Clinical Pharmacology and Drug Development

Pharmacodynamics, Mechanisms of Drug Action

Module 2 Topic 3

Pharmacodynamics

Pharmacodynamics is the study of the biological and therapeutic effects of drugs

- What drugs do and how they do it
- The nature and mechanism of drug actions

Mechanisms of Drug Action

Drug Action

- Curing a disease
- Only relieving symptoms

- Physical activity
- Chemical activity
- Enzyme interaction
- Inhibition of Ion channels
- Replacing chemical substances that the body lacks
- Drug-receptor interaction
- Acting on microorganisms invading the body

Mechanisms of Drug Action

- **Enzyme interaction**
  - Enzymes regulate the rate of chemical reactions
  - Some drugs act as **false substrates** for an enzyme, e.g. Fluorouracil replaces uracil thereby blocking DNA synthesis and hence, no cell division
  - NSAIDs inhibit enzyme Cyclooxygenase (COX), stop conversion of Arachidonic acid to Prostaglandins that mediate the inflammatory response
  - HMG-CoA Reductase Inhibitors for hypercholesterolemia (atorvastatin; pravastatin)
  - Angiotensin Converting Enzyme (ACE) Inhibitors for high blood pressure, heart failure, and chronic renal insufficiency (lisinopril, ramipril)
  - Some drugs may cause **enzyme Induction** e.g. increase in metabolism of other drugs by Barbiturates due to induction of CYP2B enzyme system in liver

Mechanisms of Drug Action

- **Replacing chemical substances that the body lacks**
  - The body requires sufficient levels of certain chemical substances to function normally
  - A lack of **vitamin C** causes a condition called **scurvy**, lack of **vitamin D** in children leads to **rickets**, and **iron** deficiency results in **anaemia**
  - Low levels of **thyroid hormones** leads to hypothyroidism or **goiter** and a less **insulin** secretion results in a type of **diabetes mellitus**

Mechanisms of Drug Action

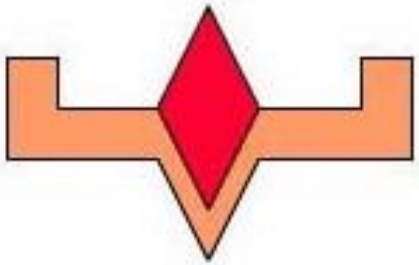
- **Drug-receptor interaction**
  - **Receptors** are specialized element of a cell or a tissue such as proteins, enzymes, or lipoproteins
  - ***Agonists*** - *d*rugs that bind to receptors and add to the effect of the body's natural chemicals thereby enhancing cellular response are called
  - ***Antagonists*** - drugs that bind to receptors and prevent the body's natural chemicals from binding to the receptors thereby blocking the cell response are called

Mechanisms of Drug Action

- **Partial agonist** is a drug which does not produce maximal effect even when all of the receptors are occupied by it.
- **Mixed agonist / antagonist** or a **selective receptor modulator (SRM**) is a type of drug that has different effects in different tissues
  - For example, Tamoxifen is a widely used SERM in the treatment of breast cancer

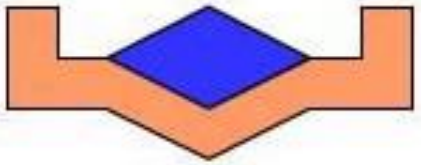
Mechanisms of Drug Action

Full Agonist



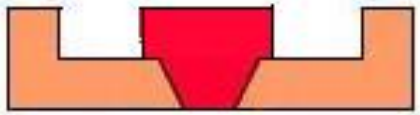
Complete conformational change leading to full activation

Partial Agonist



Partial conformational change leading to partial activation

Antagonist



No Conformational change, no activation

Mechanisms of Drug Action

- **Competitive antagonist** competes with an agonist for the receptor site
- **Noncompetitive antagonist** binds to a site other than the agonist-binding site (called the allosteric site) of the receptor
- **Irreversible antagonist** binds permanently to the receptor binding site by forming a chemical bond that cannot be overcome by an agonist

Mechanisms of Drug Action

- **Effective Concentration 50% (ED_{50})**
  - Concentration of the drug which induces a specified clinical effect in 50% of subjects
- **Lethal Dose 50% (LD_{50})**
  - Concentration of the drug which induces death in 50% of subjects
- **Median Toxic Dose (TD_{50})**
  - Dose at which 50 percent of the population manifests a given toxic effect

Mechanisms of Drug Action

- **Acting on microorganisms invading the body**
  - Infectious diseases are caused by microorganisms that attack the human body
  - Drugs destroy these microorganisms either by halting their growth or by killing them

Mechanisms of Drug Action

Placebo Response

- The word ***placebo*** – Latin for ***'I will please'*** – is used to describe any chemically inert substance
- Benefit seen because the person taking it believes that it will produce good results
- '***double blind***' study in which volunteers / patients and Doctors are not aware whether they have been given the active drug or the placebo can confirm or rule out placebo effect

Mechanisms of Drug Action

Summation and Synergism

- When two drugs with similar mechanisms are given together, they typically produce **additive** effects. This is also referred to as **summation**
- However, if the effect of two drugs exceeds the sum of their individual effects, this is referred to as **synergism** (or 'Potentiation')