3

Pharmacology

Doctor 2017 | Medicine | JU

Sheet ○ Slides

Done By

Amr & Abdallah

Contributed in the Scientific Correction

Yara AL-Adwan

Contributed in the Grammatical Correction

Yara AL-Adwan

Doctor

Dr. Alia

In the previous lecture, we have discussed the molecular targets for drugs that are available commercially. As mentioned before, the majority of the drug targets were **receptors** with a percentage of **45%**. Enzymes are another target for some drugs such as: Ibuprofen/Aspirin. (They both inhibit COX enzymes), with a percentage of **28%**. In addition to Hormones &factors, Nuclear receptors, DNA and Ion channels.

- ✓ Most drugs exert their effect by interacting with specialized target macromolecules, called receptors, present on the cell surface or intracellularly.

A receptor is a large macromolecule with a well-defined 3D shape that allows it to have a certain shape, this shape is designed for the binding of the drug or the endogenous ligand*.

*__Endogenous Ligand__: is a ligand that is originally synthesized internally in the body.

Q: What is the function of the receptor?

Ans: Transducing the signal; since some hormones can't enter the cells to exert its effect, the receptor transduces the signal from the outside to the inside by causing conformational changes or by a biochemical effect to lead to a response.

Note: We already have endogenous ligands (neurotransmitters, hormones , factors) that use these receptors so receptors aren't made originally for drugs to bind to them but we utilized them to synthesize drugs that mimic the endogenous ligands to induce a response to suit the individual's own case. .

Receptors are mostly proteins and we say mostly because recently it has been found that some receptors are made of fatty acids.

Most receptors are proteins that have undergone post-translation modifications such as: covalent attachment of carbohydrates, lipids and phosphate.

- ➢ **Cell Surface Receptor:** A receptor that is embedded in the cell membrane and functions to receive chemical information from the extracellular compartment and to transmit that information to the intracellular compartment.

- ➢ We have a subset of receptors that are present intracellularly and are much less in number than cell-surface receptors such as: **Transcription factors and nuclear receptors**. Some drugs affect these receptors, so we expect these drugs to be

lipid-soluble & small in size; for them to be able to cross the plasma membrane of the cell and interact with intracellular receptors

- So for any drug to be able to exert its action in the body it needs to fit in the shape of the receptor; in addition, it needs to bind to the target with sufficient quantity in order for that interaction to elicit an effect.
- Because a receptor has a defined 3d shape ,the concavity must match the drug So, the two fundamental properties underlying specificity in drug-receptor interactions are: **1- Complementarity** (توافق)of shape between drug and receptor, and **2- Complementarity** between the electrostatic, hydrophobic, and hydrogen bonding surfaces of each component(The drug-binding cavity of the receptor(Binding pocket) and the drug/ligand). ***Recall** that proteins are composed of amino acid residues and some of which are charged.

- Receptors are excellent drug targets because they are proteins; allowing more specificity, **How** ?
  Receptors get post-translational modification; which is the covalent attachment of Carbohydrates, lipids and phosphates. This gives the receptors additional specificity for the shape of the 3D macromolecule, thus; additional specificity for the drug/hormone.

Major receptor families.

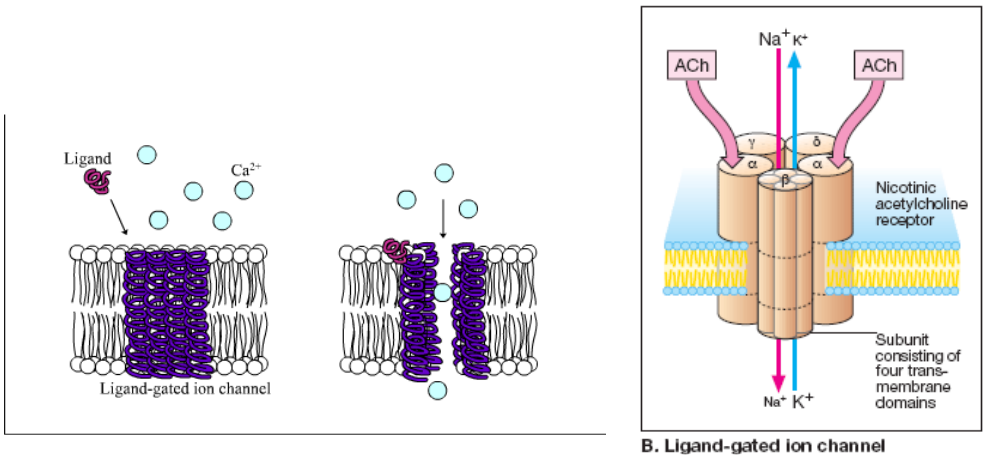
1- **Ligand-gated ion channels**
2- **Enzyme-linked receptors**
3-**G protein-coupled receptors**
4-**Intracellular receptors**

1-Ligand-gated ion channels: Ion channels can be part of the receptors ;we have certain ion channels on the surface of the cells once they bind to a ligand they will be activated (opening or closing). They are responsible for regulation of the flow of ions channels across cell membranes such as: Na+, Cl-,K+ channels which are important for regulating body functions.
For example: 1- Calcium and contraction: we can regulate the constriction/dilation of the smooth muscles of blood vessels by regulating the ion channel responsible for Calcium influx.

2- Nicotinic receptors: Are receptors for the neurotransmitter acytl choline which are present in the ganglia of **both** Sympathetic and

Parasympathetic of the **Autonomic Nervous System**, also they are present on the **skeletal muscle surface**. So once the acytl choline binds to the receptors it will cause the opening of the channel and the flow (entry and exit) of ions through this channel. **In the case of skeletal muscles** this will help induce an action potential which will activate further channels that allow the entrance of Ca++ to the cell which leads to contraction of the skeletal muscles.

*Nicotine is an extraneous material that activates these receptors, that's why muscle contraction and pain in muscles is a sign of overdose of Nicotine



B. Ligand-gated ion channel

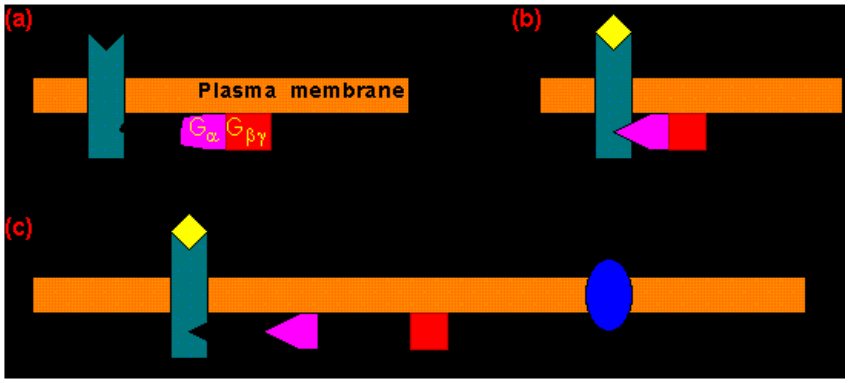
2- G protein-coupled receptors: Receptors on the inner face of the plasma membrane regulate or facilitate effector proteins through a group of Guanosine triphosphate (GTP) proteins known as G proteins. As the doctor said they are trans membranous, part of this receptor is on the outside which will bind to the hormone and the inner face is coupled to the G protein. Once the drug/hormone binds to this receptor, certain chemistry or interaction happens between the receptor and the G protein which will lead to the activation of events that will give the effect of that drug/hormone.

G proteins: Small signaling proteins that activate different transduction mechanisms in the cell that will lead to a certain effect such as: increasing Ca++, synthesis of cGMP, cAMP, activation of kinases. Once we have our agonist bound to the receptor the G protein gets active then it does its effect on the cell

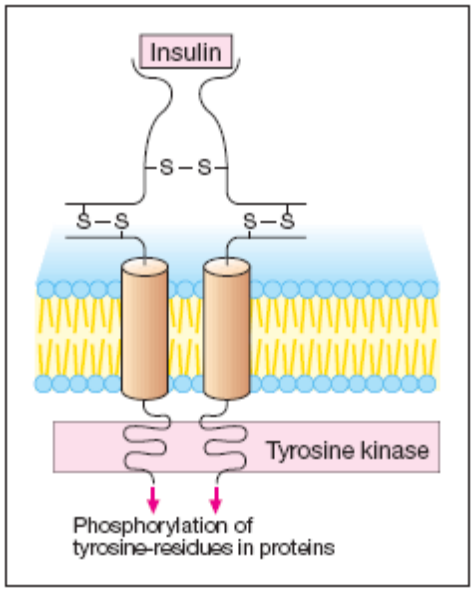
Examples:

1-**Adrenergic** receptors: Adrenaline increases Heart rate, so when it binds to its receptor the G protein gets active→it activates an enzyme Adenylyl Cyclase which converts ATP to cAMP→ cAMP does many functions including increasing the heart rate.

2-**Muscarinic** Receptors



3-Enzyme-Linked receptors: Are receptors bound to an enzyme, the binding of the ligand to the extracellular domain activates or inhibits the related cytosolic enzyme. **Example: Insulin receptor** is coupled to **Tyrosine Kinase**, once insulin binds to its receptor it activates the Kinase which will phosphorylate another protein (in this case, since it's Tyrosine Kinase, the phosphorylation will occur to Tyrosine residues of a specific protein) in the body which will lead to a cascade of events. The addition of phosphate group can modify the three-dimensional structure of the target protein resulting in molecular switch.



C. Ligand-regulated enzyme

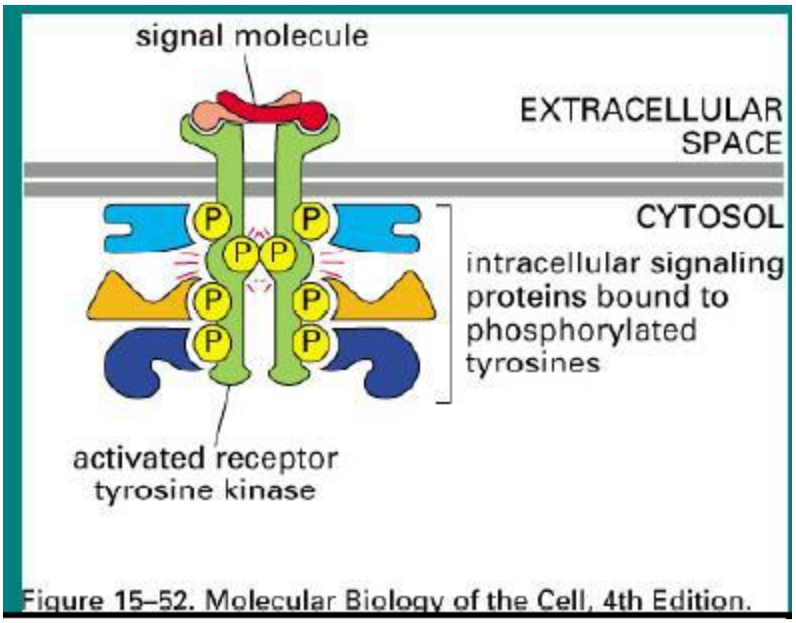


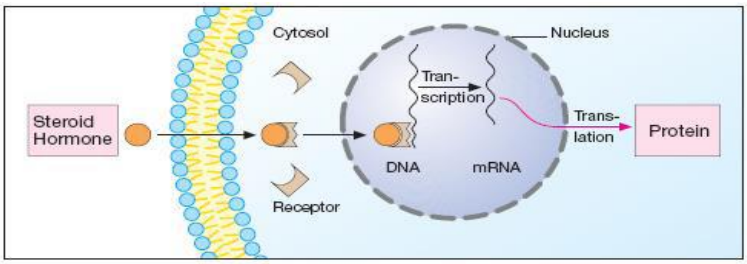
Figure 15–52. Molecular Biology of the Cell, 4th Edition.

4-Intracellular receptors: In this family the ligand must diffuse into the cell to interact with the receptors; therefore, the ligand must have sufficient lipid solubilities to be able to move across the target cell membranes.

Examples: 1-Vitamin D: It is lipid-soluble since it's made from Cholesterol, so it will cross the plasma membrane reaching its receptor that is present in the **Cytoplasm,**

forming a Drug-Receptor complex, that is translocated into the **nucleus**, then it binds to the DNA modulating the Transcription of the DNA (by either Increasing or Decreasing the rate)

2- Steroid Hormone: In which the activated ligand-receptor complex migrate to the nucleus, where it binds to a specific DNA sequences, resulting in regulation of the gene expression.



D. Protein synthesis-regulating receptor

Characteristics of receptors

1)Receptors determine the specificity of the drug action, so there is compatibility between the drug and the receptor, because each have a specific 3D shape that allow only a certain drug to bind to a certain receptor that has the complementary shape.

The following paragraph is from our book: "**Receptors are responsible for selectivity of drug action. The molecular size, shape, and electrical charge of a drug determine whether—and with what affinity—it will bind to a particular receptor among the vast array of chemically different binding sites available in a cell, tissue, or patient. Accordingly, changes in the chemical structure of a drug can dramatically increase or decrease a new drug's affinities for different classes of receptors, with resulting alterations in therapeutic and toxic effect."**

-Remember that **pharmacodynamics** is how drugs affect the body to give us the effect; what the drug is doing to the receptor or what is it doing to the enzyme.

2) **Most receptors are proteins**

3)Most drugs bind reversibly (preferable) , not all, so some of the drugs bind irreversibly to the receptor, and using one of those irreversible drugs means that you would abolish the existence of the receptor for the whole duration of binding between the drug and the receptor, basically, you would "execute" the receptor, so for example, Aspirin, which is an irreversible inhibitor (decreases the concentration of active enzymes) binds to the enzyme COX.

So**,** how could you get rid of the effect of aspirin?

Before answering, keep in mind that most Irreversible inhibitors are linked covalently and to break this bond you need high energy amounts that are not present in our body.

Answer:

By Increasing the number of receptors; synthesizing new receptors (proteins), and that is the only way to get rid of the signal of an irreversible drug, so by recycling the old Drug-receptor complex by engulfing it, and then synthesizing new receptors (Proteins), which will take hours or days.

-Note: If you have a drug that binds to the receptor irreversibly, that means that the duration of the action of the drug would be long (longer than the reversible drugs).

-**Adrenergic receptors** are present on all effectors of the sympathetic nervous system EXCEPT sweat glands, they have 2 types: Alpha & Beta, and they respond to Adrenaline; their agonist. One of their antagonists; inhibitors, is Propranolol which is a betablocker.

-**Propranolol,** used for heart disease, inhibits Adrenergic receptors reversibly, so when you decide to stop giving the patient this drug, or once the body needs more adrenaline to bind to the Adrenergic receptors (the body needs the adrenaline to act) , the Propranolol will unbind within milliseconds, because it's reversible, so there is a competition between the endogenous ligand (adrenaline) and the drug Propranolol, so if you increase doses of the adrenaline it will overcome the binding of Propranolol and get rid of its effect, and that is what we prefer, there is more tight regulation of the drug when it is reversible.

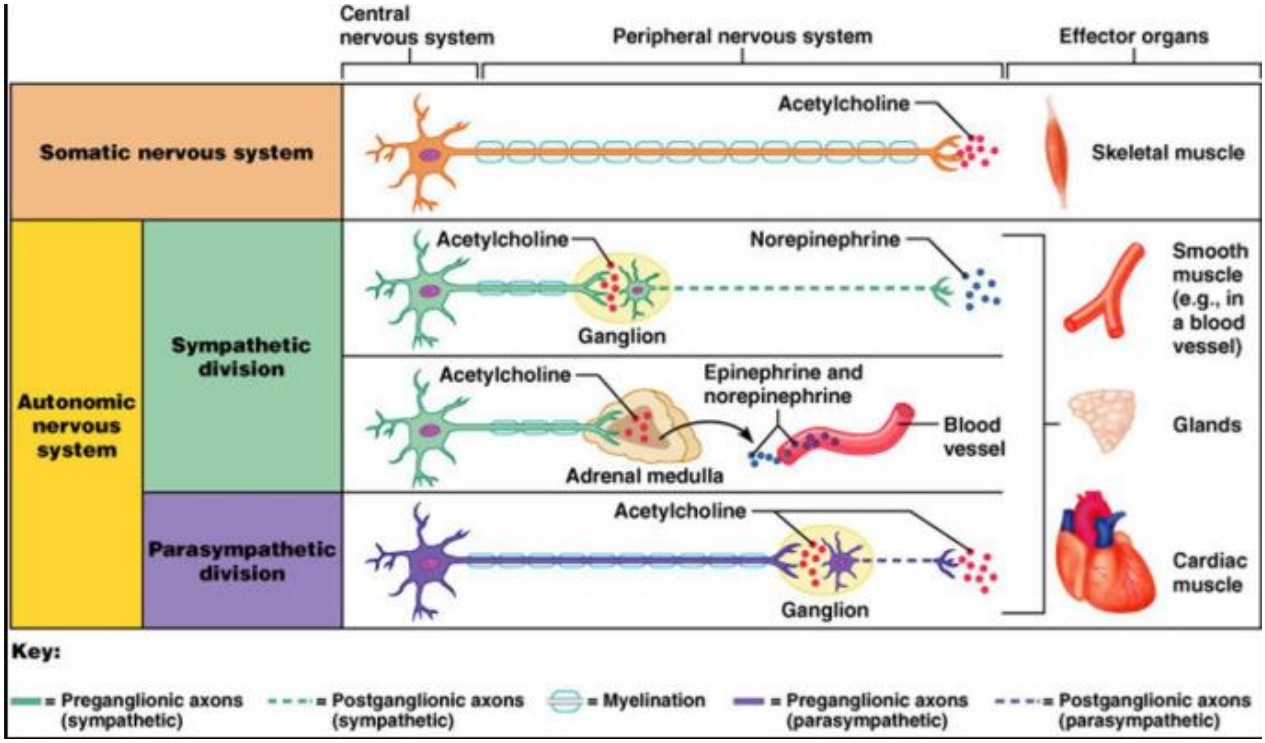
Sarin Gas, which is an organophosphate, binds irreversibly to the enzyme acetylcholine esterase (AchE), which is in charge of breaking down (degradation of) acetylcholine(Ach), a neurotransmitter responsible for transduction of signals in the Parasympathetic nervous system and also skeletal muscle activation through the nicotinic receptors. So, once this gas binds to AchE, it will no longer be able to perform its function so there would be Complete inhibition of the enzyme, so in this case, what is the solution? (try thinking before moving on to the answer).

- **Answer**: As mentioned before, the body will try to synthesize new AchE to overtake this irreversible inhibition, but it will take a long time (Hours to days) to produce enough enzymes to do so and continue doing their function, but the patient doesn't have that time, so what kills the people who inhale sarin gas is the accumulation of

Ach which will keep the parasympathetic nervous system activated, so there would be more glandular secretion, Drooling and excessive sweating (remember that sweat glands are under sympathetic control) , vomiting, myosis (excessive constriction of the pupil of the eye) but what finally kills the patients is the continuous contraction of the muscles in our body due to large amounts of Ach which will eventually lead to paralysis of the muscle (the muscle would be exhausted), one of the muscles that would be paralyzed is the diaphragm, so it could no longer function and the patient then could no longer breathe, This takes 12-24 hours.

-If a person is diagnosed with sarin toxicity in an early stage, luckily, S/he could be treated by using a drug called **antidote**, which breaks the covalent bond between AchE and Sarin gas, it should be taken early on because after a certain amount of time (almost 6 hours) the structure of AchE will change, and the drug could no longer identify AchE (basically what this drug does is save AchE)

-That's why we prefer reversible drugs, even though there are drugs sold that are irreversible



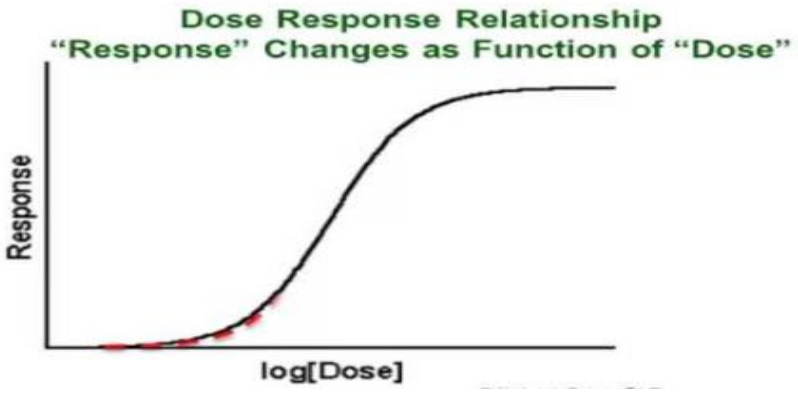
Since there was a lot of talking about the ANS, I think this might help. (this was not given in the lecture, I put it only for further understanding)

4) Not all drugs target receptors, but drugs that target receptors are more favorable because they form certain chemical bonds in between them, and there must be compatibility between the drug and receptor, **Receptors are responsible for selectivity of drug action.**

Characteristics of Drug-Receptor Interactions

- **Chemical Bond**: ionic, hydrogen, hydrophobic, Van der Waals, and covalent

- **Saturable**, increasing the dose of the drug will continue to have an effect up to a certain point where even if you take huge amounts of the drug, it will have the same effect. So, for example if a person was complaining from pain, and he took 10 mg of paracetamol, this pain would be relieved slightly, but increasing the dose to let's say, 500 mg of the same drug would relieve the pain more, and for example taking 1000mg (2 pills) would have a better effect than the 500mg dose. But taking 4 pills (2000mg) would have the same result as the 1000mg dose.
  -This could be understood by looking at this dose-response graph.



This is mainly due to the number of the receptors available for that drug on the surface of the cell, so what determines the degree of the response is the number of receptors of the drug, a nonscientific example to help understand: if you had 10 receptors for a certain drug and you took 20 molecule of this drug, you won't see a better response than 10, even if you increase the concentration of the drug more and more, you won't get a better effect. **Summary**: As the concentration of a drug increases, its pharmacologic effect also gradually increases until all the receptors are occupied (the maximum effect).

- It is **competitive** (if it is reversible); so, the drug will compete with an endogenous ligand, a hormone for example, and the ligand with higher concentration will show its effect by binding to the receptor, so if in the beginning, the concentration of the endogenous ligand was higher, their effect will be present, but my increasing the concentration of the drug, it will replace the endogenous ligand and bind to the receptor.

The rest of characteristics will be discussed in sheet 4…