- Pharmacodynamics-1
- Dr Naser Ashraf
- Learning objectives
- Explain how drugs act
- Classify and describe receptors
- Describe affinity, efficacy and potency of two drugs based on their quantal and graded dose response curve
- Explain full agonist, partial agonist, inverse agonist and antagonist

- By physical action
- By chemical action
- Through antibody production

- placebo effect
- Drug that work without binding to receptor
- Physically
  - Osmotically: Mannitol
  - Mass (Bulk): isphagula
- Chemically
  - Neutralization
  - Acidification
  - Alkalinization
- What is a Receptor
- Receptor is a macromolecule present on cell surface, cytoplasm or in nucleus where drug binds and interacts to produce cellular changes

- Receptors are Protein and have specificity and selectivity

- Dose response relationship
- The relation between the dose of drug or concentration of drug in plasma and the observed clinical effect can be plotted graphically
- This graph is known as dose response relationship curve (DRC)
- Types of DRC
- Graded DRC:
  - This curve when plotted on a graph takes form of a rectangular hyperbola, where as log dose response curve is sigmoid shape

- Quantal dose response curve:
  - Certain pharmacological effects which cannot be quantified but can only be said to be present or absent are called quantal responses. e.g drug causing vomiting or ovulation
- Definitions
- Full agonist:
  - A drug that when bound to receptor produces 100% of maximum possible biological response or effect.
- Partial agonist
- Drugs which produce less than 100% of the maximum

possible biological response no matter how higher their concentration

- Antagonist
- Drugs which bind to receptor but are not capable of producing biological response or effect.
- Inverse agonist
- Drug that binds to receptors but produces biological response opposite to the agonist drug.
- Receptor mediated mechanisms

- Ion channels

- Ion channel
- These are cell surface receptors
- These proteins are selective for a particular ion (Na^+, K^+, Ca^{++}, Cl^-)
- Agonist binding opens these channels and cause depolarization or hyperpolarization
- They are the targets of many important drugs
- Examples of ion channel receptors
- Nicotinic

- These are membrane bound receptors coupled to the effector system (enzyme/channel) through GTP binding proteins called G-proteins.
- Examples:
  - Muscarinic cholinergic, adrenoceptors
  - Dopaminergic receptors
  - Opioid receptors

- GPCR – contd.
- G-proteins and Effectors
- Large number can be distinguished by their α-subunits

- GPCR - 3 Major Pathways (Transducer mechanisms)

➓ **Adenylyl cyclase:cAMP pathway**
➓ **Phospholipase C: IP3-DAG pathway**
➓ **Channel regulation**

- 1. Adenylyl cyclase: cAMP pathway
- 2. Phospholipase C:IP3-DAG pathway

- 3. Channel regulation
- Activated G-proteins can open or close ion channels

- These effects may be without intervention of 2nd messengers – cAMP or IP_3/DAG
- Bring about depolarization, hyperpolarization or Ca ++ changes etc.
- Gs – Ca++ channels in myocardium and skeletal muscles
- Go and Gi – open K+ channel in heart and muscle and close Ca+ in neurones

- Enzyme Linked Receptors
- These receptors are directly linked to enzyme like tyrosine kinase or guanylate cyclase

- E.g receptors for peptide hormones like insulin, Atrial Natriuretic Peptide (ANP)

- Intra cellular receptors
- These are intracellular (cytoplasmic or nuclear)
- Receptors for corticosteroids, mineralocorticoids, thyroid hormones, sex hormones and Vit. D etc. stimulate the transcription of genes in the nucleus by binding with specific DNA sequence – called - “Responsive elements”
- Pharmacodynamics-2

- Learning objectives
- Differentiate between different types of antagonists based on its effect on dose response curve with examples.
- Explain the effect of drug concentration on receptor binding
- Compare and contrast the mechanism of cholinergic and adrenergic receptors with distribution and action.
- Explain Therapeutic index and therapeutic window with examples
- Antagonist
- Drugs which bind to receptor but are not capable of producing biological response or effect are called antagonist.

- Drug Antagonism
- The effect of one drug is decreased or abolished in presence of another drug
- Antagonist drug decreases or abolishes the action of agonist.
- Types of antagonism
- Physical antagonism:
  - The opposing action of two drugs is due to their physical property
  - Example: charcoal adsorbs toxic substances
- Chemical antagonism:
  - The opposing action of two drugs is due their chemical property

  - Example: antacids neutralize gastric acidity
- Types of antagonism
- Physiological antagonism:
  - Two drugs act on different receptors or by different mechanism but have opposite effects on same physiological system
  - Examples:
    - Histamine and adrenaline on bronchial muscles
    - Glucagon and insulin on blood sugar level
- Types of antagonism
- Receptor antagonism: (2 types)

  - The antagonist binds to the same receptor as agonist and inhibits its effect
  - Competitive antagonism:
    - Both agonist and antagonist bind reversibly to same site on receptor
  - Non-competitive antagonism:
    - The antagonist binds to different site so that agonist cannot displace it from receptor
- Effect of antagonists on dose response curve
- Effect of drug concentration on receptor binding
- The relation is graded drug bound to receptors (B) relates to

the concentration of free (unbound) drug (C)

- Contrast between cholinergic receptors & adrenergic receptors
- Cholinergic
- Nicotinic: N_N and N_M
- Muscarinic: M_1, M_2, M_3, M_4 & M_5
- Adrenergic receptors
- Alpha receptors
  - α_1, α_2
- Beta receptors
  - β_1
  - β_2
  - β_3

- Mechanism of α receptor action

- Therapeutic index (TI)
- It is index of safety of drug
- TI= Median lethal dose (LD_{50})

  Median effective dose (ED_{50})
- Wider the value of therapeutic index safer is the drug
- Example penicillin has a high therapeutic index
- Digoxin, lithium, phenytoin have low TI

- Therapeutic window
- The optimal therapeutic range of plasma concentration at which most patients experience desired effect.