Doctor 021

PHARMACOLOGY

Sheet no. 5

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PHARMACODYNAMICS

Let's make a quick check-up for our course definitions:

-Pharmacology is the study of the biochemical and physiological aspects of the drug effects including absorption, distribution, metabolism, elimination (kinetics), toxicity and specific mechanism of action(dynamics).

--The main areas of pharmacology are:

-Pharmacokinetics حركيّة الدواء**: the way the body handle drug absorption, distribution, biotransformation, and excretion. (ADME)**

*what the body does to the drug, the effect of the body on the drug.

Ex: for headaches, we use PARACETAMOL (the scientific name for Panadol), we take a pill orally, and it will reach the stomach then the intestine where absorption takes place, then it goes to the liver to be metabolized and eliminated, reaching the circulation to be distributed to the tissues.

So **kinetics** is about: Distribution, metabolism (biotransformation), absorption, and elimination. **(ADME)**

The second area of pharmacology, which is our main topic for this sheet is :

-Pharmacodynamics فعّاليّة الدواء**: the study of the biochemical and physiological effect of the drugs and their mechanism of action.**

*the effect of the drug on the body, or what the drug does to the body.

We guess from 'dynamic' that this area studies the interaction between the drug (as an exogenous ligand) with the target(receptors, enzymes,…)to know what will happen at that molecular level to see the **therapeutic effect**, **pharmacologic effect**, and **adverse effect**.

-we conclude that the importance of studying pharmacodynamics is to know the mechanism of the interaction in addition to its effect on different body systems.

**Good news: some examples of drugs will be mentioned just for clarification not to memorize them, bad news: your memories from physiology and your pathology studying are needed somehow, but I will help you:)

Ex: COX is an enzyme that contributes to inflammation by producing prostaglandins that are responsible for pain, fever, and producing inflammatory cytokines which cause swelling, redness,…

To inhibit this enzyme "COX " we use some drugs such as :

- **Aspirin** is the prototype (father) of the nonsteroidal anti-inflammatory drug (NSAID) and is used to reduce pain, fever, and inflammation, and as an anticoagulant. مميّع

It is mainly used as an antiplatelet, however, some normal people take it to prevent coagulation.

- **Ibuprofen** is a pain killer (analgesic), and high fever reducer (antipyretic), also it has anti-inflammatory properties.

So it is used to inhibit cyclooxygenase (COX).

Notice that recognizing the mechanism of the drug helps in determining its therapeutic effect. **But** we mentioned previously that the drug has also **adverse effects**, so what is it for ibuprofen?

You have to take it after meals (على معدة مليانة), because it may cause peptic ulcer

Or irritation of the stomach.

WHY ???

To reduce the excessive acid secretions in the stomach, prostaglandins secrete more mucous and fewer acid secretions (NORMALLY)

So taking ibuprofen will inhibit prostaglandins, reducing the mucous and increasing the acid concentration, causing **peptic ulcer** (قرحة معدية)

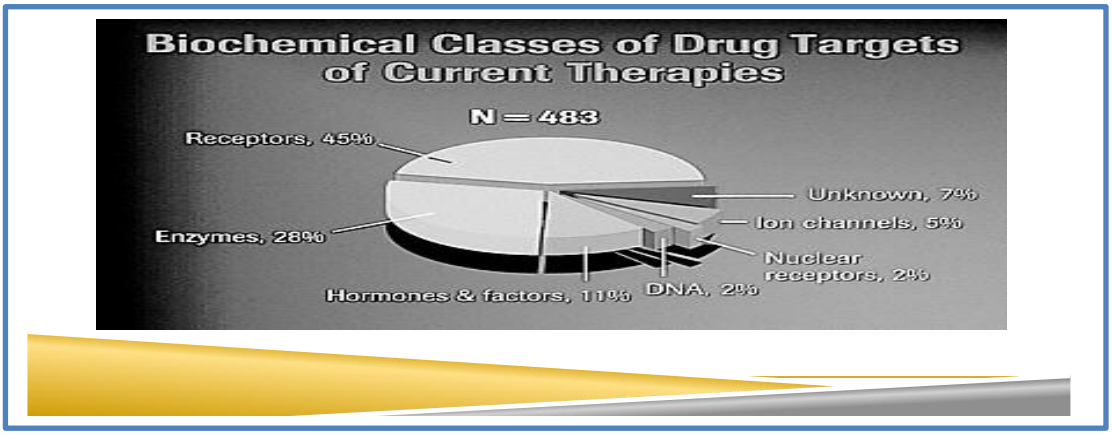
We can avoid this side effect either by eating before ingestion or using an alternative bioequivalent drug.

-Drug targets are usually receptors or enzymes. The drug needs to bind a sufficient number of target proteins at a reasonable dose, so the drug should be potent.

-pharmacodynamics: The study of the biochemical and physiological effect of the drugs and their mechanism of action.

-The study of the relationship of drug concentration to drug effects.

contemplate the chart !



The majority of drugs interact with the RECEPTORS(45 %), followed by interacting with enzymes(28%).

MECHANISM OF DRUG ACTION

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

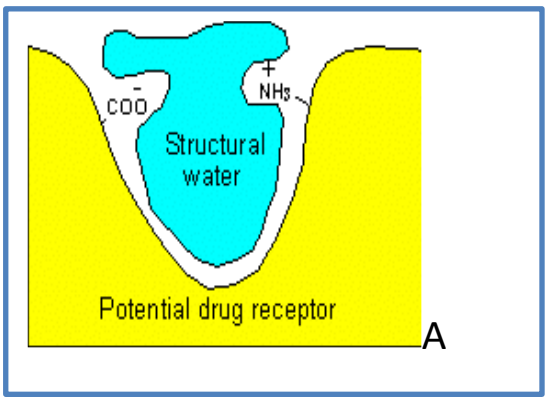
-The receptors will transduce the binding into a response by causing conformational changes or biochemical effects.

- Most of the receptors are found on the cell surface
- These receptors can bind with **endogenous** ligands (neurotransmitters and hormones) and **exogenous** (drugs).
- Receptors have specific shapes to fit the specific shapes of the drugs
- Receptors are excellent drug targets, they mediate a lot of signaling cascades toward components in the cells.

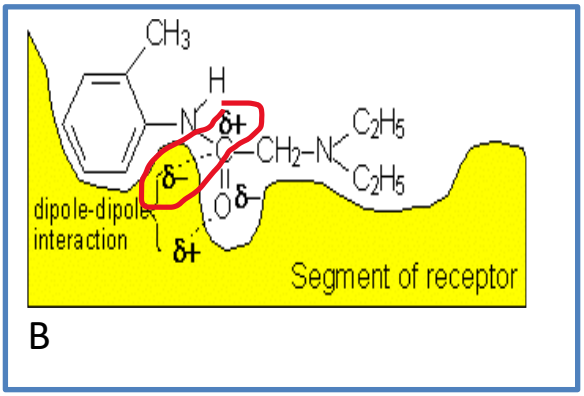
-Receptors are large macromolecules with a well-defined 3D shape.

-The two fundamental properties underlying specificity in drug-receptor interactions are complementarity of shape between drug and receptor, and the complementarity between the electrostatic, hydrophobic, and hydrogen bonding surfaces of each component.

LOCK AND KEY



A



B

Again, receptors and drugs have to have complementarity,

In **A**, they fit each other in the shape (actually it is water not drug)

THE SAME CONCEPT IS APPLIED ON B (interaction is made between the drug and receptor by +ve interacts with –ve)

*what does induce the interaction between the drug and receptor ?

The **Complementarity** in the shape between the ligand and the receptor.

*most of these receptors are found on the cell surface to transfer the message from outside the cell to the inside because most of the drugs can't enter the cell according to their physical properties, but some drugs are lipid soluble like steroids can enter the cell.

ALMOST DRUGS PATHWAY:

Binding to the receptor→inducing conformational changes→generating sequence of events→making the effect (activation or inhibition)

RECEPTORS

The characteristics that make the receptors excellent targets :

1. determine the specificity of drug action

Clarification: adrenaline (epinephrine) has lots of functions including increasing glucose in the bloodstream by different mechanisms, one of these is **Glycogenolysis** (breaking down the glycogen to glucose)

So when there is a stimulus that causes adrenaline secretion, adrenaline binds to its receptor, glucose percentage increases.

Epinephrine : it is secreted in fight and flight (by the sympathetic nervous system), causing muscle contraction, and bronchodilation,…

2. most are proteins

3. Most drugs bind reversibly (noncovalent):

The purpose is to bind the drug with the receptor for short time only milliseconds, inducing the effect and then dissociating allowing another drug or endogenous ligand to have the chance to bind.

Note: some molecules are considered endogenous ligand and are also used as a drug like adrenaline.

Although there are some exceptions of drugs that bind irreversibly.

4. Not all "drugs" use receptors(**it could interact with enzymes,…)**

CHARACTERISTICS OF DRUG-RECEPTOR INTERACTIONS

» Chemical Bond: ionic, hydrogen, hydrophobic, Van der Waals, (reversible, noncovalent binding) and covalent. (irreversible, nonpreferable)

*irreversible binding is unfavorable because we want the interaction to be for short time, to activate or inactive the receptors.

irreversible drugs have longer half-lives and more actions than reversible ones

Ex: histamine is an amino vasodilator that is used to treat allergic and inflammatory response when an antigen enters the body .

- If we want to encounter histamine effects (regarding its exaggerated adverse effects like swelling, congestion,..), we could use an **antihistamine**
- If an antihistamine was bound to the receptor irreversibly, histamine would be inhibited for a long time, and this will affect the normal inflammatory response.

Ex: a drug that irreversibly binds: esomeprazole (the scientific name for Nexium) is used to treat peptic ulcer, it binds to its receptor(pump) to reduce the acid secretion, it is given with accurate doses

To get rid of the drug effect, we have to completely get rid of the proteins (pumps) that are bound with, and that happens by regenerating new proteins which takes 1-2 days, and maybe longer.

» Saturable

» Competitive

Reversible binding is considered as competitive binding between the drug and the inhibitor (competitive for antagonism (inhibitor))

» Specific and Selective

» Structure-activity relationships

» Transduction mechanisms

RECEPTORS ARE EXCELLENT DRUG TARGETS

» Activated receptors directly, or indirectly, regulate cellular biochemical processes within and between cells to change cell function.

» Recognition sites are precise molecular regions of receptor macromolecules to which the ligand binds providing: (3 important terms, Google definitions)

1. **Specificity**: the characteristic of a binding site or receptor to be activated only by a single molecule or class of molecules

Ex : adrenergic receptors can bind **only** with adrenaline and its isomers , but Ach won't bind.

2. **Selectivity: is used to describe the ability of a drug to affect a particular gene, protein, signaling pathway, etc, in preference to others.**

Ex 1: there are subsets of enzymes: COX1, COX2

It was discovered that COX2 isn't found in the stomach, so they produce selective ibuprofen for COX2 **only**, preventing its adverse effects on the stomach.

Ex 2 : Subsets of receptors: adrenergic receptors : alpha (a1, a2) & beta (B1,B2,B3)

Let's discuss B1 and B2 specifically, both of them bind to adrenaline, but with different functions depending on their locations **HOW !!**

B1 is found in cardiac muscles and it increases the heart rate and contractility for fight and flight response.

B2 is found in the muscles of the bronchi, causes the relaxation of them (bronchodilation), so more O2 enters the lungs for fight and flight.

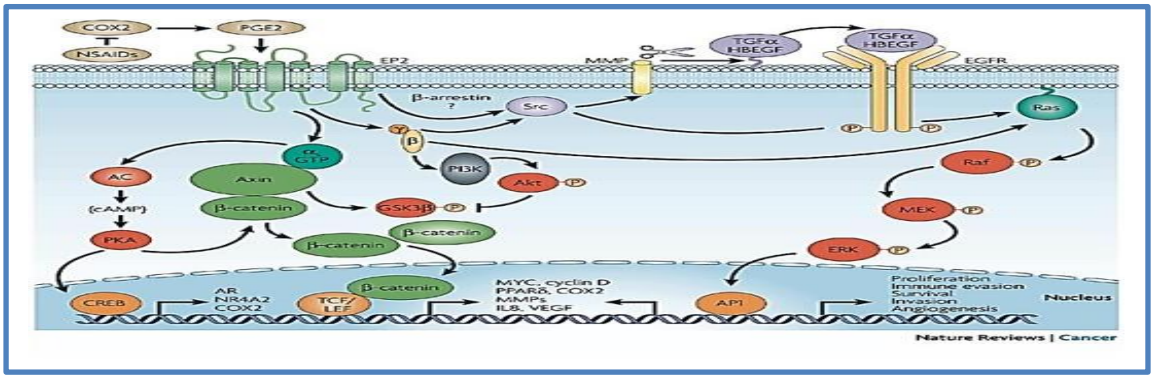
--Be aware to Use selective B2 drug for asthma without affecting heart functions.

**one drug causes both contraction and relaxation in different organs, it is selectivity guys😊

Scientists use this feature to make drugs

By forming a B1-blocker for cardiac diseases and a B2-agonist for treating asthma

agonist: activator, antagonist: inhibitor



See the figure above:

There are different signaling cascades, for example, there is an elevation in cAMP level to increase cardiac contractility.

While different subsets in another organ cause decreasing cAMP levels though relaxation.

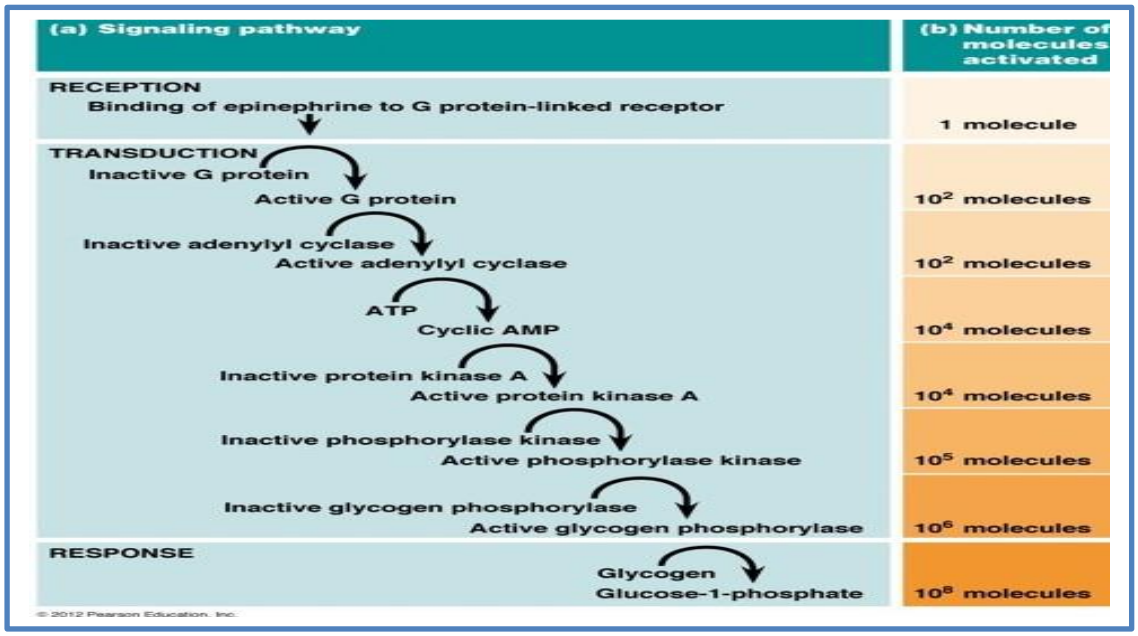
3. **Sensitivity : small amount of the drug will induce a large effect (signal amplification)**

Ex: G protein-coupled receptors (7 transmembrane proteins of 3 subunits types (alpha, beta , gamma) binds to epinephrine, activating 10^2 G-protein coupled receptors, activating adenylyl cyclase, producing cAMP.

*1 epinephrine → 10^4 cAMP→activating PKA→ activating phosphorylase kinase→ increasing products(10^8 conversions of Glycogen to Glu)

It is Noticeable amplification!

Ponder the figure, not for memorization:



Quick and unexpected note from the doctor :(

- Pharmacodynamics and -kinetics are 2 areas but they are never separated, they are completely intercalated they connect in distribution, reaching the target and giving interaction.
  SO ' ADME and drug-receptor interaction don't happen in sequence, but they all happen simultaneously, part of the drug is being distributed, and another part is being eliminated at the same time , … with a certain rate

MAJOR RECEPTOR FAMILIES

1. Ligand-gated ion channels

2. G protein-coupled receptors

3. Enzyme-linked receptors

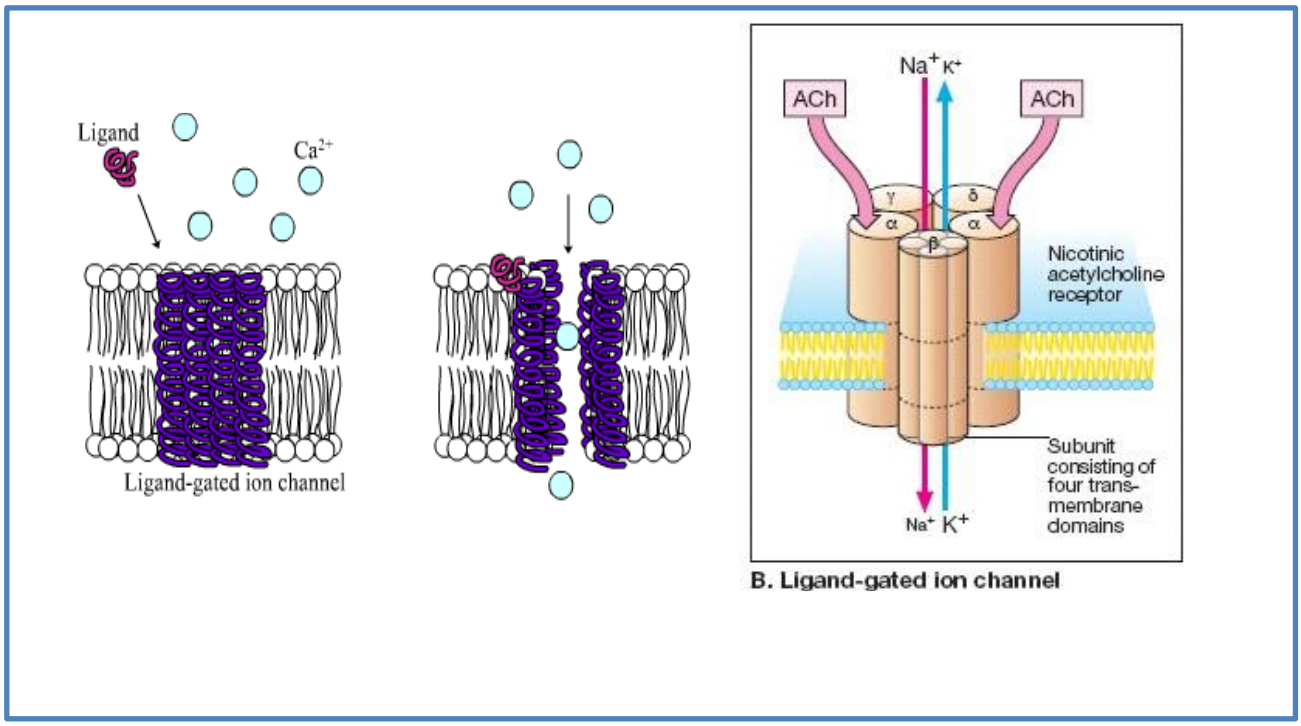
4. Intercellular receptors

LIGAND-GATED ION CHANNELS

- Responsible for regulation of the flow of ions channels across cell membranes.

- Regulated by binding of a ligand to the channels

- The best example is the nicotinic receptor, in which the binding of the acetylcholine results in sodium influx and the activation of contraction in skeletal muscle.



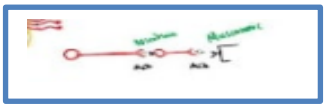
B. Ligand-gated ion channel

Ex: Ach is the main neurotransmitter in parasympathetic it binds with cholinergic receptors, which have 2 types **(**nicotinic and muscarinic receptors)

- When Ach binds to the nicotinic receptors, it causes Na+ influx and K+ efflux, this type of ligand-gated ion channel is found in the skeletal muscle end plate

Ach binding to the nicotinic receptor induces Na+ entry, causing depolarization, and activating Ca+2 channels to enter Ca+2, resulting in muscle contraction.

Tubocurarine drug is an inhibitor for this ligand-gated ion channel. When it binds to it, it will prevent Ach binding thus muscle relaxation what will happen.



PAST PAPERS

- Drug effects are thought to be proportional to the number of occupied receptors

A) true

B) false

Ans : A

- Major roles of receptors:

A) determine rate of drug elimination

B) determine drug action selectivity

C) provide a means of blocking drug action as well as mediating drug action

D) act as drug storage sites

E) b+c

Ans: e

Best wishes