Pharmacodynamics
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Pharmacodynamics is the study of the biochemical and physiological effects of drugs, in certain period.

In brief, it can be described as what the drug does to the body.

- Drug receptors
- Effects of drug
- Responses to drugs
- Toxicity and adverse effects of drugs
MECHANISMS OF DRUG ACTION

Drugs can act through:

1. Physical action:
   Drug can produce a therapeutic response because of it’s physical properties. e.g: **Mannitol** as diuretic because it increase osmalerity, **Radio-isotopes** : emit ionizing radiation

2. Simple chemical reaction:
   Drug may act through a chemical reaction. e.g: **Gastric antacids** work by neutralizing the stomach acidity with a base, **Chelating agents** that bind heavy metals in body.

3. Receptors:
   A receptor is a specialized target macromolecule mostly protein, present on the cell surface or intracellular, that binds a drug and mediates it’s pharmacological actions.
- **Receptors** can either be enzymes, nucleic acids or structural proteins to which drugs may interact.

- A molecule that binds to a receptor is called a **ligand**, and can be a peptide or another small molecule like a neurotransmitter, hormone, or drug.

- Ligand binding changes the **conformation** (three-dimensional shape) of the receptor molecule. This alters the shape at a different part of the protein, changing the interaction of the receptor molecule with associated biochemicals, leading in turn to a cellular response mediated by the associated biochemical pathway.
TYPES OF LIGAND-RECEPTOR INTERACTIONS

- Not every ligand that binds to a receptor also activates the receptor. The following classes of ligands exist:

1. **(Full) agonists** are able to **activate the receptor and result in a maximal biological response**. The natural endogenous ligand with greatest efficacy for a given receptor is by definition a full agonist (100% efficacy).

2. **Partial agonists** do not activate receptors thoroughly, causing responses which are partial compared to those of full agonists (efficacy between 0 and 100%).

3. **Antagonists** bind to receptors but **do not activate** them. This results in receptor blockage, inhibiting the binding of agonists and inverse agonists.

4. **Reverse agonist**
Signal transduction

- The drug–receptor complex
- Receptor states
Signal transduction

- Drugs act as signals, and their receptors act as signal detectors. Receptors transduce their recognition of a bound agonist by initiating a series of reactions that ultimately result in a specific intracellular response.

- **AGONIST** refers to a naturally occurring small molecule or a drug that binds to a site on a receptor protein and activates it.

- **Second Messenger or effector** molecules are part of the cascade of events that translates agonist binding into a cellular response.

- **The drug–receptor complex.**

- Cells have many different types of receptors, each of which is specific for a particular agonist and produces a unique response.

- The magnitude of the response is proportional to the number of drug–receptor complexes. This concept is closely related to the formation of complexes between enzyme and substrate or antigen and antibody.

- These interactions have many common features, perhaps the most noteworthy being specificity of the receptor for a given agonist.

- Most receptors are named for the type of agonist that interacts best with it. For example, the receptor for histamine is called a histamine receptor. Although much
Receptor states

- Receptors exist in at least two states, inactive (R) and active (R*) that are in reversible equilibrium with one another, usually favoring the inactive state.
- Binding of agonists causes the equilibrium to shift from R to R* to produce a biologic effect.
- **Antagonists** occupy the receptor but do not increase the fraction of R* and may stabilize the receptor in the inactive state.
- Some drugs (partial agonists) cause similar shifts in equilibrium from R to R*, but the fraction of R* is less than that caused by an agonist (but still more than that caused by an antagonist).
- The magnitude of biological effect is directly related to the fraction of R*.
- Agonists, antagonists, and partial agonists are examples of ligands, or molecules that bind to the activation site on the receptor.
CLASSIFICATION OF RECEPTORS

• This is based on the type of **the transduction mechanism that these receptors activate** when stimulated by their agonists:

  1. Transmembrane ligand-gated ion channels:
• These receptors are present in the walls of ion channels in cell membranes.
• When activated by their specific agonist, they open these ion channels & lead to movement of ions across cell membrane.
• These mediate diverse functions, including neurotransmission, cardiac conduction, and muscle contraction.
Examples:

1. **Nicotinic receptors** for acetylcholine (Ach.) : when stimulated, they open receptor-operated Na\(^+\) channels, and thus increase influx of sodium ions across membranes of neurons or NMJ (neuromuscular junction) in skeletal muscle and therefore activation of contraction in muscle.

2. **γ-aminobutyric acid (GABA) receptors:**
   Benzodiazepines enhance the stimulation of the GABA receptor by GABA, resulting in increased chloride influx and hyperpolarization of the respective cell.
Major Receptors Families

A. Ligand-gated ion channels
   Example: Cholinergic nicotinic receptors
   - Ions
   - Changes in membrane potential or ionic concentration within cell

B. G protein-coupled receptors
   Example: α and β adrenoceptors
   - Protein phosphorylation

C. Enzyme-linked receptors
   Example: Insulin receptors
   - Protein and receptor phosphorylation

D. Intracellular receptors
   Example: Steroid receptors
   - Protein phosphorylation and altered gene expression

INTRACELLULAR EFFECTS
2. Transmembrane G protein–coupled receptors:

- When these receptors are stimulated by their specific agonists, they will activate a regulatory G-protein in cell membrane which in turn change activity of membrane enzymes (either adenyl cyclase or phospholipase C).

- Leading to a change in intracellular level of a second messenger like cAMP (cyclic adenosine monophosphate), or IP₃ (inositol triphosphate), respectively, and this would lead to cell response.

- Examples: e.g. Receptors for transmitters: Stimulation of muscarinic receptors (M₁ and M₃) for (Ach) will activate G and leads to increase intracellular level of IP₃
guanosine triphosphate (GTP), guanosine diphosphate (GDP)
3. Enzyme-linked receptors:

- These membrane receptors have an extra-cellular site that binds to specific agonists and an intra-cytoplasmic domain which contains tyrosine and other amino acids.

- Binding to specific agonist and activation of these receptors usually lead to phosphorylation of tyrosine in intra-cellular domain which then acquires kinase activity and leads to activation of intracellular substrates or enzymes that finally leads to cell response.

- Examples:
  - Receptors for insulin,
  - Receptors for growth factors like EGF or PDGF,
  - Receptors for immune cytokines
1. Insulin binding activates receptor tyrosine kinase activity in the intracellular domain of the β subunit of the insulin receptor.

2. Tyrosine residues of the β subunit are auto-phosphorylated.

3. Receptor tyrosine kinase phosphorylates other proteins, for example, insulin receptor substrates (IRS).

4. Phosphorylated IRSs promote activation of other protein kinases and phosphatases, leading to biologic actions of insulin.

Activation of multiple signaling pathways

Biologic effects of insulin
4. Intracellular receptors:

- These receptors are located in cytoplasm (e.g. steroid receptors) or nucleus (receptors for thyroid hormones or vitamin D₃).

- The specific agonist must cross cell membrane to inside of cell, binds and activates these receptors, which will then bind to DNA gene response elements in nucleus and lead to change in gene transcription, and thus synthesis of new proteins.
A lipid-soluble drug diffuses across the cell membrane and moves to the nucleus of the cell.

The drug binds to a receptor.

The drug–receptor complex moves to the nucleus and interacts with chromatin, activating the transcription of specific genes.

Specific proteins are synthesized from mRNA, leading to biologic effects.
• Some characteristics of signal transduction

• Signal transduction has two important features:

1. The ability to amplify small signals and

2. Mechanisms to protect the cell from excessive stimulation.

1. Signal amplification:

• A characteristic of G protein–linked and enzyme-linked receptors is their ability to amplify signal intensity and duration. For example, a single agonist–receptor complex can interact with many G proteins, thereby multiplying the original signal many fold.

• Additionally, activated G proteins persist for a longer duration than does the original agonist–receptor complex.
Signal amplification

- Because of this amplification, only a fraction of the total receptors for a specific ligand may need to be occupied to elicit a maximal response. Systems that exhibit this behavior are said to have spare receptors.

- **Spare receptors** are exhibited by insulin receptors, where it is estimated that 99% of receptors are “spare.” This constitute an immense functional reserve that ensures that adequate amounts of glucose enter the cell.
Desensitization and down-regulation of receptors

- Repeated or continuous administration of an agonist (or an antagonist) may lead to changes in the responsiveness of the receptor.
- To prevent potential damage to the cell (for example, high concentrations of calcium, initiating cell death), several mechanisms have evolved to protect a cell from excessive stimulation.
- When a receptor is exposed to repeated administration of an agonist, the receptor becomes desensitized resulting in a diminished effect.
- This phenomenon, called tachyphylaxis, is due to either phosphorylation or a similar chemical event that renders receptors on the cell surface unresponsive to the ligand.
• receptors may be **down-regulated** such that they are internalized and sequestered within the cell, unavailable for further agonist interaction.

• These receptors may be **recycled** to the cell surface, restoring sensitivity, or, alternatively, may be further processed and degraded, decreasing the total number of receptors available.

• Some receptors, particularly ion channels, require a finite time following stimulation before they can be activated again.

• During this recovery phase, unresponsive receptors are said to be "**refractory.**"

• repeated exposure of a receptor to an antagonist may result in **up-regulation of receptors**, in which receptor reserves are inserted into the membrane, increasing the total number of receptors available.

• Up-regulation of receptors can make the cells more sensitive to agonists and/or more resistant to the effect of the antagonist.