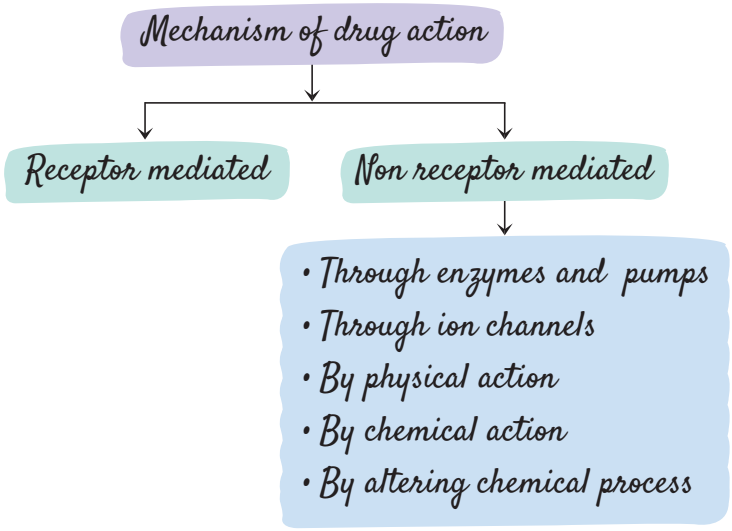
Definition

It is the study of effects of drugs and their mechanism of action in our body

How does the drugs act

- ⇨ Stimulation - Act by increasing activity in specialized cells
- ⇨ Depression - Act by decreasing activity in specialized cells
- ⇨ Irritation - Act by causing inflammation, corrosion, and necrosis of cells
- ⇨ Replacement - Act as a replacement whenever there is a deficiency of a natural substance
- ⇨ Anti-infective or cytotoxic action - Act by destroying infective organism
- ⇨ Modification of immune status - Act by improving or depressing immune system

Mechanism of drug action



Receptor-mediated

Drugs act by interacting with specific receptors in our bodies.

Receptor

It is a macromolecular site on the cell with which an agonist binds to bring about a change. (receptors are proteins)

Drug receptor interaction

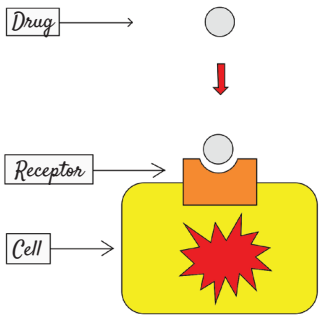
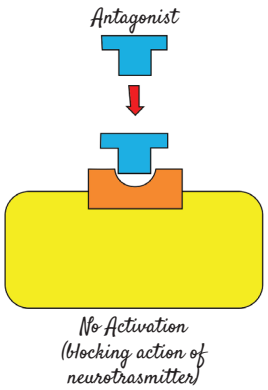
Drug + receptor ⟶ drug-receptor complex ⟶ produces a response

Characteristics of interactions

⇨ Affinity - The ability of the drug to bind to the receptor

⇨ Efficacy or intrinsic activity – The ability of the drug to produce an action

The drug interacts with target receptors to produce effects through agonist and antagonist

Agonist	Antagonist
It's a substance that binds to the receptor and produces action.	It's a substance that binds to the receptor and prevents the action of the agonist on the receptor
It has both affinity and efficacy.	It has only affinity and no efficacy
• Partial agonist +receptor = effect less than agonist. • Inverse agonist + receptor =opposite effect of agonist	
• Agonist + receptor → Action 	• Antagonist +receptor → No action 

Functions of receptors

⇨ Recognition and binding of the ligand(ligand is a molecule which binds selectively to a specific receptors) - Ligand binding domain

⇨ Passage of message - Effector binding domain

Theories of drug receptor interaction

⇨ Lock and key theory - Drugs fits the receptor like a key to the lock

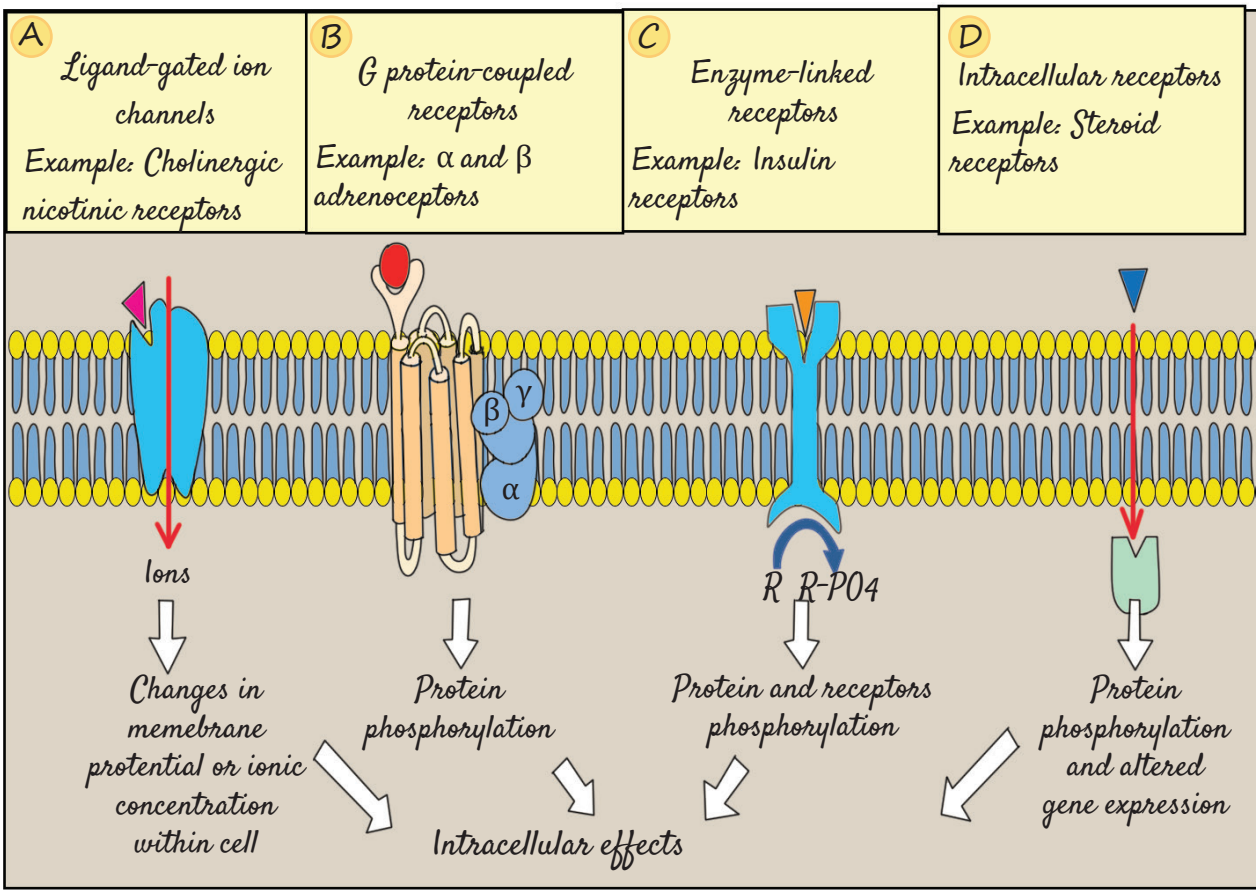
⇨ Rate theory - Depends on agonist receptor association and dissociation

⇨ Occupation theory - Depends on the proportion of receptors occupied by drugs

Agonist +receptor → changes in receptor → signals to effector → second messenger → final response

Receptor families

Types of receptor



⇨ Ion channels - Agonist binds to ion channels to open channel allowing ions to cross the membrane undergoes either hyperpolarization or depolarization to produce effects

⇨ G protein coupled receptor - Ligand binds to g proteins to activate them to produce intracellular changes via the second messenger. Proteins work through 3 pathways

- Adenylcyclase pathway
- Phospholipase pathway
- Lon channel regulation

⇨ Enzymatic receptor - Binding of agonist to ligand binding domain causes autophosphorylation of intracellular domain resulting in a response

⇨ Transcription factors - Agonist binds to them to activate and form agonist receptor complex, they move to the nucleus interacts with dna to regulate gene transcription to synthesis proteins to regulate the activity of target cell.

Receptor regulation

We can regulate the number and sensitivity of receptors by

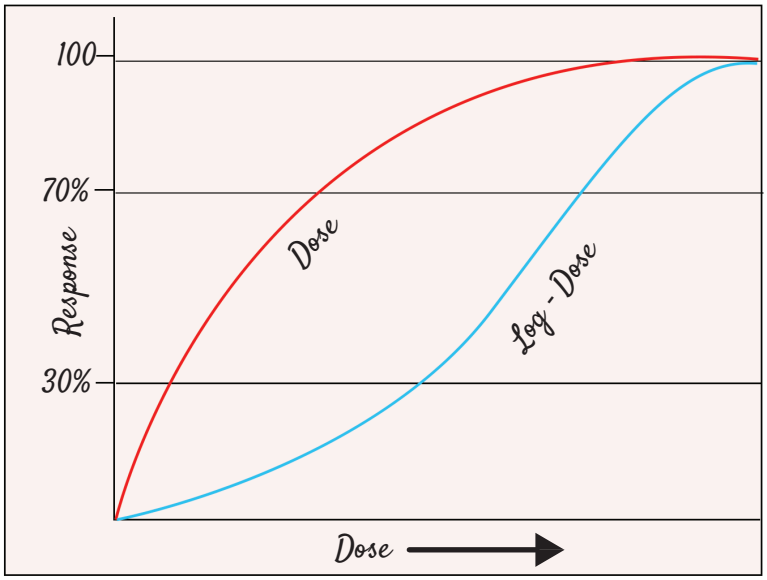
⇨ Up regulation - Prolonged use of the antagonist increases receptor number and sensitivity

⇨ Down regulation - Prolonged exposure to high conc. Of agonist reduces the number of receptors available for activation

Dose receptor relationship

An increase in dose is ∝ to increase in response till the maximum response is achieved after which it produces no effect.

Dose relation ship curve (DRC)



⇨ Clinical response to the increased dose of the drug is defined by the shape of DRC

⇨ Drc has the shape of a rectangular hyperbola

⇨ If dose is plotted in log scale, The curve becomes sigmoid.

Steep slope-small increase in dose ⟶ large response

Flat slope-small increase in dose ⟶ little response

⇨ Drug potency - The amount of drug required to produce a response

⇨ Maximal efficacy - It indicates the maximum response that can be produced by a drug

Therapeutic index (TI)

It is a measure of the relative safety of a drug for a particular treatment.

Higher the TI safer the drug.

$$\text{Therapeutic index} = \frac{LD_{50}}{ED_{50}}$$

LD_{50} = median lethal dose

ED_{50} = median effective dose

Drugs synergism and antagonism

Synergism (supra additive)

⇨ (1+1=3) The combined effect of two drugs is higher than either individual effect.

⇨ Ex:- Sulfamethaxazole+ trimethoprim.

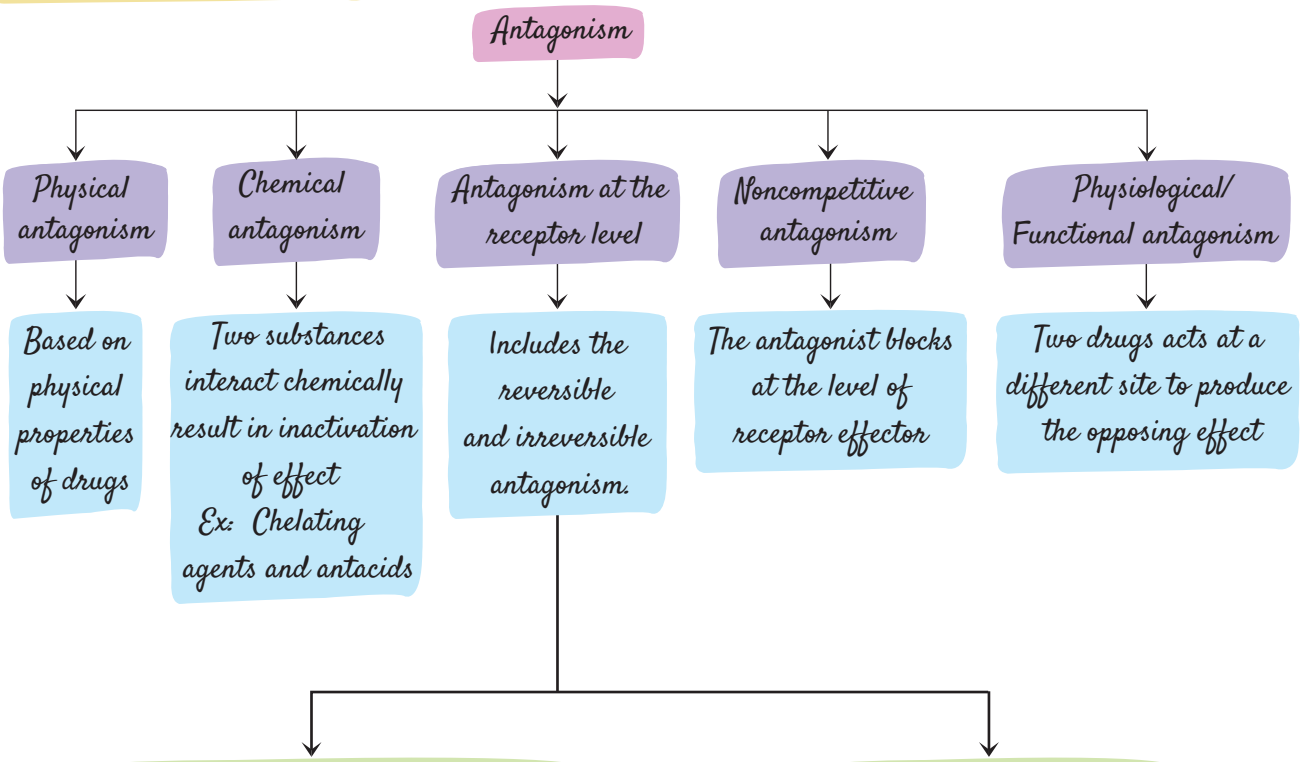
Effect of drug A + B > effect of drug A + effect of drug B

Antagonism

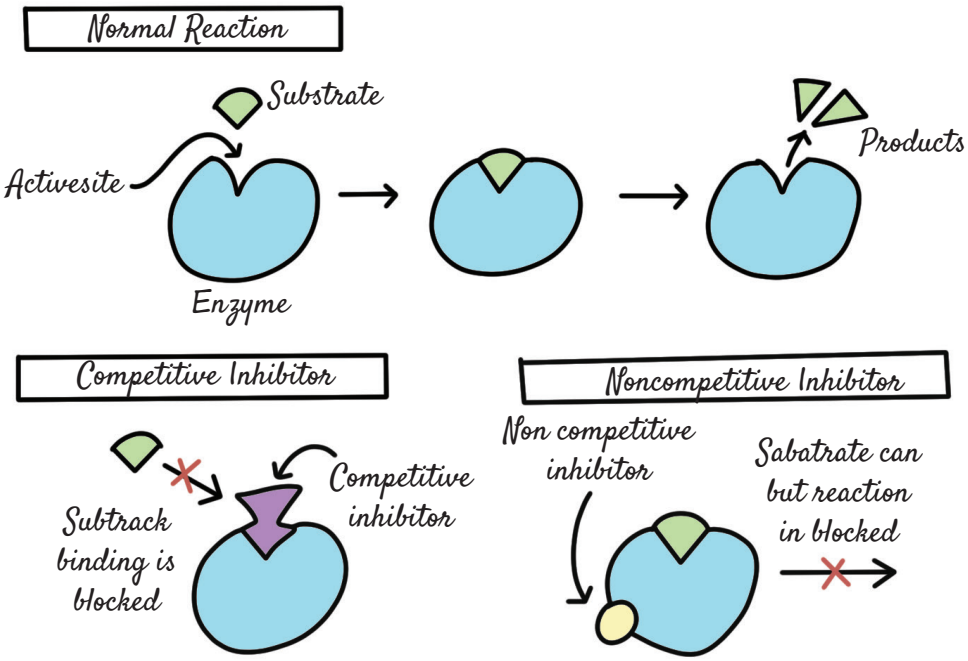
⇨ Effect of two drugs is less than the sum of the effects of the individual drugs.

Effect of drugs A + B < effect of drug A + effect of drug B

Types of antagonism



Reversible antagonism(competitive)	Irreversible Antagonism
This inhibition is commonly observed with antagonists that bind reversibly to the same receptor site as that of an agonist	It occurs when the antagonist dissociates very slow or not at all from the receptors and block the action of the agonist
This type of inhibition can be overcome by increasing the concentration of agonist	The antagonist effect cannot be overcome even after increasing the concentration of the agonist



Factors modifying the effects of drugs

Individuals differ both in the degree and the character of the response that a drug may elicit. The various factors are:

⇨ Bodyweight/size: It influences the concentration of drug attained at the site of action The average adult dose refers to individuals of medium build. For exceptionally obese or lean individuals and for children dose may be calculated on a bodyweight basis

Hamburgar's Rule

$$\text{Patients Dose} = \frac{\text{Body weight in kg}}{70} \times \text{Average Adult Dose}$$

⇨ Age: Infants and Children: The dose of the drug for children is often calculated from the adult dose

$$\text{Child dose Dose} = \frac{\text{Age}}{\text{Age} + 12} \times \text{adult dose... (Young's formula)}$$

$$\text{Child dose Dose} = \frac{\text{Age}}{20} \times \text{adult dose... (Dilling's formula)}$$

⇨ Sex : Females have a smaller body size, and so require doses of drugs on the lower side of the dose range 'They should not be given uterine stimulants during menstruation, quinine during pregnancy, and sedatives during lactation

⇨ Species and race : Response to drugs varies with race and species

⇨ Diet and environment: Food interferes with the absorption of many drugs

⇨ Route of administration: It modifies pharmacodynamics responses

⇨ Genetic factors: Variation in response is also controlled by individuals genetic factor

⇨ Disease: The presence of disease can affect drug response

⇨ Repeated dosing: Results in cumulation, tolerance and tachyphylaxis.

Tolerance: Increased amount of drug required to produce an initial pharmacological response

Types of tolerances: Innate tolerance, Acquired tolerances, and cross tolerances

⇨ Physiological factor: ex; doctor patient relation (Placebo effect)

⇨ Presence of other drugs