Medical Committee
The University of Jordan

PHARMACOLOGY

Lecture No.: 9

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SHEET ■

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Mechanism of drug action (Continued)

How the drug exerts its effect on our body?

By mimicking or antagonizing endogenous ligands (produced by the body).

Mainly drugs work by binding to receptors, but not all of them. Only *95% of drugs bind to receptors*. Sometimes they do not bind to anything (e.g. Mannitol, an osmotic diuretic drug that stays in the blood; it induces hyperosmolarity (withdrawal of water from cells))

The act of a drug molecule binding to the receptor is called **Coupling.**

- Biochemical and conformational changes occur during binding which lead to the required response.
- Coupling may cause an action (Agonist), or it may block an action (Antagonist).

Example on activation (agonist): In our body, there are Mu (Morphine) receptors for endogenous ligands called **Enkephalins**, which have an analgesic (pain relieving) effect on our bodies. When enkephalins bind to Mu receptors, it will cause a therapeutic effect (pain relief). This is called **Transduction** *(coupling between the ligand and its receptor was translated into a therapeutic effect)*.

Intrinsic activity (Efficacy): refers to the relative capability of the drug-receptor complex to produce a maximum therapeutic response. It can be activation or inhibition. Through certain drugs, we may either activate the receptor to produce an effect, or inhibit the receptor, so no effect will be produced. When we give a patient Morphine, it will mimic Enkephalins in binding to the Mu receptors and producing an analgesic effect (therapeutic effect). For example, if we considered Enkephalins as a drug, both Mu and Enkephalins have the same therapeutic effect but with different efficacy. (This will be re-explained shortly)
Note: Usually there are no antagonizing drugs for Enkephalins.

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Example on inhibition:

Let's say a patient has Tachycardia (Arrhythmia/ fast heart rate), which is caused when adrenaline (epinephrine) binds to the beta1 receptors in the heart. In order to reduce the patient's heart rate, we require a drug that will antagonize adrenaline in binding to the beta1 receptors (antagonist) and decrease the heart rate.

The above examples (Activation/ Inhibition) summarize the basic function of most drugs.

The important question is: How many receptors do we have in our bodies?
We have hundreds of thousands of all kinds of receptors (Mu, Beta1, etc.). This means that the higher the concentration (dose) of a drug, the more receptors it will bind to, and the greater effect it will have. So taking 1 mg of morphine will have a certain analgesic effect, 2 mg will have a greater effect, and so on until we reach a saturation of morphine receptors. This is called the **Ceiling Point.**

Receptors are large macromolecules with a specific 3D shape that can be found on the cell surface or can be intracellular. Attachment of a drug to its receptors depends on affinity. The higher the affinity of a drug to its receptors, the greater effect it will have. Affinity of the drug depends on several factors, including complementary shape of the drug to the receptor, charges (attraction/ repulsion), etc.

One receptor can bind to several different drugs. If more than one of these drugs is present, the drug with the highest affinity will be most active and effective.

Types of receptors: We have 4 types of receptors in our bodies:

1) **Ligand-Gated Ion Channels**
2) **G-Protein-Coupled Receptors**
3) **Enzyme-Linked Receptors**
4) **Intracellular Receptors**

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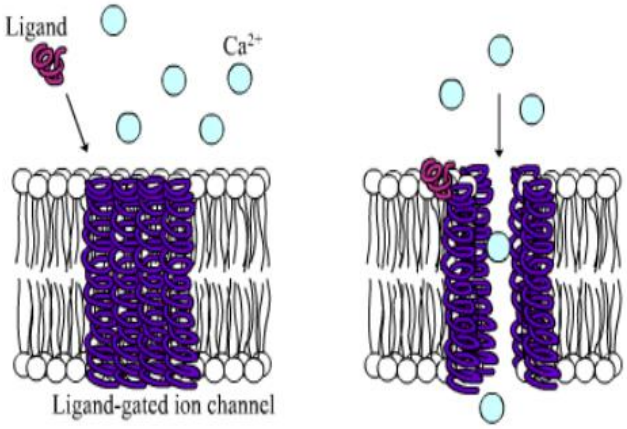
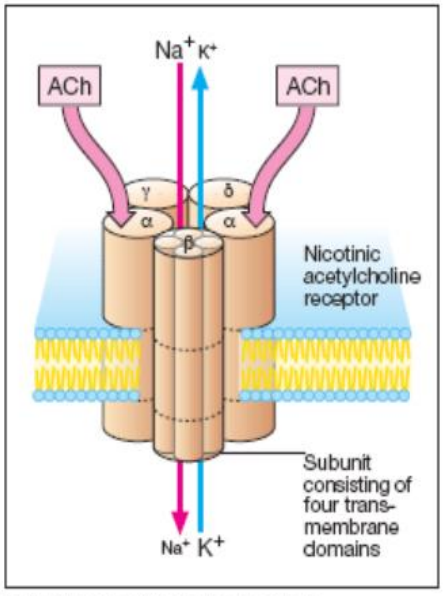
1)Ligand Gated Ion Channels control the flow of Ions in and out of the cell (e.g. Na+ and K+ in action potential). Binding of a ligand to these receptors will affect this flow of ions.

Example: Seizures are caused from the increased activity of Nicotinic receptors, which bind the neurotransmitter Acetyl Choline, causing an increased flow of Na+ ions inside the cell and K+ ions outside (Hyperpolarization). To treat seizures, we need a drug that will antagonize Ach in binding to the nicotinic receptors and inhibit action potential, relaxing the patients' muscles. This procedure is also done to patients about to have surgery, in order to insure they remain still (relaxed) throughout the surgery.

There are also cases where we need to increase Ach activity, like in the disease Myasthenia Gravis, which causes extreme muscle fatigue. These patients require Ach (nicotinic) agonists to activate the receptors to some extent by mimicking the activity of Ach. But over-activation of the receptors may cause the muscles to be hyperactive and this leads to paralysis and can be fatal.



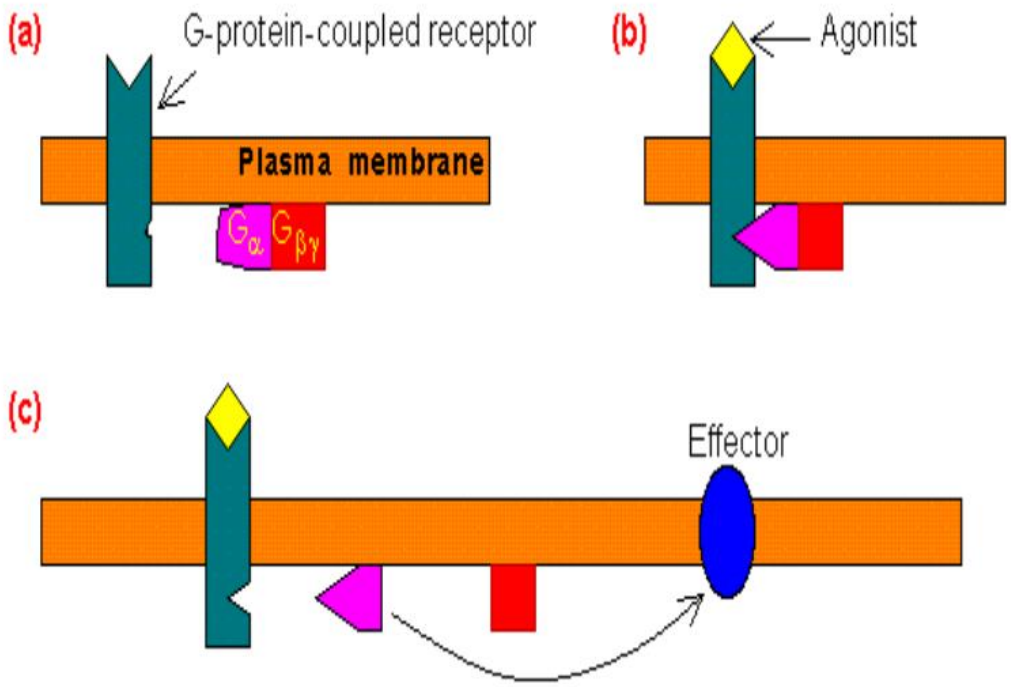


B. Ligand-gated ion channel

2) G-protein Coupled Receptors like Beta receptors (Sympathetic receptors) (β1, β2...). As we mentioned, adrenaline binds to the β1 receptors and increases the heart rate.

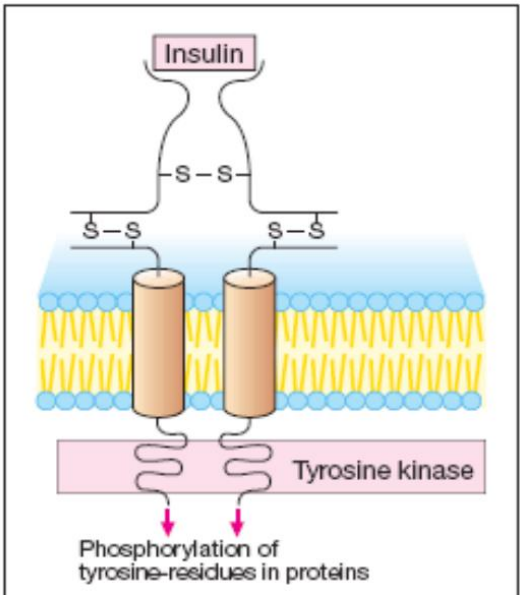
Example: Certain drugs, known as stage drugs (β- blockers), are used by some people before they present themselves to an audience. People are naturally nervous in these cases, so they take stage drugs to relax and these drugs antagonize adrenaline and stabilize their heart rate.

There are some cases where we want to increase the heart rate like Bradycardia. Drugs like Dobutamine and Epi-pens (Epinephrine autoinjector) are used to activate the Beta1 receptors and increase the heart rate.



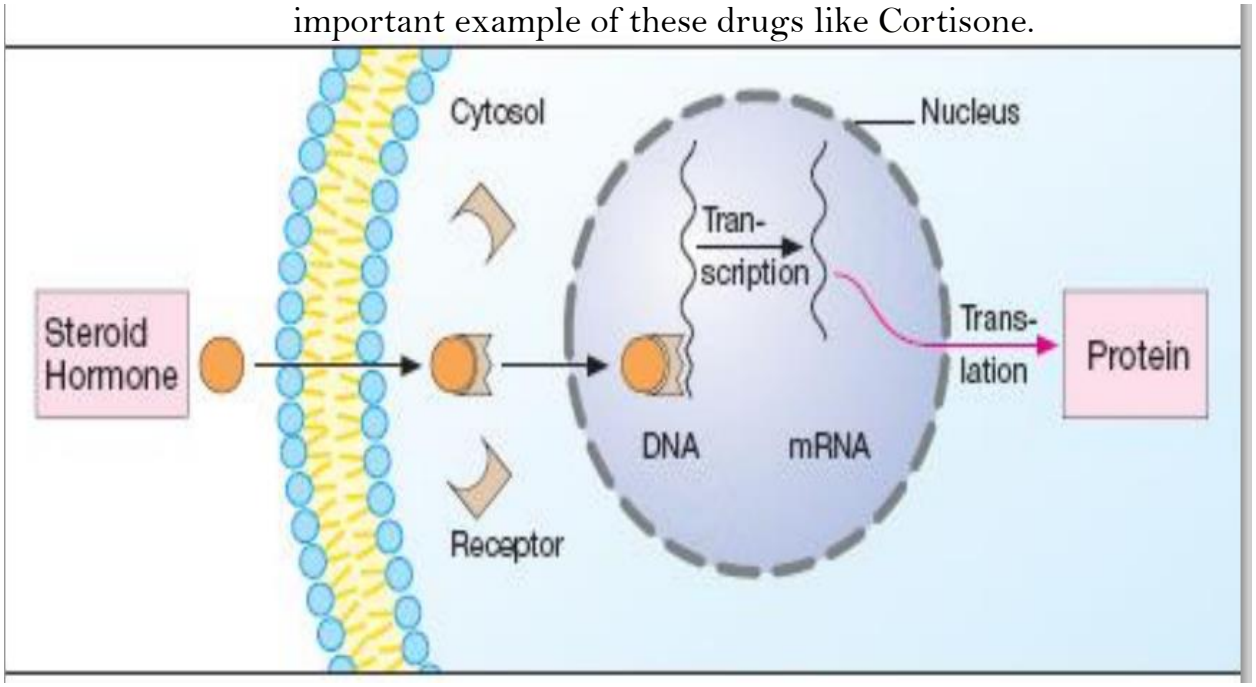
3) Enzyme- Linked Receptors have an extracellular and an intracellular side. The intracellular portion usually has a Tyrosine Kinase enzyme. The function of this enzyme is to phosphorylate (add a phosphate group) to its substrate. The substrate may phosphorylate another substance, and so on. So the drug in this case will start an activation process. The most

important ligand that binds to these receptors is *insulin*. Binding of insulin to these receptors will start what is known as an AKT pathway.



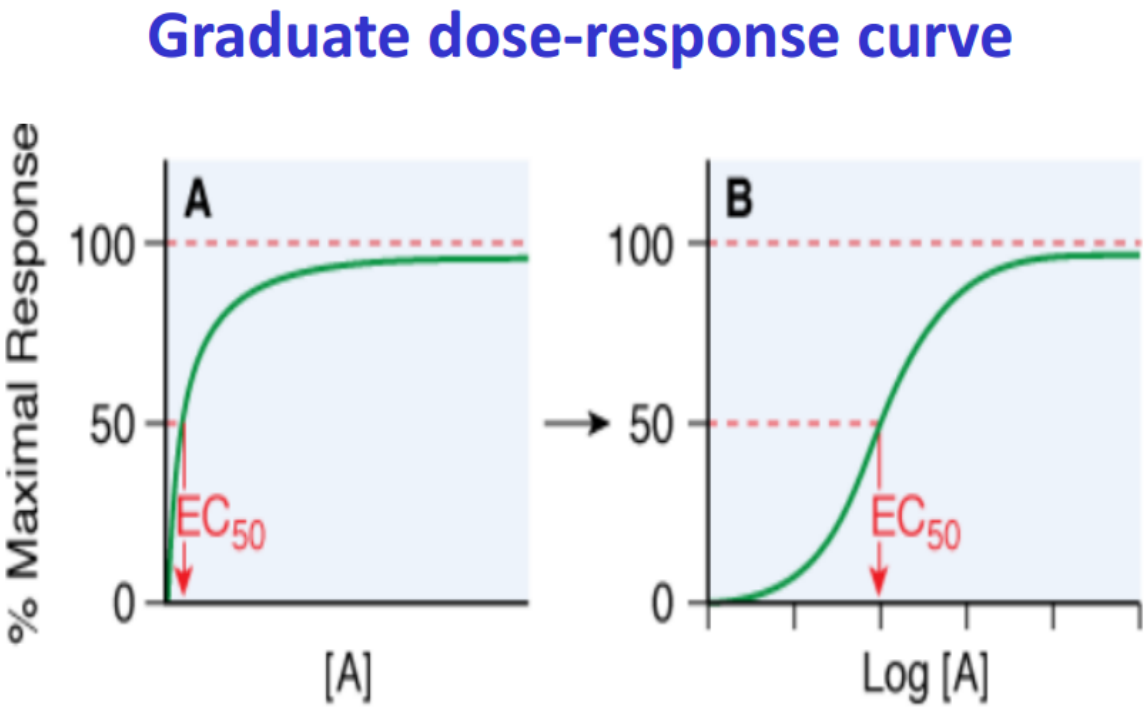
4) Intracellular receptors:

As implied by the name, these receptors are located inside the cell. The drugs that bind to these receptors must be hydrophobic (lipid soluble) and capable of crossing the cell membrane. *Corticosteroids* are the most important example of these drugs like Cortisone.



Dose- Response Relationship:

As mentioned before, we have millions of receptors in our body. If we give a Tachycardiac patient 10mg of Beta1 blocking drug (for example), we may stop or prevent the Tachycardia temporarily, but we would not defeat the risk of Angenia Pectoris (ischemia of the heart muscle), so we give him 50mg to prevent any risk of a rising heart rate. We also mentioned that raising the dose of a drug will increase the therapeutic effect by binding to more receptors until saturation (Ceiling point) is reached.



(We use log concentration instead of just concentration to make it easier to analyze)

E_{max} : is the maximal response that can be produced by the drug.

EC_{50} : is the concentration of the drug that produces 50% of the maximal effect.

As seen above in the figure on the right, low doses of a drug will have almost no effect in our body (**sub-therapeutic effect**) because not enough amounts of receptors are activated. Therapeutic effects are reached as we increase the concentration (dose) means as we activate more receptors.

For example, if you walk into a pharmacy to buy Ibuprofen (Painkiller) pills, you will find that 200mg is the lowest possible does, since anything under that is sub-therapeutic and will have little or no effect. Depending on the extent of the pain you can take:

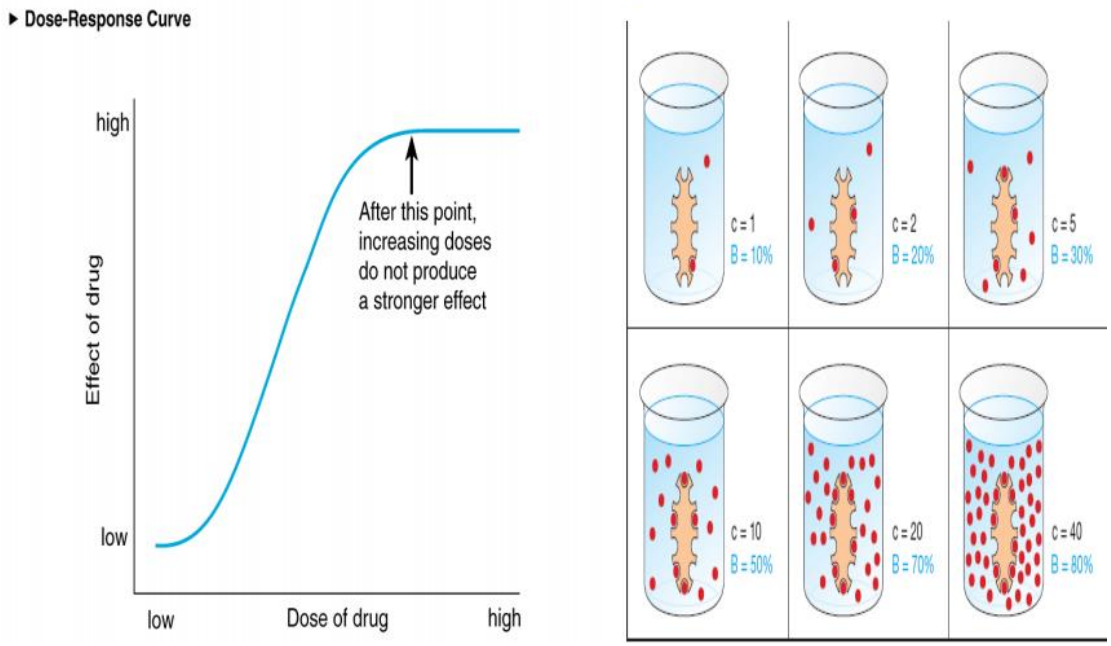
200 mg (mild pain)
400 mg (moderate pain like toothache)
600 mg (severe pain)
So the higher the dose, the higher the effect.
>600 mg: No extra effect. The reason behind this is that 600mg is the ceiling point (E_{max}) for this drug (Ibuprofen), so all the receptors for this drug are saturated at this point. In other words, any concentration of a drug above E_{max} will have no extra effects (may also induce toxic effects). In cases of Cancer or Migraines (severe headaches), where the pain is so extreme that the E_{max} for Ibuprofen is not sufficient to relieve the pain, we need to use other drugs with a higher E_{max} (Ceiling point) than Ibuprofen, in order to compensate the degree of pain.

In other words, we need a drug with **higher Efficacy.**

Efficacy (Efficiency) simply is the maximum effect a drug can have.

Example: A hypertension patient has a blood pressure of 190/130. There is no single drug that can lower the blood pressure of this patient to the normal level (120/80) without exceeding its Efficacy. So what we should do is to combine drugs together to increase the efficacy and reduce the blood pressure (the maximal response).

Graduate dose-response curve



Bottom line: There are many different analgesic drugs that have the same pharmacological effect (Paracetamol/ Ibuprofen/ Morphine), but vary in their efficacy. It is a doctor's job to determine the severity of the patient's condition and prescribe the drug with the suitable efficacy, or the combination of drugs that will have the maximum effect. For example if he's suffering from a severe pain, we don't give him Paracetamol because the maximal effect is for mild pain only. In other words, if the saturation level of a certain drug does not achieve the desired effect, you can either use a drug with higher efficacy, or add another drug that binds to different receptors than the first, until the desired result is achieved. The figure on the right illustrates clearly the saturation level.

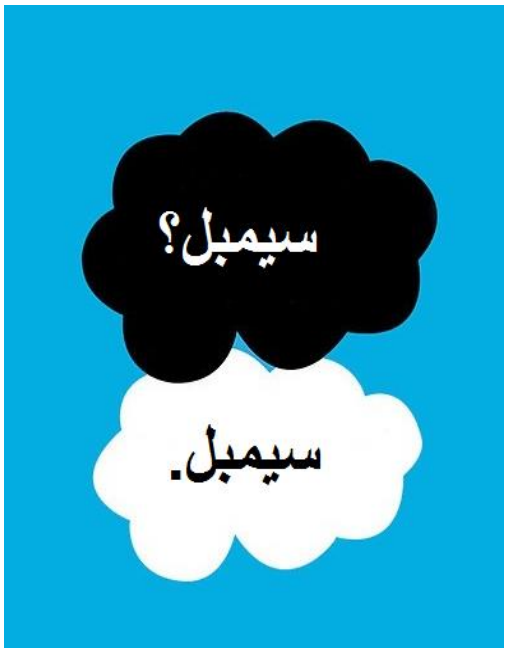
Potency (Brief Intro.): As mentioned earlier, Efficacy is the maximum effect a drug can achieve. Potency, on the other hand, is the amount of the drug necessary to produce a certain effect.

To measure potency, we use the Half Maximal Effective Concentration (called EC50), which is the concentration of a drug at half the maximal effect (Emax). It is inversely proportional to the Potency. And we use it to compare between drugs.

Potency will be revised and discussed in greater detail after Eid.

Correction note: In pharmacological sources , intrinsic activity and efficacy are considered the same without significant difference but to be more accurate: Intrinsic activity is only considering the biochemistry of the protein and its ligand at the two molecule level, say in a test tube with an optimal condition. Efficacy has to be taken to the organism level, say what and how it does to you when you are administrated with the drug/stuff.

The doctor didn't mention this during our lectures and we'll discuss it with him after holiday because it's not that simple after all. :P



شكر خاص للأخت علا زقيبة والأخت راية المجالي على "المساعدة"
Special thanks to Mohamad Hindi for co-writing this short and hopefully easy sheet.