Pharmacodynamics

Terms ...

- **Pharmacology**: is the study of biochemical and physiological aspects of the drug’s effects. In addition, absorption, distribution, metabolism, excretion of the drug. (Pharmacokinetics and pharmacodynamics).

- We will focus on 2 main parts of pharmacology (pharmacokinetics [previously discussed] – pharmacodynamics)

- **Pharmacokinetics**: the way the body handles drug (Absorption, Distribution, Metabolism, and Excretion (ADME)) , what the body does to the drug

- **Pharmacodynamics**:
  - The study of the biochemical and physiological effects of the drug and their mechanism of action, **what the drug does to the body**
  - The study of the relationship between the concentration of the drug and its effects

- These 2 main parts are very related to each other so **How do they meet?**

  - The drug during its journey will be absorbed then distributed (go to all tissues) (kinetics). Some of these are target tissues (contain enzymes or receptors which drug binds to them and performs an action) (dynamic).

  - So here they meet at the level of distribution (Kinetics-distribution) and interacting with the target cell (dynamics-effect on the body tissue by effecting its enzymes, receptors....). After that it will continue its way and the body will metabolize and eliminate it.

- Most drugs exert their effects by interacting with a **specialized target macromolecules**, called receptors, present on the cell surface or intracellularity.

- The targets of the drug where it can affect the body are mainly enzymes (28%) or receptors (45%)
Now let’s talk about **Receptors**:

- Most of them are **proteins**
- They locate extracellularly (on the cell surface) or intracellularly
- The main function of the receptors in the body is to bind to **endogenous** molecules (hormones, neurotransmitters...) to conduct a signal from out to inside the cell so inducing certain function in the cell. DRUGS mimic these endogenous molecules to enhance or inhibit their function.
- Large macromolecules with a well-defined 3D shape which gives them the **specificity**.
- In the protein (receptor) synthesis steps they go through modification steps (folding, glycosylation..etc). Modifications result in the **distinct shape** which gives specificity.
- Specificity includes the **complementarity of shape** between drug and receptor, and **complementarity between the electrostatic, hydrophobic, and hydrogen bonding surfaces** of each component.

![Potential drug receptor](image1)

![Segment of receptor](image2)

- Same receptor with the same ligand but in a different places will give a different action (signaling events), **due to different signaling component**. And subtypes of these receptors vary in how the cells response (different mechanisms) ...this is called **selectivity**.

Ex: **Adrenaline which bind to Beta receptors** (B-1 in the heart - B-2 in the bronchi)

In the heart it increases the contractility of the muscle, in the bronchi causes relaxation of the muscles (**same ligand and receptor but different results due to different cellular component**), so if we want to give a B-blocker to angina patient it will affect the heart and constrict the bronchi (non-selective drug). We can not give this to asthmatic patient it will cause him a serious problems.

* For asthmatic patient with heart condition ➔ selective drug for B-1 receptors
• How does the receptors transmit the signal?

After the ligand binds to its receptor, the receptor will transduce the binding into a response by causing a conformational changes or biochemical effects.

• kinds of binding between the receptor and the ligand?

1- **Reversible binding**: the optimum condition, non-covalent bonds between the ligand and receptor (weak bond, easily breakable)

2- **Irreversible bonding**: covalent bonds (very strong bonds, need high energy to be broken), NOT found normally in the body (may be done by some drugs)

**This example is a little bit exaggerated just to understand why irreversible bonding is bad**

We have hormone and neurotransmitter which is called adrenaline binds to B-1 receptor in the heart and its effects will increase the heart rate (increase the contractility of the heart), so if the signal is prolonged for a long time due to certain reasons (like in angina-ischemia) the heart will get tired. The drug that we will use to reduce heart’s fatigue is B blocker that will bind with the receptor irreversibly for example instead of adrenaline to stop or decrease the adrenaline signal, but the results of this covalently binding are:

1- inability to get rid of the B blocker signal.

2- the adrenaline can not bind again so I will lose the adrenaline effect which I need.

3- the only way to get rid of B blocker signal and effect is to damage these receptors.

4- the cell should make new receptors to let adrenaline bind again and gives its effect (making new protein (receptor) will take about 24 hrs so this will lead to a delay).

SO it’s better for B-blocker to bind reversibly (dynamically) which means binding & releasing in a competitive way = depends on the concentration and affinity
NOTE: not all receptors will bind to the drug, even if the binding is irreversible, but all the receptors that take this drug will be inactive.

Another example:

Sarin gas: dangerous gas, which binds irreversibly, we have only the first few hours to save the patient by breaking the bonds between the gas and the receptors. After these few hours, the bonds will be hard to be broken and the patient will die.

- Not all drugs uses receptors or enzymes we have other types that can be used:

  In vit-D deficiency, lack in growth hormones, hemolytic diseases: we give the patient supplement drugs to compensate this deficiency, which will not work on a receptor.

- Types of receptors:
  1- Ligand gated ion channels.
  2- G protein – coupled receptors
  3- Enzyme linked receptors.
  4- Intracellular receptors.

1-Ligand-gated ion channel receptor

- Regulated by binding of a ligand to the channels.
- Regulating the flow of ions across cell membrane.

EX: In the skeletal muscle and Autonomic nervous system.

Nicotinic receptor (5 subunits) binds to acetylcholine. This receptor has 2 alpha subunits which bind to acetylcholine, so we need 2 acetylcholine molecules to activate this receptor.
After the 2 ach bind to the receptor it will cause a **conformational change** (opening the channel) once it’s open sodium get in , the sodium causes a depolarization and activates other channels of sodium. Sodium influx activates calcium channels, so intercellular calcium increases which will eventually cause skeletal muscle contraction.

**2-G-protein – coupled receptor**

- Receptor (has extracellular and intracellular domains) on the plasma membrane regulate or facilitate effector proteins through a group of guanosine triphosphate (GTP) proteins known as G-proteins.

-How does G-protein-coupled receptor work?

  Drug/ molecule binds ➔ change in the receptor structure ➔ activate small protein(GEF) ➔ GDP is released from the G protein and replaced by GTP. ➔ will activate further signaling events (activate adenylyl cyclase) ➔ more cAMP which will increase the contractility of the muscle

  there is an enzyme(GTPase) which can return GTP back to GDP keep them in balance and ensure that this cycle will be active (we do not want any permanent signal).

- Some hormones, peptide receptors and neurotransmitter receptors (e.g., adrenergic and muscarinic receptors depend on the G proteins) mediate their action on cells

**3-Enzyme-linked receptors.**

It has a cytosolic enzyme as a part of it.

- Binding of the ligand to the extracellular domain activates or inhibits the related cytosolic enzyme.
- The most common are the receptors that have a **tyrosine kinase** activity as part of their structures, in which the binding results in the phosphorylation of tyrosine residues of specific protein
- The addition of phosphate group can modify the three-dimensional structure of the target protein, and so resulting in molecular switch
Ex: insulin receptor

Insulin binds to the alpha subunit of its receptor, which causes autophosphorylation of the beta – receptor subunit that in turn induces tyrosine kinase activity.

Insulin function: uptake of glucose (regulate glucose level in the body) so insulin will activate GLUT-4 receptors to induce cells to take glucose up.

- in this kind of receptors when the ligand binds it will make a conformational change and this will induce the enzyme (kinase) to phosphorylate which will lead to further events.

4-Intercellular receptors:

- location: intracellularly

- ligand: must be lipid soluble so it can pass the membrane to reach its receptor.

- The best example is the steroids hormones. In which the activated ligand-receptor complex migrates to the nucleus, where it binds to a specific DNA sequences, resulting in regulation of the gene expression.