**Introduction:**

Chemical identification of the receptors allowed us to synthesize many ligands or drugs with different characteristics.

The result of interaction between a ligand and its receptor is determined by the chemical structure of that ligand, since the receptor is fixed inside the body, we can't make any changes to it, so if we want to alter the response for any drug we change its chemical structure; any minor modification of the drug could lead to a whole different effect than the original one.

Several drugs don’t require receptors for their action; instead they depend on the physiochemical mechanisms such as inhibiting certain enzymes or activating them directly. (Non-Receptor Mediated Mechanisms)

**Receptor mediated mechanisms:**

Drug + Receptor $\rightarrow$ Drug receptor complex + response

Simply speaking, the formation of the Drug –Receptor complex triggers several reactions inside the target cell, which eventually lead to a response to that drug.

**Receptors:**

Macromolecules (proteins) or the component of a cell or organism that interacts with a drug and initiates the chain of biochemical events leading to the drug’s observed effects.

Since receptors are proteins we don’t always expect them to be found in all humans due to genetic factors, so in several cases the drug could have no effect on the patient due to the absence of the required receptor for that drug.

**Example:**

Cholesterol, which is synthesized by the body itself, is very essential for the human body due to its role in the plasma membrane, and that it’s the precursor for steroids which give rise to the sexual hormones in our bodies, but the accumulation of cholesterol in the body vessels leads to many diseases such as atherosclerosis. Our body gets rid of the excess cholesterol in the blood by receptor mediated mechanisms using a specific receptor called “LDL receptor”, unfortunately lots of people have a genetic defect affecting these “LDL” receptors either by reducing their number, or altering their chemical structure; eventually leading to hypercholesterolemia.
• Not all hypercholesterolemia cases are genetic related, some are acquired
• Most of the cases are due to conformational change of the “LDL” receptor (Genetic)

Receptors may be found in several places in the cell such as:

• Cell surface (Plasma membrane)
• Cell’s cytoplasm
• Nucleus
  
  *Only high lipid soluble drugs can bind to the nuclear receptors due to the fact that the nuclear membrane is the strongest membrane of the cell (it envelopes the chromosomes)*

*Receptors functions:*

Receptors are widely spread all over tissues and organs:

• Determine the dose or concentration of drug required to form a significant No. of drug-receptor complexes.

  Note that the number of receptors can affect the maximal response of the drug, so if we have a high dose of a certain drug but with only few receptors, the response for that drug would be lower than the maximal one.

• Mediate effects of agonists and antagonists, how?

  By knowing the chemical structure and conformation of the receptor, scientists have managed to make different changes in the structure of the drugs, altering their potency, efficacy, and their binding strength with the receptor.

  *Very little changes in the structure of the agonists could also lead in forming an antagonist (these changes have to be minimal in order to maintain the general shape of the drug)*.

• Responsible for the selectivity of drug actions, how?

  Size, shape, electrical charge of drug determines binding to a receptor
  
  Changes in a drug’s chemical structure can alter the affinity for the receptor where therapeutic and toxic effects may be altered

• Drugs are designed based on the structure of their receptors with the help of modern technology.
Drug receptor interaction:

As mentioned before, the binding of the Drug to its receptor and the formation of the Drug – Receptor complex is the reason why the response occurs.

Lock – Key theory:

Lots of theories have been put in order to explain the interaction between both the drugs and their receptors, the best (according to the doctor) is the Lock – Key theory.

According to this theory, each drug has a specific receptor for it, and in order for the reaction between the drug and the receptor to occur, the drug should be relatively close to its receptors. In some cases, a force is needed to put the drug in the appropriate distance with the receptor.

This theory also suggests that the drug should be in a complementary shape with the receptor (imagine a lock and a key).

Both agonists – antagonists could work on a receptor only if they were very close in shape! Antagonist: A particular drug that binds to a receptor producing no effects. The effect is only caused if an agonist is bound to the same receptor, reversing its action.
The main use of antagonists is to prevent toxicity (due to an overdose of a certain agonist) 
e.g.: a patient with hypertension took two pills of a certain drug instead of one (overdose), what 
should be done?  
The patient should be immediately given an antagonist for that drug, in order to reverse the toxicity 
caused by the overdose!  
After that, the patient should be monitored; if his blood pressure is rising again he should be given 
the drug (agonist) but with suitable amounts this time!  

So, simply speaking, both agonists and antagonists reverse the action of each other in order to 
control the patient’s condition.

**Binding of Drug to Receptor requires that:**

- Both D and R should be close enough to each other (relatively close)  
- The R has to be complementary in its chemical structure to the D  
- Binding of the D to the R should be reversible (important to stop the response)

**The interaction of the D with the R depends on:**

- Chemical structure of D and R  
- Sites of loss:  

  Different sites in the blood circulation or in tissues that cause a decrease in the amount of the drug 
  before reaching its target receptor such as:  
  - Plasma proteins : complete disassociation does not always occur between the plasma protein and 
    the drug  
  - Pharmacokinetics : absorption, metabolism ( mentioned before )  
  - Glycosaminoglycans  

  - Intermolecular binding forces

**Binding forces between Drug and Receptor**

Binding forces are required in order to fix the Drug in its receptor, many forces have been recognized to be 
present at the site of Drug Receptor complex differing in affinity, strength, and reversibility, summing them up:

- Van der Waals :
  - requires close approximation
- **Weakest bond**
  - Reversible *(no energy required to unbind the complex)*
  - No outer force is required to make the binding

- **Hydrogen bonding**:  
  - Connects 2 Nitrogens or 2 Oxygens (H atom should be between them)  
  - Stronger than Van der Waals (still weak though)  
  - Reversible *(no energy required to unbind the complex)*

- **Ionic bonding**:  
  - Receptor and drug oppositely charged (e.g. Na+ on the receptor, Cl- on the drug)  
  - Stronger than both Hydrogen bonding and Van der Waals  
  - Reversible *(no energy required to unbind the complex)*  
  - Enforced ionic bonds: several atoms are included in the formation of the bond

- **Covalent bonding**:  
  - Strongest bond  
  - Least common  
  - Irreversible (needs energy to break it)

  *Note that one Drug Receptor Complex could be bound with more than one of these bonds, depending on the chemical structure of these complexes!*

  *E.g.: Acetyl–choline binds with more than one of the bonds above.*

**Three aspects of drug-receptor function:** *(the Doctor read them literally from the slides)*

1. Receptors determine the quantitative relation between drug concentration and response  
   - This is based on receptor’s affinity to bind and it’s abundance in target cells or tissues  
   - Drug response depends on:  
     - Affinity of drug for receptor  
     - Drug’s efficacy (degree to which a drug is able to induce maximal effects)
2. Receptors (as complex molecules) function as regulatory proteins and components of chemical signaling mechanisms that provide targets for important drugs  
3. Receptors determine the therapeutic and toxic effects of drugs in patients
**Drug Receptors Families:**
Represent the bases of pharmacological studies

1- **Ligand-gated ionic channels** (located on the cell surfaces):

The Drug (ligand) attaches to its receptor, forming the Drug-Receptor Complex, interaction occurs, causing either opening, or closing of a specific ionic channel, which is attached to the receptor.
These channels could be Na+, Ca++ , k+ ... channels!

E.G. : Acetyl- choline ( ligand ) acts on nicotinic Receptors found on voluntary muscles, the attachment causes activation of a sodium channel which leads to an influx of sodium, causing initiation of the action potential, eventually leading to muscle contraction.
After milliseconds an enzyme called “Acetyl-Choline Esterase” destroys the Acetyl-Choline in order to stop muscle contraction, or it will lead to paralyses!!

Note that acetyl choline is one of the most important neuro-transmitters in the CNS, its receptors are called Cholinergic Receptors, which are divided into; muscarinic and nicotinic receptors, spread over the sympathetic and parasympathetic nervous system!

2- **Tyrosine-Kinase linked Receptors** (found on cell surface):

The ligand (insulin for example) binds to its specific receptors, which is attached to the enzyme tyrosine Kinase, this enzyme helps phosphorylate certain proteins inside the cell, altering their conformation which eventually leads to a physiological or pharmaceutical response in the cell!

The effect of insulin is very quick, causing a response in few seconds!

Another example is anti-histamine (Therapeutic – diagnostic drug) helps cure Allergic Rash in less than half an hour, if not cured, then we know that the rash is not of an allergic cause!

3- **Intracellular receptors**: (found inside the cell):

The binding of a drug (highly lipid soluble) to these kinds of receptors, leads to production of specific proteins; depending on the action of the drug; whether inhibition or activation

*Example for this family is steroid hormones and their receptors!*

4- **G-Protein coupled receptors** : (found on cell surfaces)
This family depends on a mechanism of 2 messengers; first and second. The first is always the drug, whilst the second differs from a receptor to another, but they (second messengers) all mediate the effects of the drug (first messenger).

Mechanism:

The drug interacts with its receptor, which is connected to a “G-protein” (a transmembrane protein) which in turn transfers the signal of the Drug-Receptor complex to other things, mostly plasma membrane enzymes.

E.g. Adrenergic enzymes and receptors:
Epinephrine and nor-epinephrine enzymes act on beta adrenergic receptors, the drug interacts with its receptors, which are attached to G-Proteins that transfer the signal to a plasma membrane enzyme, called “Adynelyl-Cyclase” which converts “AMP to cAMP” (major Second messengers) Which mediates the drug action!
Another important second messenger is Ca+2

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