Pharmacodynamics

- **Drug:** A chemical affecting biological systems.
- **Pharmacodynamics:** Studies drug effects and mechanisms of action.
    - **Drug action:** Mechanism of how a drug works.
    - **Drug effect:** Consequences of the drug's action on the body.
    - **Example:** Aspirin inhibits prostaglandin synthesis (action), resulting in pain relief and fever reduction (effects).

Mechanisms of Drug Actions

1. Non-Receptor Mediated

- **Enzyme interaction:** e.g., Neostigmine inhibits acetylcholinesterase.
- **Direct chemical action:** e.g., Sodium bicarbonate neutralizes acidity.
- **Inhibition of cellular division:** e.g., Vincristine (anticancer drug).
- **Physical properties:** e.g., Lactulose (osmotic laxative), radioactive iodine (destroys cancer cells).
- **Nutrients and immune modulation:** e.g., Vitamins, vaccines.

2. Receptor-Mediated

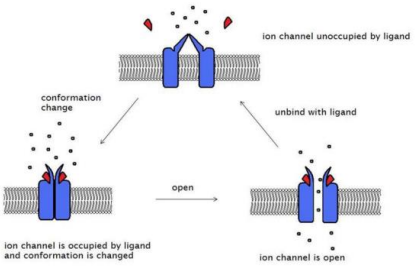
- **Receptor:** Cellular macromolecule (usually proteins or nucleic acids) to which a drug binds, initiating effects.
- **Key Concepts:**
    - **Affinity:** Drug's ability to bind to a specific receptor.
    - **Efficacy (intrinsic activity):** Cellular changes resulting from drug-receptor binding.

- **Drug-Receptor Interaction:** Works like a 'lock and key'; the drug (key) fits into the receptor (lock) to activate it.
- **Types of Drugs:**
    - **Agonist:** Activates receptor, mimicking natural substances.
    - **Antagonist:** Blocks receptor action.
    - **Partial Agonist:** Partially activates receptor.
    - **Inverse Agonist:** Produces opposite effect (e.g., beta-carbolines close GABA receptor chloride channels).

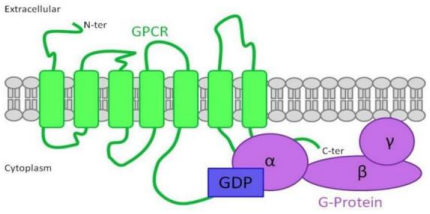
Drug-Receptor Coupling & Signaling

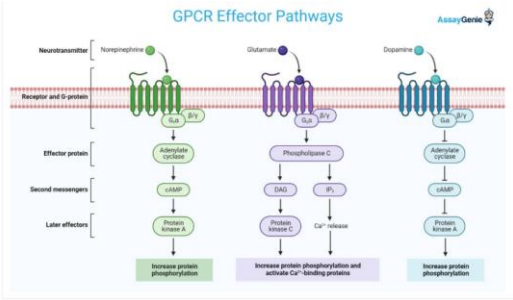
	Type 1 Ligand gated ion channels or Ionotropic receptors	Type 2 G-protein coupled receptors or metabotropic receptors	Type 3 Tyrosine -kinase linked receptors	Type 4 Nuclear receptors
Location	Trans membrane	Trans membrane	Trans membrane	Intracellular
Effectors	Ion channel	Channel or enzyme	Enzyme	Gene transcription
Coupling	Direct	G-protein	phosphorylation	Via DNA
Example	Nicotinic receptor and GABA type A receptors	Muscarinic receptor and adrenoceptors	Insulin, growth factor and cytokine receptors	Steroid & thyroid hormone receptors
Response	Very fast (fraction of millisecond)	Fast (few milliseconds)	Long lasting	Long lasting

Type 1
Ligand gated ion channels or Ionotropic receptors

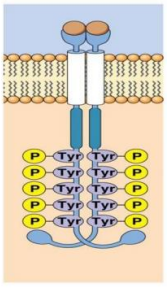


Type 2
G-protein coupled receptors or metabotropic receptors

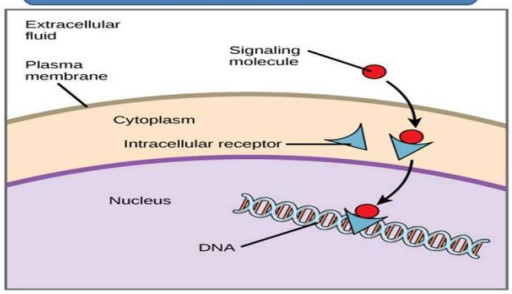




Type 3
Tyrosine -kinase linked receptors



Type 4
Nuclear receptors



G protein coupled receptor:

Activation of G-protein coupled receptors leads to

1. Activation or inhibition of adeny cyclase

2. Activation of phospholipase C

3. Activation of ion channels (e.g. calcium channels)

• Activation of adenylcyclase by (Gs) would increase cellular cAMP

• Inhibition of adenylcyclase by (Gi) would decrease cellular cAMP

• Activation of phospholpase C. (Gq) would increase cellular inositol triphosphate (IP3) and diaceylglycerol (DAG)

Activation of calcium channels would increase cellular calcium.

Secondary messengers produce the final cellular response (e.g contraction, relaxation, secretion, etc)

1. CAMP

2. 1P3

3. DAG

4. Calcium

Receptor Regulation

1. **Down-regulation**: Decrease in receptor number/sensitivity due to prolonged agonist stimulation, leading to reduced effect (pharmacodynamic tolerance). Example: Beta-2 adrenergic receptor agonists used repeatedly for asthma lose effect due to fewer receptors.

2. **Up-regulation**: Increase in receptor number/sensitivity due to prolonged antagonist use. Withdrawal of an antagonist can cause exaggerated responses. Example: Sudden withdrawal of beta-blockers in angina patients can lead to overstimulation by normal catecholamine levels.

3. . The number of certain receptors is regulated by regulatory factors and hormones that do not bind to these receptors at all (e.g. thyroid hormone excess in patients suffering from hyperthyroidism causes increase the number of cardiac beta-adrenoceptors).

4. The number and function of receptors can be affected by diseases like autoimmune antibodies which destroy the receptor itself or affect the coupling efficiency. Examples: diabetes due to destruction of insulin receptors ,myasthenia gravis due to destruction of muscular nicotinic receptors

Drug Tolerance

- **Pharmacodynamic tolerance**: Reduced response due to receptor down-regulation. (examples include beta 2 agonists in treatment of asthma and most addicting drugs).A drug holiday may help.

- **Pharmacokinetic tolerance**: Increased drug metabolism (e.g., phenobarbital). Higher doses may be needed.

- **Tachyphylaxis**: Rapid tolerance after a few doses.

- **Cross tolerance**: Tolerance to drugs with similar effects

  Examples: Opioids tolerance (Morphine/heroin).

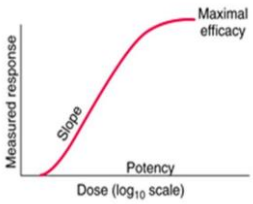
  Benzodiazepines tolerance (Diazepam/lorazepam)

  Barbiturates tolerance (phenobarbitone/thiopental).

  CNS depressant tolerance (alcohol/ anesthetics/opioids/barbiturates)

- **Drug intolerance**: Extreme sensitivity to low drug doses.

Dose-Response Curve



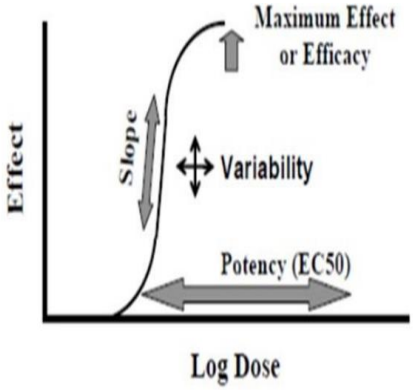
An S-shaped curve showing drug dose (x-axis, often log-scaled) versus response (y-axis).

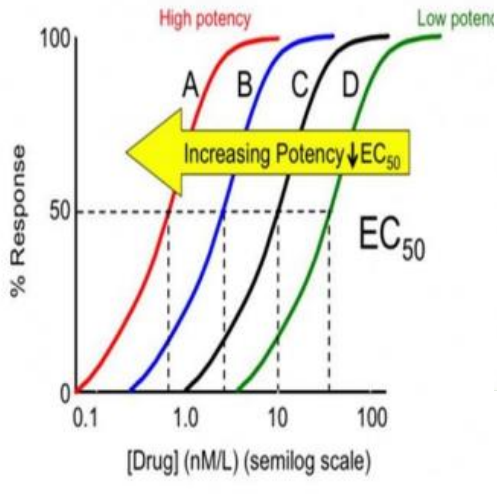
Types of Dose-Response Curves

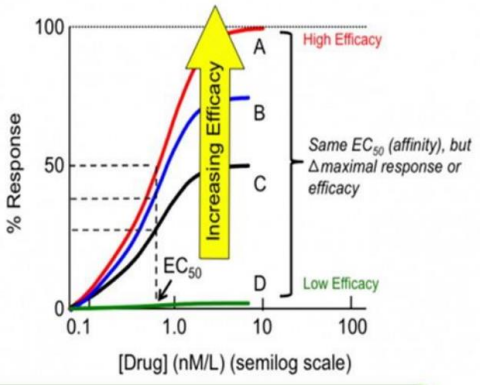
1. **Graded (Quantitative)**: Measures continuous responses (e.g., blood pressure).
2. **Quantal (Qualitative)**: Measures all-or-none responses (e.g., percentage of convulsions or deaths at different doses).

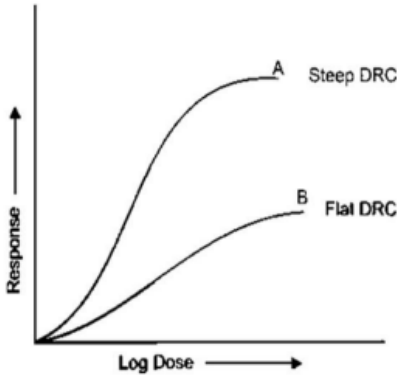
Characteristics of Graded Dose-Response Curve

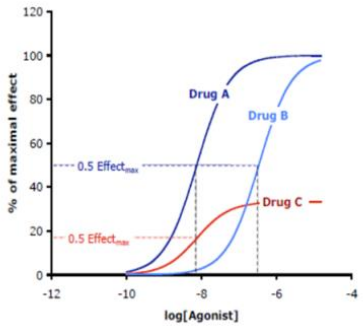
1. **Potency**: The dose required for a specific response. Lower ED50 indicates higher potency.
2. **Efficacy**: Maximum effect a drug can produce, regardless of dose increase. Higher efficacy is clinically significant.
3. **Slope**: Indicates safety margin. Steep slopes suggest narrow safety margins (e.g., barbiturates).
4. **Variability**: Different responses across individuals.











Quantal Dose-Response Curve

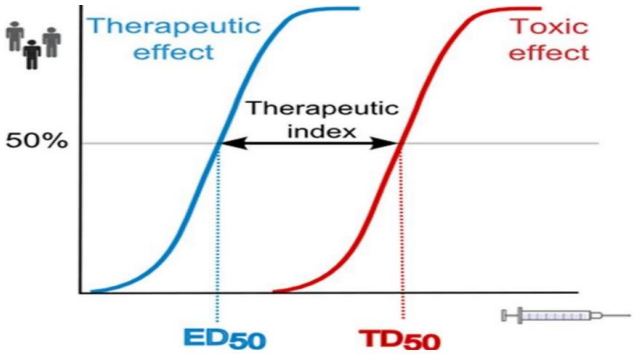
Used to measure all-or-none responses in populations. Determines:

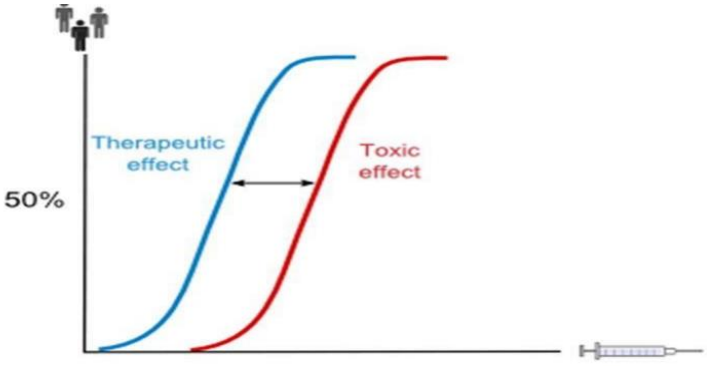
- **Median Effective Dose (ED50)**: Dose effective for 50% of the population.
- **Median Toxic Dose (TD50)**: Dose causing toxicity in 50%of experimental animals.
- **Median Lethal Dose (LD50)**: Dose causing death in 50%of experimental animals.

Therapeutic Index (TI)

is a quantitative measurement of the relative safety of drugs

- TI = TD50 / ED50, measuring relative drug safety.
- TI > 1 is safe; TI = 1 indicates a poison.
- Drugs with narrow therapeutic windows require monitoring (e.g., digoxin, lithium, aminoglycosides, immunosuppressive drugs, antiepileptic drugs, some anticancer drugs and warfarin).





Types of Antagonism

1. **Chemical Antagonists**: One drug neutralizes another directly by binding to it. E.g., protamine binds to heparin, inactivating it.

2. **Kinetic (Dispositional) Antagonists**: One drug affects the absorption or disposition of another. E.g., cholestyramine inhibits digoxin absorption.

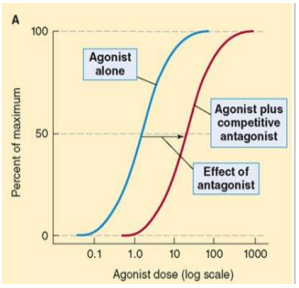
3. **Physiological Antagonists**: Two drugs produce opposite physiological effects. E.g., glucagon raises blood glucose, while insulin lowers it. Another example is histamine (causes bronchospasm and vasodilatation) and its physiological antagonist adrenaline (causes bronchodilation and vasoconstriction).

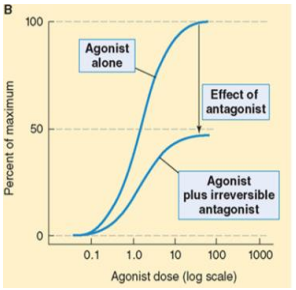
4. **Pharmacological Antagonists**: Drugs bind to receptors without activating them, blocking agonist effects. Includes:

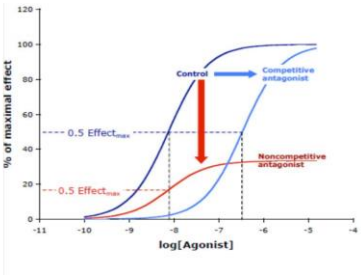
   - **Competitive antagonists** (reversible, concentration-dependent). can be overcome by using an excess of agonist. This is identified in dose response curve as shift to the right.

     Examples: beta blockers, histamine blockers and atropine

   - **Non-competitive antagonists** (irreversible, not overcome by increasing agonist). Results in a decrease in the maximal effect obtained usually by the agonist (downward shift) of the concentration-effect curve. Example is the binding of organophosphorus compounds to cholinergic receptors







Drug Interactions

- **Beneficial Drug Interactions**: Combined drugs provide additive or synergistic (e.g.: aminoglycosides and beta lactam antibiotic) or when one drug prevents the adverse effect of another (e.g. thiazides and spironolactone, magnesium oxide and aluminum hydroxide)

- **Enhancement of Drug Effect**:
    - *Additive*: if two drugs with the same effect are given together, the end product is an effect which is equal in magnitude to the sum of their individual effects (1+1=2).
    - *Synergism*: if two drugs with the same effect are given together, the end product is an effect which is greater in magnitude than the sum of their individual effects (1+1>2).
    - *Potentiation*: if a drug which does not have an effect of its own increases the effect of a second active drug (0+1>1).
- **Harmful Drug Interactions**: Result in toxicity or therapeutic failure if one drug increase the other's concentration can cause toxicity and decreased conc. can cause therapeutic failure or if one drug augments the side effect of the other (e.g. two CNS or cardiac depressant drugs given concurrently)

Mechanisms of drug interactions:

1. **Pharmacodynamic**: One drug affects another's action at receptors (e.g., naloxone for morphine poisoning).
2. **Pharmacokinetic**: Changes in absorption, distribution, metabolism, or excretion.

Factors Affecting Drug Dose and Action

- **Age**: Children need lower doses than adults. Either Young's formula (based on age) or Clark's formula (based on weight) can be used for calculating the doses for children
- **Sex**: Females may need smaller doses due to body fat differences.
- **Body Weight**: Dose adjustments needed for extreme weights.
- **Severity of Disease**: More severe cases may require higher doses.
- **Health & Nutrition**: Malnourished or anemic patients may need lower doses.
- **Pathological State**: Dose adjustments based on organ function (e.g., lower morphine dose in liver disease).
- **Tolerance and Drug Combinations**: Combining drugs can lead to additive, synergistic, or antagonistic effects.
- **Route of Administration**: Absorption rates vary; IV is fastest, while oral is slower, requiring higher doses.
- **Genetic Factors**: Can influence how drugs are processed and act in the body.