pharma sheet (4)

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**Pharmacodynamics**

Is the study about how the drug works on the body and what it does to the body?

We will study about:

1. Drug receptors
2. Effect of the drug
3. Responses to drugs
4. Toxicity and adverse effects of drugs

**Mechanism of drug action**

#### Physical action

Drug produces its therapeutic activity because of its physical properties

الدواء ينتج فعاليته بسبب خصائصه الفيزيائية

**Ex:**

1. Amnnitol as diuretic that increase osmolarity
   so it will increase the water volume and increase the secretion of water outside the body, so it will decrease the pressure of patient

   اشعاعات ونظائر


**simple chemical reaction**

الدواء ينتج فعاليته بسبب تفاعل كيميائي بسيط

**Ex:**

Gastric antacids in the hyper acidity or in the gastric upset

By the chemical reaction between the acid inside the stomach and the basic drug compounds that reduces the acidity of the stomach.

مضادات الحموضة تعمل في المعده على معادلة الحموضه بسبب وجود القواعد منها

#### Receptors

The receptor: *main function* means to interact or to bind certain receptor or to oxidize or produce certain action in the body.
In general a receptor is a specialized target macromolecule mostly protein, present on the cell surface or intracellular, that binds a drug and mediates its pharmacological actions.

It can either be enzyme, nucleic acid or structural protein that will interact with drugs.

The receptors are inactive and when the drug interacts it will activate it and produce the action.

**Ligand:** is any molecule that binds to receptor and and can be a peptide or another small molecule like a neurotransmitter, hormone, or drug. Ligand binding changes its conformation (3D) shape during the interaction between the drug and receptor.

The compound or molecule that binds to the receptor (the ligand) that produces the action may be:

1. **Full agonist:** are able to activate the receptor and result in a maximal biological response. The natural endogenous ligand with greatest efficacy for a given receptor is by definition a full agonist (100% efficacy).

2. **Partial agonist:** do not activate receptors thoroughly, causing responses which are partial compared to those of full agonists (efficacy between 0 and 100%).

3. **Antagonist:** a compound that interacts to receptor and it will not produce any activity or any biochemical activity. This results in receptor blockage, inhibiting the binding of agonists and inverse agonists.

4. **Inverse agonist:** A drug with preferential affinity for $R_i$ (receptor active) actually will produce an effect opposite to that of an agonist.

Slide 6: There are many types of receptors

1. **Trans membrane ligand-gated ion channels:**
These receptors are present in the walls of ion channels in cell membranes. When activated by their specific agonist, they open these ion channels & lead to movement of ions across cell membrane. So it is need the drug to open and close according to it.

- These mediate diverse functions, including neurotransmission, cardiac conduction, and muscle contraction.
- Example: cholinergic nicotinic receptors

2. **Enzyme-linked receptors:**

It has a certain shape, certain type and binding site, binding to specific agonist and activation of these receptors usually lead to phosphorylation of tyrosine in intracellular domain which then acquires kinase activity, because this membrane receptor has an extra cellular site (they are specific agonist) and an intra-cytoplasmic domain which contains tyrosine and other amino acids.

You can imagine the binding between receptor and the drug like puzzle; The puzzle has certain shape it will bind in certain place and certain direction.

The receptor - drug binding ... according to the ancient theory about drugs and activity of drugs is the (key and lock theory) that means the receptor binding site is like the lock and the drug is like the key, so every key has the same lock to open or close.

**Example of the enzyme-linked receptors:**

Receptors for insulin, Receptors for growth factors like EGF or PDGF, Receptors for immune cytokines

When enzyme links to the receptor of insulin, receptor of hormone binds because of phosphorylation.

The idea of it the drug will bind to the receptor, and then the sequences of the reaction will happen.

This sequences of reaction will end in the critical* activity not only binding of receptor to the drug will produce the physiological activity.
Insulin binds to insulin receptor and that activates receptor tyrosine kinase activity in the intracellular domain of the beta-subunit of insulin receptor → tyrosine residue of the beta-subunit are auto-phosphorylated → receptor tyrosine kinase phosphorylates other proteins for example insulin receptor substrates (IRS) → activation of multiple signaling pathways → phosphorylated (activated) IRSs promote activation of other protein kinases and phosphatases, leading to biologic actions of insulin.

3. Transmembrane G protein–coupled receptors:

G-protein is the type of protein which has 7 layers within the membrane and it has adequate binding site, maybe an enzyme–bind receptor.

You should know that after the drug binds, in general the introgenious drug or hormone or transmitter bind with the pocket of the receptor, the activity will not be produced quickly, it will need a sequence of activity to achieve their (alpha-beta-gama) for the Gs protein.

When the drug binds to the receptor which will activate adenylyl cyclase to convert ATP to cAMP, then it will produce the activity.

After finishing the work they will feedback or return to beginning.

3. Intracellular receptors:

These receptors are located in cytoplasm (e.g. steroid receptors) or nucleus (receptors for thyroid hormones or vitamin D₃).

The specific agonist must cross cell membrane to the inside of cell to reach the cytoplasm or the nucleus to produce the physiological activity.
This is an example that the drug should enter the cytoplasm then activate certain compound to enter the nucleus, that means this is not superficial, this is inside the cell.

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After the drug reaches the receptor, there are many types of the drug-receptor bonding:

1. Covalent
2. Electrostatic
3. Hydrophobic

**Covalent bond**: very strong, that is rare to bond between the drug and receptor; when they bind covalently, the bond is irreversible, so the receptor will be lost.

*(18:40)* These covalent bonds only in anti-cancer drugs or in toxins such as the organic phosphate toxins, and in general the anti-cancer drug kills the cell because they bind to the receptor forever and irreversibly, it is rare to be in the drug or in the anti-cancer or to be in organic phosphate of the toxins.

**Electrostatic**: (19:10)

Common type of the intermolecular forces between ligand and receptor, it may be:

1. Hydrogen bond
2. Induced dipole like Van der Waals

- Hydrogen bond: (H-O) (H-N) (H-F) (H-H)
- Induced dipole: receptor non-polar + ligand non-polar attract to each other by induced dipole because after binding there will be transient dipole and there will be transient interaction, positive or negative interaction which is weak.

**Van der Waals forces**: van der Waals refers to the scientist that discovered this force. In general, there are few compared of this electrostatic with the covalent bond, these are weaker than covalent and reversible. Most common.

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**Hydrophobic interaction**: action between highly lipid-soluble drugs, is very important that means lipid or lipophilic, in general in the receptor there are many sites, if there is hydrophobic bond (lipid soluble) and the drugs are hydrophobic on lipid soluble group. They will attract to each other and then will produce activity. In general, this is very very weak interaction between receptor and drug, very very important, why?
Because it is very specific, this interaction will not appear until there is a certain distance between the drug and the receptor that means it will not produce or exist only for the specific drug on the receptor. This bond is weak alone but the mutability of these bond it will produce a strong bond because weak bonds require a very precise fit of the drug to its receptor if an interaction occur so this requires certain distance and certain conformation 3D shape to occur then hydrophobic will result.

**Slide 16 >> (22:10)**

After the drug interact with the receptor there’s a physiological activity produced, this physiological activity should be terminated to will be not to liver. ((in general how this activity will be terminated because if we need insulin to decrease blood sugar, if the insulin exist more than enough it will reduce the sugar level so we need for certain lipid and then to leave)).” doctors exact words that we couldn’t understand or correct”

How the activity will be terminated? By the dissociation of the drug receptor complex, sometimes after the drug had dissociated from the receptor the activity will continue.

Drugs that bind covalently to the receptor, the effect may persist until the drug-receptor complex is destroyed and new receptors are synthesized, there will not be used again that means the cell will be killed.

Many receptor-effectors systems incorporate desensitization mechanisms for preventing excessive activation when agonist molecules continue to be present for long periods that mean you have agonist and you have receptor but there is no physiological activity. Desensitization has many reasons why the receptor doesn’t respond for the same drug.

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In order to make rational therapeutic decisions, the prescriber must understand how drug-receptor interactions underlie

In general the main factor that determines therapeutic effect of certain drug is the dose; because the toxic dose or the lethal will kill the patient; toxicity will make adverse effects, therapeutic effect will produce activity or physiological activity.
In general the relationships between dose and response in patients and the nature and causes of variation in pharmacologic responsiveness that means how there is a variation? Sometimes we give the same drug with the same indication to 2 different patients there will be different responses, what the cause? Because there is a variation in the pharmacological responses, you should know why? 

The clinical implications of selectivity of drug action >> why we use this drug to that, you should know.

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The relationships of the dose to its activity or response are explained in two ways:

A. Graded dose–response relationships (individual):

Graded effect that means: the 5 ml-gram gives certain activity, the 10 ml-gram gives different activity the 20 ml-gram and so on >> that means as we increase the dose the activity will be increased for each person, as well as having a continuous and gradual response so as you increase the dose you will reach a better therapeutic effect within thin therapeutic range), after this it will be toxic if you exceeded the lethal dose.

B. Quantal dose–response relationships (population) describe an all-or-no response, either there’s a response or not.

Slide 19 >> (29 : 00 )

Graded dose–response relationships

The magnitude of the drug effect depends on the drug concentration at the receptor site, we agreed in the beginning that the concentration of the drug at the site of the action should be in a certain concentration to produce a certain physiological activity, less than this concentration there is no effect, more than that it will be toxic

Plotting the magnitude of the response in the Y-axis against increasing doses in the x-axis of a drug produces a graph, the graded dose–response curve.
Two important properties of drugs, can be determined by graded dose–response curves which are:

1. **Potency**
2. **Efficacy**

There is a difference between the potency and efficacy, they seem the same thing but there is a difference between their responses.

**Ec50:** “effective concentration 50%” is the concentration of the drug that produces a 50% response of the maximal response, this value that is used to compare any 2 drugs which has an effect.

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**Potency:** A measure of the amount of drug (in ml-gram) necessary to produce an effect of a given magnitude.

The concentration of drug producing an effect that is 50 percent of the maximum is used to determine potency and is commonly designated as the **Ec50**

Drug A is more potent than Drug B, because a lesser amount of Drug A is needed when compared to Drug B to obtain 50-percent effect.
Potency is affected by many factors:

Potency is so important for your drug; to determine what is the adequate amount of drug that produces therapeutic or physiological effect?

1. **Receptor concentration or density in tissue**, the two factors that affect the efficiency of the drug or activity and also the potency is two factor drug and the receptor, the amount or the number of the receptor determines how much the drug provided the more receptors the more the activity, less receptor the activity will be less.

2. **Efficiency of stimulus-response coupling** mechanism some of the actions are direct interaction between the drug and the receptor and some interaction will be in a sequence of stimulus other mechanism, maybe the interaction between the drug and receptor is good but the sequence is not efficient, so the efficiency of these stimulus response which consequence to the first binding of the drug and receptor is also important and will affect the amount of your drug that is needed to produce 50% effect.

3. **Affinity**: the strength of the interaction (binding) between a ligand and its receptor. Like lovo you have 2 pieces they will bind together, the other won’t be, this is called the affinity, that 3D shape of the receptor will bind to 3D shape of the drug**

   * if there is much more interaction there will be more affinity.

4. **Efficacy** : Potent drugs are those which elicit a response by binding to a critical number of a particular receptor type at **low concentrations (high affinity)** compared with other drugs acting on the same system and having lower affinity and thus requiring more drugs to bind to the same number of receptors.

   **potent drug**: little amount produces high activity or the 50% of EC.

   Why do we prefer to use the potent drug? We prefer the drug that has little dose to get us the same physiological activity of the other.

   As we increase the dose you increase the activity and also decrease the toxicity of your drug.
The efficacy:

- It is the ability of a drug to elicit a response when it interacts with a receptor.
- The maximum activity
- Is an ability to produce or not.
- Not all the drug will produce activity when they bind to the receptor, some will increase, decrease, and some will inhibit the activity.

Efficacy is depends on:

1. Number of drug–receptor complexes formed
2. The efficacy of the coupling of receptor activation to cellular responses.

- A drug with greater efficacy is more therapeutically beneficial than one that is more potent.
- Maximal efficacy (Emax) of a drug assumes that all receptors are occupied by the drug, and no increase in response will be observed if more drugs are added.
- The height of maximal response is used to measure maximal efficacy of agonist drug, and to compare efficacy of similar acting agonists.

In this figure: drug A and drug B have the same efficacy but differ in the potency while Drug C has a different potency and efficacy, so the drug A is the best drug.

Effect of drug concentration on receptor binding
You should distinguish between potency and efficacy and what is the factor effect of each one.

The quantitative relationship between drug concentration and receptor occupancy is expressed as follows:

Drug + Receptor $\leftrightarrow$ Drug–receptor complex $\rightarrow$ Biologic effect

- As the concentration of free drug increases, the ratio of the concentrations of bound receptors to total receptors approaches unity.

- In general you have many receptors the more drug you bring the more active sites will be reached, you can administer your drug in high dose but it won’t reach the same amount of active sites.

- As much as the active site concentration in the drug increases means you have many free drugs that can bind to the receptor after binding there will be biological activity.

- If the concentration is less, there will be less binding, less activity and no therapeutic effect.

- In general sometime they make the bound receptor / total receptors with the dose in ml-gram and the log dose give the sigmoidal shape (S shape) this determine that as you increase the concentration of your drug it will increase the number of the bound receptor.

**Slide 24 >> (45:25)**

*Concept of drug receptor binding & agonists*
A receptor can exist in at least two conformational states, active (Ra), and inactive (Ri). These states are in equilibrium, & the inactive state Ri predominates in absence of agonist drug, thus basal activity will be low or absent.

- If a drug that has a higher affinity for Ra than Ri is given, it will drive the equilibrium in favor of active state and thus activate more receptors.

- You have two choices … the active and inactive
  - if your drug chooses the active form it will produce activity (physiological activity) and it will be agonist.
  - if it chooses partially inactive it is partial agonist
  - if it chooses the inactive and active at the same equilibrium it will damage the activity.

- Such drug will be an agonist << the drug that use the active form of the receptor and bind it then produce the physiological activity.

- A full or strong agonist is sufficiently selective for the active conformation
  - if your agonist is full or pure agonists that means you choose only the active without using any inactive that means it won’t use any of more drugs in the inactive form.
  - that at a high concentration it will drive the receptors completely to the active state

- If a different but structurally similar compound binds to the same site on R but with only slightly or moderately greater affinity for Ra than for Ri, its effect will be less, even at high concentrations. Such a drug that has intermediate or low efficacy is referred to as a partial agonist

- If a drug binds with equal affinity to either conformation of receptor but doesn’t change the activation equilibrium, then it will act as a competitive antagonist.

- A drug with preferential affinity for Ri actually will produce an effect opposite to that of an agonist, and thus named inverse agonist. It further reduces the resting level and effect of receptor activity.