6

Pharmacology

Doctor 2018 | Medicine | JU

◉ Sheet ○ Slides

Done By

Nabil G. Sweis

Contributed in the Scientific Correction

Nabil G. Sweis

Contributed in the Grammatical Correction

Nabil G. Sweis

Doctor

Alia Shatanawi

Pharmacokinetics … continued

❖ We commenced our discussion in pharmacokinetics by shedding light upon two of the processes that a drug undergoes: **Absorption** and **Distribution**. We will now proceed with a third pharmacokinetic process: **Metabolism**.

❖ What is Metabolism (also called: Biotransformation)?

✓ It is the process by which a substance (e.g. a drug) is **converted** (transformed) from one chemical form to another.

✓ **The purpose of drug metabolism:** Metabolism of a drug serves to **promote its excretion (elimination)** from the body through converting the drug into a form that can be easily discharged. *How does this occur?*

✓ **Urine** is the fluid "vehicle" through which the metabolized drug usually leaves the body. Therefore, metabolic processes predominantly aim to modify the drug such that it is altered from a ***lipid-soluble form*** to a more ***water-soluble form***, enhancing its solubility in urine (which is water-based). Consequently, excretion is facilitated.

In other words, many lipid-soluble drugs are not readily eliminated from the body and must be conjugated or metabolized to compounds that are more polar and less lipid-soluble before being excreted.

❖ **Metabolism of a drug can:**

✓ **Inactivate** the drug

✓ **Activate** the drug

✓ **Produce** other active metabolites (sometimes metabolic processes give rise to new metabolites that display some activity but less than that of the original drug).

✓ **Note:** The kidney is the main route of excretion. However, other routes do exist, and thus there are other metabolic mechanisms that promote drug elimination through the other routes.

✓ In addition to affecting solubility as previously discussed, metabolism also affects the **activity of drugs.**

➢ Most of the time (NOT always), metabolism of the drug results in its **inactivation** (conversion from an active to an inactive form). It can no longer exert its effect due to alterations in its chemical structure.

✓ **However, there are exceptions where drug metabolism activates the drug. What conditions call for cases like these?**

- In some cases, the chemical structure of the active form of certain drugs may actually hinder their distribution to their site of action (perhaps due to permeability-related reasons). Thus, they are initially administered in their dosage form as **pro-drugs** (drugs in the inactive form) which distribute more efficiently and once they reach their target tissue, they are activated by metabolic enzymes to be able to exert their effects.

✓ In our discussion, we will mainly refer to metabolism as an "inactivation step".

❖ Site of metabolism:

✓ The liver is the major site for drug metabolism. Other sites include:

- Kidneys
- Gastrointestinal Tract (GIT)
- Plasma
- Lungs

❖ Factors affecting metabolism (mainly in Liver):

1. **Disease state:** In the case of liver diseases for example, the concentration of liver enzymes (many of which are involved in metabolism) is affected. Hence, metabolic rate is also impacted.

2. **Blood flow:** If **blood flow** to the liver is **reduced**, this will **lower** the **rate of drug delivery** to the liver (remember that blood carries the drug to various parts of the body, so logically, less blood flow to a particular type of tissue would imply less drug delivery to that tissue). When the liver receives less amounts of the drug, **rate of metabolism** in the liver becomes **slower**.

3. **Use of inducers and inhibitors** (to be discussed later).
4. **Genetic background of the patient** (to be discussed later).

❖ Phases of metabolism:

- In general, drugs undergo two different types of reactions during metabolism. Accordingly, there are two phases of metabolism, each of which involves a particular set of related reactions.

1. Phase I :

✓ Phase I reactions seek to alter the chemical reactivity and increase the water solubility of the drug. **These reactions include:** oxidation, reduction, hydrolysis.

✓ Reactions of this phase **increase** the **chemical reactivity** of the drug to prepare it for reactions of Phase II. Note that **chemical reactivity** differs from **pharmacologic activity** (We are not increasing the pharmacologic activity or effect of the drug. Instead, we are actually deactivating it most of the time. Increasing chemical reactivity implies that the drug can more readily participate in further (metabolic) chemical reactions serving to aid its excretion)

✓ **An Example of how chemical reactivity could be increased in Phase I:**

- Through oxidation or reduction reactions for instance, the drug may **acquire a charge** that causes it to readily proceed to reactions of Phase II.

✓ The reactions of this phase are frequently catalyzed by the **cytochrome P450 system** (also called microsomal mixed-function oxidase).

Example of a Phase I reaction: **Drug + O_2 + NADPH + H^+ → Drug(modified)+ H_2O + $NADP^+$**

➢ Cytochrome P450 system:

- ✓ This system represents the executionary machinery of Phase I (i.e. it catalyzes the reactions of Phase I)

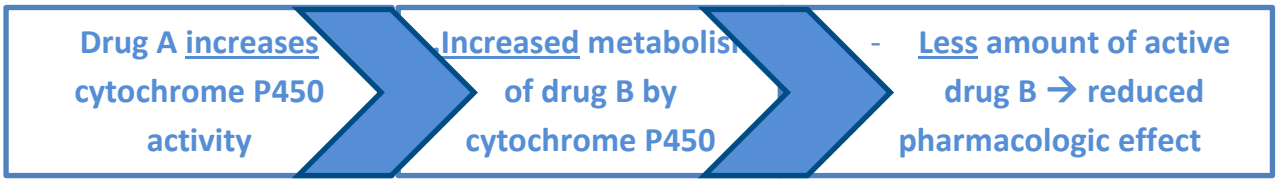
- ✓ It is a **SYSTEM**; It is composed of a group of enzymes. More specifically, **12 unique isoforms** of this enzymatic system (CYP2D6, CYP3A4) have been identified to play a role in human drug metabolism. They are involved in metabolism of most of the drugs we take, often resulting in their conversion to inactive forms.
- ✓ Additionally, the significance of this system also emerges from the fact that it is a key player in **drug-drug interactions**.

➢ Cytochrome P450 and drug-drug interactions:

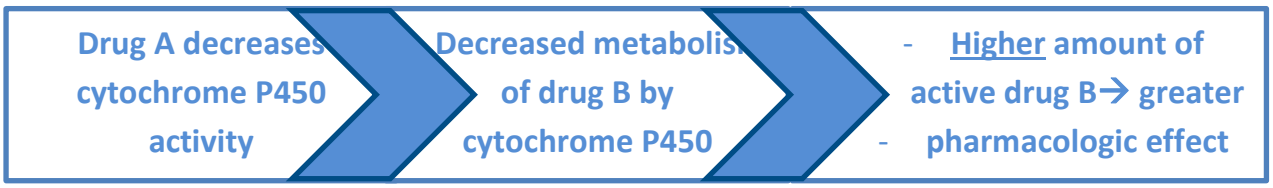
- ✓ Recall that drug-drug interactions refer to the impact of one drug on the activity of another drug when simultaneously present in the body (observed when multiple drugs are administered together to the patient)
- ✓ Certain drugs affect the activity of cytochrome P450 (either by induction or inhibition) leading to altered metabolism rates of the other drug by this system.

- ✓ **The general concept of the role of Cytochrome P450 in drug-drug interactions will be briefly presented, followed by a series of examples:**

➢ Induction (activation) of Cytochrome P450:



➢ Inhibition of Cytochrome P450:



➢ **Examples of induction:**

❖ Rifampin *with* Warfarin

- ✓ **Warfarin** is an anticoagulant, it is metabolized by cytochrome P450 where it is inactivated.
- ✓ Let's assume a patient is on **Warfarin**. For some reason, the patient also needed **Rifampin** (an antibiotic). When **Rifampin** is administered, it will induce more expression of one or more isoforms of cytochrome P450. (Rifampin is an inducer).
- ✓ Normally, **cytochrome P450 deactivates Warfarin**. But with the **increased synthesis of cytochrome P450 isoforms due to Rifampin**, even **faster inactivation of Warfarin takes place**, leading to **reduced Warfarin levels in plasma**. Thus, the anticoagulative effect of Warfarin is largely diminished and no longer observed, increasing the risk of clotting in the patient.
- ✓ **Note:** Taking **"Carbamazepine"** with **"Warfarin"** would result in the same pattern of events as that described in the previous example.

Note: During the lecture, the doctor stated that Rifampin *binds* to cytochrome P450 and activates the enzyme itself, thus increasing its activity. The slides, however, mention that Rifampin increases metabolic activity by increasing expression of more cytochrome P450 enzymes. Perhaps both methods are possible mechanisms of cytochrome induction. In both cases, the end result is the same: Increased metabolic activity.

❖ Rifampin or Carbamazepine *with* HIV protease inhibitors

- ✓ A patient with HIV takes **HIV protease inhibitors** as part of his medication.
- ✓ HIV patients are more prone to infections. So let's assume the patient suffered an infection, and his doctor (unaware of potential drug-drug interactions) happened to prescribe Rifampin to treat it.
- ✓ **Rifampin will result in more extensive synthesis of cytochrome P450 isoforms**, **increasing the rate of metabolism (inactivation) of HIV protease inhibitors**, and a subsequent **decrease in HIV protease inhibitor concentration in plasma is observed.**

➢ **Example of inhibiton:**

❖ **Omeprazole *with* Warfarin**

✓ **Omeprazole** is a drug used to treat peptic ulcers (by acting as a proton-pump inhibitor). In addition to that, it also happens to be a cytochrome enzyme inhibitor (it inhibits three CYP isoforms that are responsible for Warfarin metabolism).

✓ If a patient who is on Warfarin has a peptic ulcer and is prescribed **Omeprazole**, the **cytochrome P450 enzymes will be inhibited** → **Decreased metabolism (decreased inactivation) of Warfarin** →**Elevation of Warfarin concentration in blood** → **Greater inhibition of coagulation** (Recall Warfarin has anticoagulative activity) → **Leading to higher risk of bleeding reactions.**

✓ Sometimes, certain food items may affect cytochrome P450 activity, such as grape juice. Therefore, a patient on Warfarin should refrain from grape juice consumption to avoid the complications mentioned previously.

➢ So far, we became familiar with Phase l of drug metabolism. If the metabolite from phase l is polar enough, it will be excreted by the kidney. But if it is still too lipophilic to be retained in the kidney, the metabolite proceeds to Phase ll metabolism.

2. Phase ll :

✓ Similar to Phase l, Phase ll reactions also aim to increase water solubility of the drug. However, the difference resides in the types of the reactions that occur in this phase.

➢ **Phase l reactions** include oxidation, reduction and hydrolysis.
➢ **Phase ll reactions** consist of conjugation reactions with endogenous substances, such as glucuronic acid, sulfuric acid or an amino acid. Phase ll results in polar and usually more water-soluble compounds.

➢ **Let's revisit the two phases, but this time linking them as a series of events:**

- ➢ Our drug enters **Phase I** in an attempt to become water-soluble, so it undergoes oxidation, reduction and hydrolysis reactions that may give the drug a charge, or perhaps unmask an already present polar group, increasing its water-solubility. If our drug reaches the desired extent of water solubility, it skips Phase II and is excreted immediately.
- ➢ If our drug is not water-soluble enough, it proceeds to **Phase II**. Recall that Phase I commonly results in highly reactive forms of the drug (modified), which explains why it can readily enter Phase II, where we start attaching (conjugating) polar substances like (glucuronic acid) to the drug (modified) to further enhance its water solubility. Our metabolized drug should be ready for excretion by now.

❖ **Effect of genetic background on drug metabolism:**

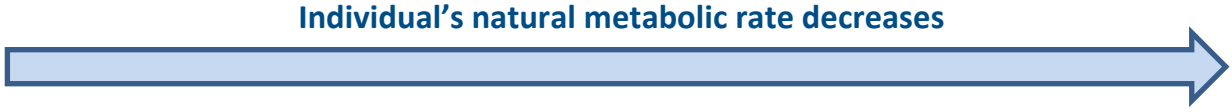
✓ We came across the terms **"Pharmacogenomics"** and **"Pharmacogenetics"** in previous lectures, both of which are related to the study of the effect of the genetic makeup on the body's responsiveness to drugs.

➢ **How is this relevant to our current topic?**

✓ The cytochrome P450 gene is a common site of **polymorphisms** (genetic variations among individuals) resulting in phenotypic variations in the cytochrome P450 enzymes from one person to another. These variations in metabolic enzymes are reflected in the rate of metabolism in people. Based on that, individuals are classified with respect to their natural rate of metabolism into:

1. Ultra-rapid Metabolizers	2.Extensive Metabolizers	3.Intermediate Metabolizers	4.Poor Metabolizers

Individual's natural metabolic rate decreases



✓ At one end of the spectrum, we have **ultra-rapid metabolizers** whose natural rate of metabolism is high. While at the other end, we have **poor metabolizers** with naturally low metabolic rates. In between, we have **extensive** and **intermediate metabolizers**.

➢ **Why is this important?**

- ✓ It is of clinical relevance when it comes to determining the proper dose for a patient. The same dose cannot be given to all patients, as different types of metabolizers require different doses of the same drug to achieve the same effect.
- ✓ Therefore, we have to tailor (adjust) the dose of the drug depending on what type of metabolizer the patient is.

- ✓ **Ultra-rapid metabolizers** need **higher doses** to compensate for their rapid inactivation and metabolism of the drug.
- ✓ **Poor metabolizers** need **lower doses** as their metabolism is slow and thus a small amount of the drug would last longer.

- ✓ **Example:** Sometimes, a patient (with HIV for example) may not respond to a certain drug (protease inhibitors) due to his ultra-rapid metabolism. We may need to increase the dose in this case if we want to achieve the desired pharmacologic effect.
- ✓ Genetic makeup tests are expensive and are therefore not conducted on everyone. It is mainly applied when using drugs that may have severe adverse effects where a wrong dose may be fatal (this drug must also be a substrate for cytochrome P450, otherwise it would not be affected by cytochrome P450 genetic variations and so there would be no need for the genetic test).

➢ We will now move on to the last pharmacokinetic process, which is **Elimination** (excretion).

❖ **Elimination:**

- ✓ It is a process in which drugs are **transferred** from the **internal** *to the* **external** environment.
- ✓ Elimination **MAJORLY** occurs through the **kidney into the urine. Other sites include** the bile, intestine (feces), lung, sweat or milk in nursing mother.

- ✓ For drugs to be excreted from the **kidney**, they need to be **water-soluble**.
- ✓ For drugs to be eliminated through **other routes**, they need to be **lipid-soluble and unionized.**

✓ **Weak bases** are **excreted faster** in **acidic urine**.

(***Why?*** For efficient excretion in urine, the drug must be water-soluble. In acidic urine, H+ concentration is high, and so the weak base (B) will accept protons more easily and will be mostly present in the charged form (BH+)→ The charge enhances water-solubility and prevents reabsorption through the lipid bilayer of cells in kidney tubules→ Faster excretion).

✓ **Weak acids** are **excreted faster** in **alkaline urine.**

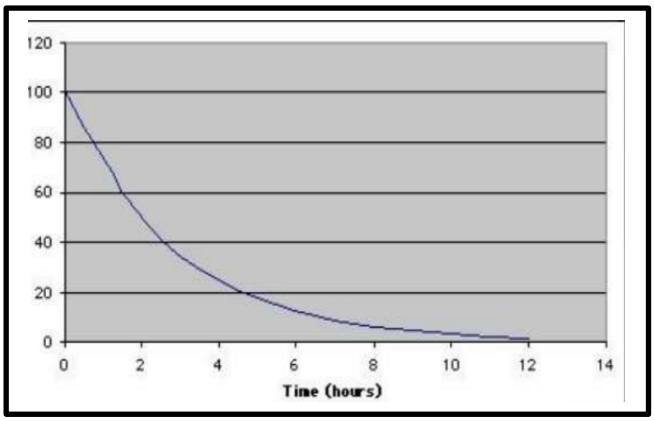
(***Why?*** In alkaline urine, H+ concentration is low, so equilibrium will favor the dissociation of the weak acid (HA) into (A-). More of the drug is present in the charged form → Higher water-solubility and less reabsorption through lipid-bilayer of kidney cells → Faster excretion).

✓ Elimination follows first-order kinetics of decay.

❖ **Plasma half life (t1/2) of a drug:**

✓ The time it takes for a drug's concentration to decline to half its initial concentration.

✓ Look at the adjacent graph (**y-axis:** drug concentration, **x-axis:** time)
✓ Initial conc. At t=0 → 100
✓ **When does the drug conc. reach half its initial conc.? (when is conc.=50?) → At t=2 hours**
✓ **So the half life of this drug ($t_{1/2}$) = 2 hours.**



❖ We calculated half-life based on graphical information. Another possible way of calculation is using **the following equation:**

$$t_{1/2} = (0.7 \times V)/CL$$

- **$t_{1/2}$:** Half-life of the drug
- **V:** Volume of distribution
- **CL:** Clearance

- ✓ The drug half-life is one of the measurements concerning elimination of a drug. Another measurement used is the drug **Clearance**.

- ✓ **Clearance:** a pharmacokinetic measurement of **the volume of plasma** from which **a substance is completely removed** **per unit time**; the usual units are mL/min. The quantity reflects the rate of drug elimination divided by plasma concentration.
- ✓ **CL = Rate of elimination/C (Plasma concentration of drug)**

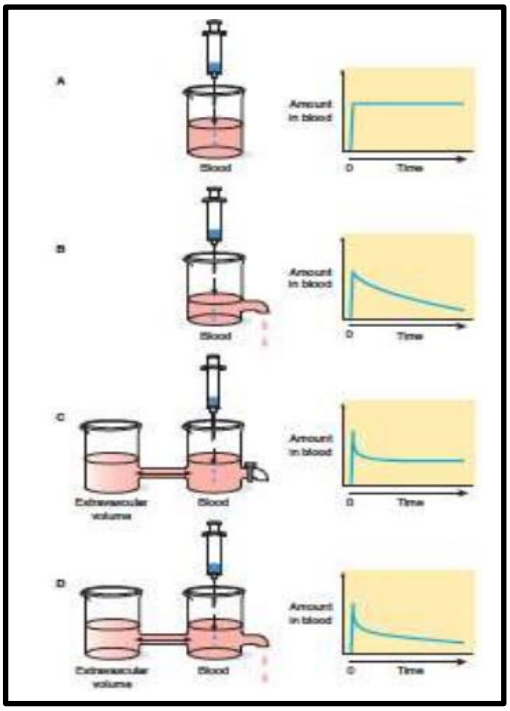
- ✓ A clearance of **5 mL/min** means that **5 mL of plasma** is being **emptied** of the drug **each minute.**

- ✓ The doctor mentioned that we are mainly required to be familiar with the terms "Half-life" and "Clearance", as we do not have time to delve into calculations.

- ✓ From the clearance equation, we noticed that it depends on the rate of elimination. The rate of elimination may follow **zero-order** or **first-order kinetics.**

  - **Zero-order kinetics:** rate is constant and is not affected by concentration.
  - **First-order kinetics:** the rate changes with concentration changes (it depends on concentration)

- ➢ The adjacent figure shows how rates of elimination differ from one drug to another (in terms of which order of kinetics they follow). Details are not required.



- ➢ **When does the elimination of a drug follow zero-order kinetics? (that is, when is rate of drug elimination independent of drug conc.?**
- ✓ An example of this is a drug which needs to bind to a transporter in the kidney to be excreted. If transporters are saturated, drug elimination will follow zero-order kinetics, as no matter how high the drug conc. is, the rate of elimination is constant because all of our transporters are occupied. In other words, the rate of elimination here depends on the number of transporters not the conc. of the drug.

Pharmacodynamics

❖ The main areas of pharmacology are:

1. **Pharmacodynamics:** the study of the biochemical and physiological effect of the drugs and their mechanism of action. Or simply, what the drug does to the body.
2. **Pharmacokinetics:** (which we discussed) the way the body handles the drug: absorption, distribution, biotransformation and excretion.

❖ What are common targets for drugs?

✓ Drug targets were classified into multiple classes:

1. 45% of drug targets are **receptors**
2. 28% are **enzymes**
3. 5% are **ion channels** (which may also be considered receptors)
4. 2% are **Nuclear receptors**
5. 11% are **hormones and factors**
6. 2% are **DNA**
7. 7% are **unknown** (We know that the drug has an effect, but we do not know its target or how it works yet).

✓ Notice that drug targets are **usually receptors or enzymes**.
✓ For a drug to be potent (effective), it needs to bind to a sufficient number of target proteins at a reasonable dose.
✓ Pharmacodynamics does not only study biochemical and physiological effects of drugs and their mechanisms of action, but also the relationship between drug concentration and drug effects.
✓ We will mainly focus on drugs that target receptors.

➢ Receptors:

✓ Large **macromolecules** with a well-defined **3D-shape** present on the **cell surface** or **intracellularly**. They **transduce** binding of a **ligand** into a **response** by causing **conformational changes** or a biochemical effect.
✓ Most drugs exert their effect by interacting with receptors, where they bind and induce conformational changes ending with a physiological response.

- ✓ Most receptors are **proteins** that have undergone various **post-translational modifications** such as covalent attachments of carbohydrates, lipids and phosphate groups.
- ✓ Receptors are naturally present in the body because they have endogenous ligands (like neurotransmitters or hormones). We exploit the presence of such receptors in synthesizing drugs to modulate physiologic effects.

- ✓ **Cell surface receptors** are embedded in the cell membrane and function to receive chemical information from the extracellular compartment and transmit it to the intracellular compartment.

- ✓ **What makes receptors (cell-surface receptors particularly) a favorable target for drugs?**

- ➢ Cell-surface receptors are **easily accessible** targets for drugs, as they are located on the "cell surface" as the name implies. This facilitates drug binding as we would not have to worry about the drug crossing the lipid membranes of cells (no need to worry much about the lipid-solubility of the drug).
- ➢ However, some receptors are intracellular. Therefore, drugs targeting such receptors must cross the plasma membrane, which means they have to be lipid-soluble.

- ❖ **The two fundamental properties underlying specificity in drug-receptor interactions are:**

  1. **Complementarity of shape** between the drug and receptor.
  2. **Complementarity between the electrostatic, hydrophobic, and hydrogen bonding** surfaces of each component.

- ✓ These two factors cause a certain drug to be able to bind specifically to certain receptors and not others.

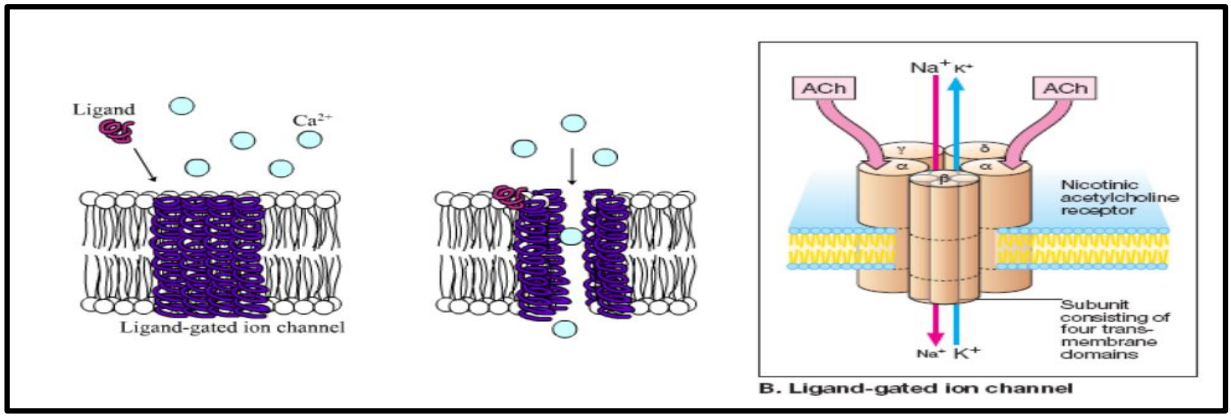
- ✓ A protein receptor is synthesized such that its 3D structure is compatible with certain compounds. Post-translational attachments to the receptors further add to the specificity by enhancing chemical structure and charge. This is important for us in designing specific drugs for a receptor.

❖ Major receptor families:

- ✓ **Ligand-gated ion cannels** (e.g. Nicotinic receptors)
- ✓ **G protein-coupled receptors** (e.g. Adrenergic G protein-coupled receptors)
- ✓ **Enzyme-linked receptors** (e.g. Tyrosine receptor kinase)
- ✓ **Intracellular receptors**

➢ *Ligand-gated ion channels:*

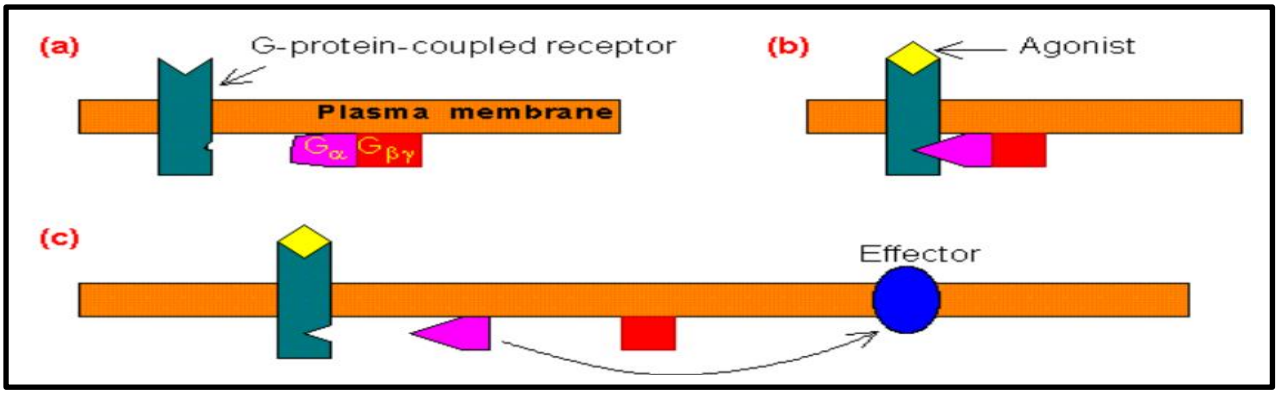
- ✓ **Function:** Regulation of the flow of ions across cell membranes.
- ✓ Regulated by binding of a ligand to the channels.
- ✓ The best example is the **Nicotinic receptor**, in which the binding of acetylcholine causes the channels to open resulting in sodium influx and the activation of contraction in skeletal muscles.



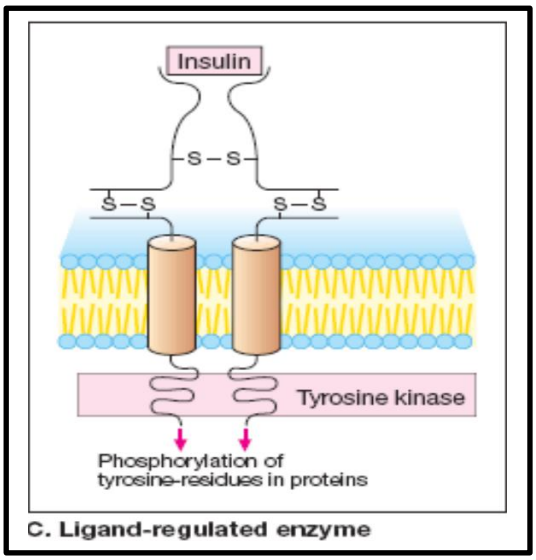
➢ *G protein-coupled receptors:*

- ✓ These receptors regulate or facilitate effector proteins through a group of guanosine triphosphate (GTP) proteins known as **G proteins** (on the inner face of the plasma membrane). These G proteins can also bind other regulatory proteins like (GAPs).

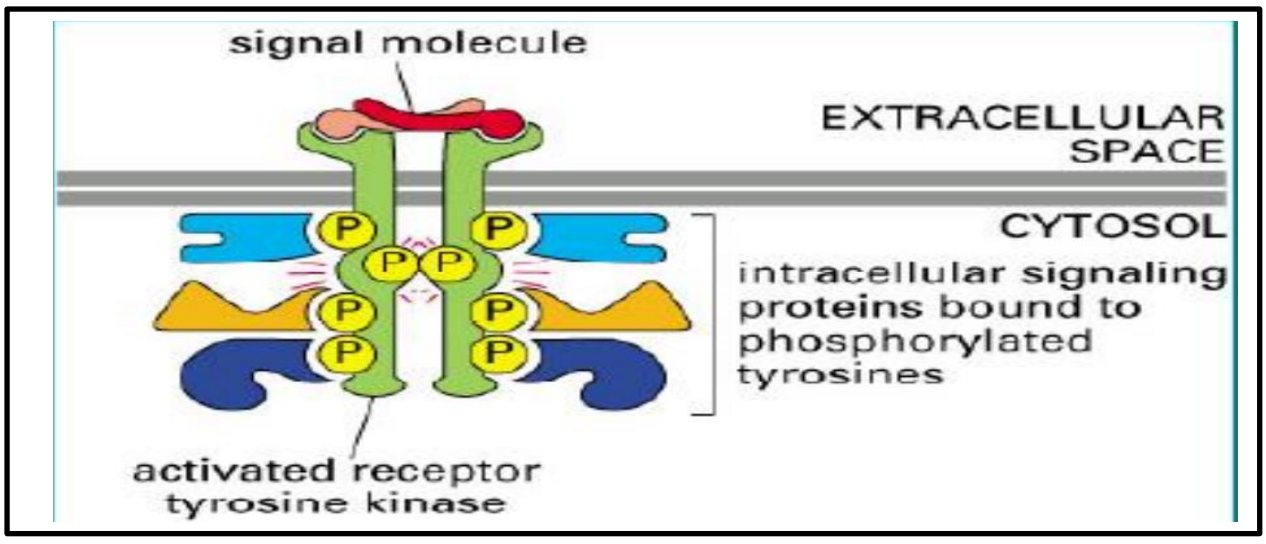
- ✓ **Example:** Some peptide hormone receptors and neurotransmitter receptors (e.g. **adrenergic** and **muscarinic** receptors) mediate their action on cells through G proteins.



➢ ***Enzyme-linked receptors:***

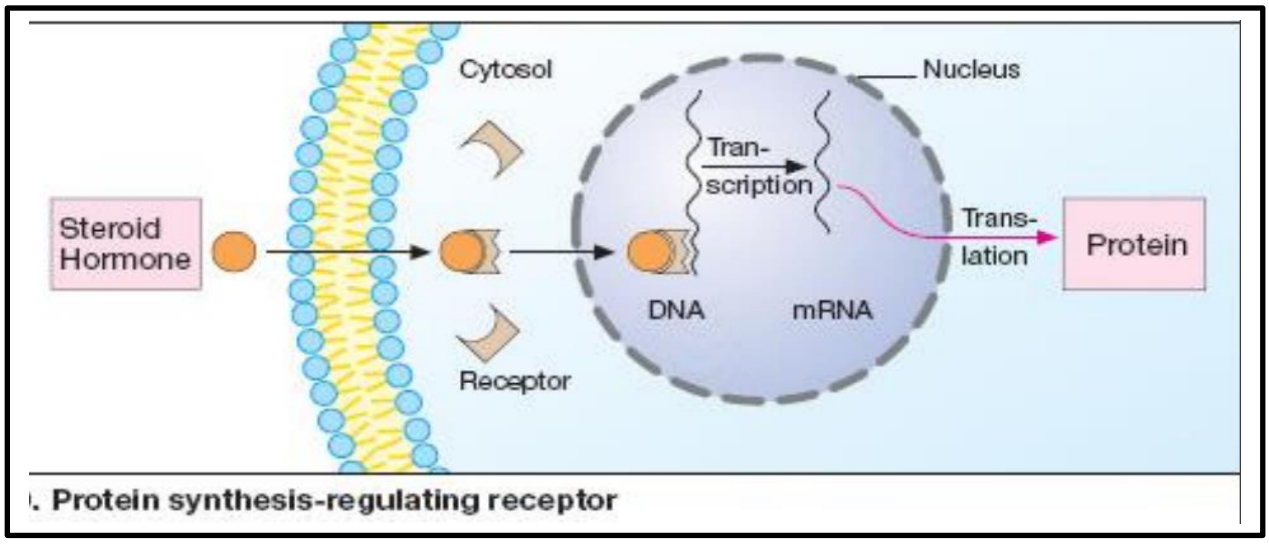


- ✓ Binding of the ligand to the extracellular domain activates or inhibits the related cytosolic enzyme.
- ✓ **Example:** The most common are receptors that have **tyrosine kinase activity** as part of their structure, in which ligand binding to the extracellular domain results in **phosphorylation** of **tyrosine residues** of specific proteins. Then, further signaling events take place, resulting in modification of an action inside the cell.
- ✓ (The addition of phosphate groups can modify the three-dimensional structure of the target protein, resulting in a molecular switch).



➢ ***Intracellular receptors:***

- ✓ A drug that targets such receptors must be **lipid-soluble** to cross the plasma membrane and enter the cell.
- ✓ **An example** of **endogenous ligands** for intracellular receptors: **Corticosteroids** like cortisone. They diffuse through the membrane.
- ✓ **Mechanism:** A hormone (e.g. steroid hormone) or drug diffuses through the cell membrane and binds to the intracellular receptor. The activated **ligand-receptor complex** is **translocated into the nucleus** and acts as a **transcription factor** that binds to **specific sequences of DNA**, modulating the expression of certain genes (activation or inhibition) → Changing levels of certain proteins in the body → increasing or decreasing a particular function (effect).



. Protein synthesis-regulating receptor

The End…Good Luck!