DOCTOR 2020 | JU

PHARMACOLOGY

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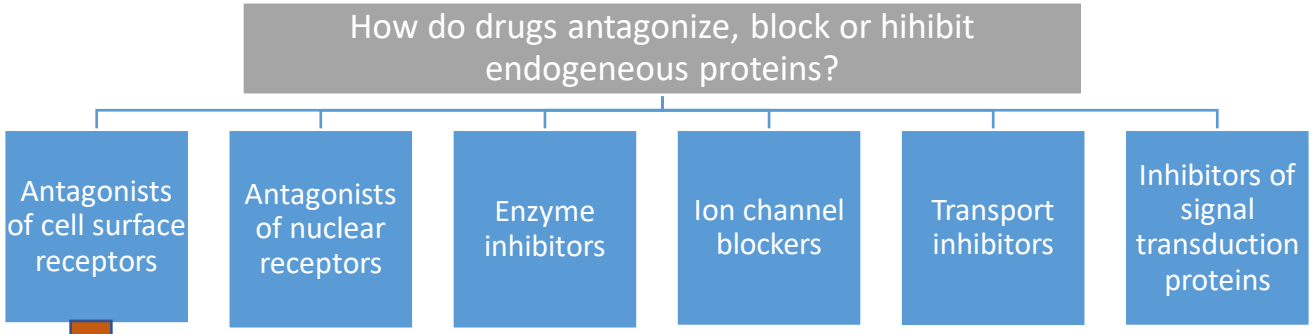


We talked about last lecture

Note: The doctor said we are not required to memorize the names of the drugs

Antagonists of Nuclear Receptors

Some important examples are:

- Mineralocorticoid Receptor Antagonists ⟶ it is called spironolactone (it is a diuretic مدر للبول). It works on an intracellular receptor called Mineralcorticoid.
- Remember that for intracellular receptor the drug needs to be able to diffuse through the plasma membrane, and this drug because it is a corticoid (it belongs to the family of steroids)it can pass through the plasma membrane and antagonize the effect of that receptor.
- **Mineralocorticoid Receptor Antagonist for edema due to liver cirrhosis and for heart failure.**

- Estrogen Receptor Antagonist ⟶ this drug is used for the treatment **(and prevention)** of breast cancer, it is called (Tamoxifen).

Enzyme Inhibitors

Examples: Ibuprofen ⟶ It is a drug that binds to an enzyme and inhibit the enzymatic activity.

Ex.1 It is a cyclooxygenase inhibitor, It is used for pain relief like aspirin & ibuprofen.

Ex.2 HMG-CoA Reductase Inhibitors ⟶ used for hypercholesterolemia (their group is called statin)

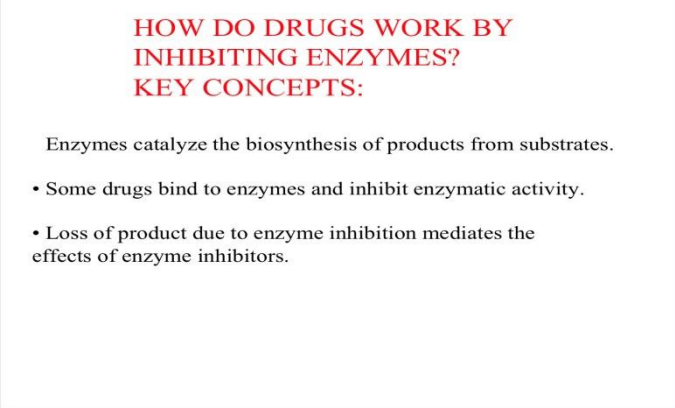
Statins are drugs that inhibit enzyme that is part of the synthesis of cholesterol in our body.

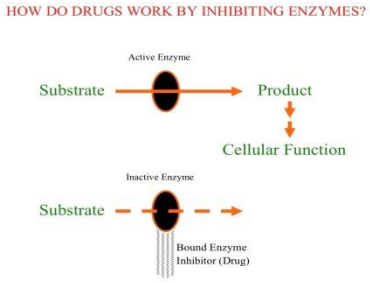
- So these drugs are used to lower the cholesterol levels in patients who have elevated cholesterol levels which is named hypercholesterolemia.
- **Ex; atorvastatin [Lipitor]; pravastatin [Pravachol].**

Ex.3 Angiotensin Converting Enzyme (ACE) Inhibitors ⟶ these are group of drugs that also target the Angiotensin but in this case they don't target the receptor, instead they target the enzyme that makes up Angiotensin II. (used in cardiovascular system)

- (Ex captopril [capoten]; ramipril [altace]) used for high blood pressure, heart failure, and chronic renal insufficiency.

Notice that they end with pril.





Ion Channel Blockers

Some important examples:

- Calcium Channel Blockers (CCBs) ⟶ used for cardiovascular conditions such as angains and high blood pressure (ex. Amlodipine, diltiazem)
- Sodium Channel Blockers ⟶ these are drugs that are used to suppress cardiac arrhythmias (ex. Lidocaine, amiodarone)

Transport Inhibitors

Transporters: are proteins that are used to transport certain molecules cross the GI track, blood brain barrier. Ex. Glucose transporter, and amino acid transporter.

Some important examples:

- Selective Serotonin Reuptake Inhibitor (SSRIs) ⟶ these are group of drugs used for the treatment of depression. **(fluoxetine [Prozac]; fluvoxamine [luvox])**
- Inhibitors of Na-2Cl-K Symporter (loop diuretics**) in renal epithelial cells to increase urine and sodium output for the treatment of edema.**
  Also, we have some diuretics that inhibit certain transporters in the kidney. (furosemide [Lasix]; bumetanide [bumex])used for edema or hypertension.

Inhibitors of Signal Transduction Proteins

These are from the newer drugs. Why????

Because not until recently we were able to identify these second messengers thst are present intracelllularly and to be able to target these.

Some important examples:

- Tyrosine Kinase Inhibitors for the treatment of chronic myelocytic leukemia (imatinib)⟶ these are antibodies that target this enzyme.
- Type 5 Phosphodiesterase Inhibitors ⟶ these are drugs that are used for the treatment of erectile dysfunction (sildenafil).

This is the major focus of drug development.

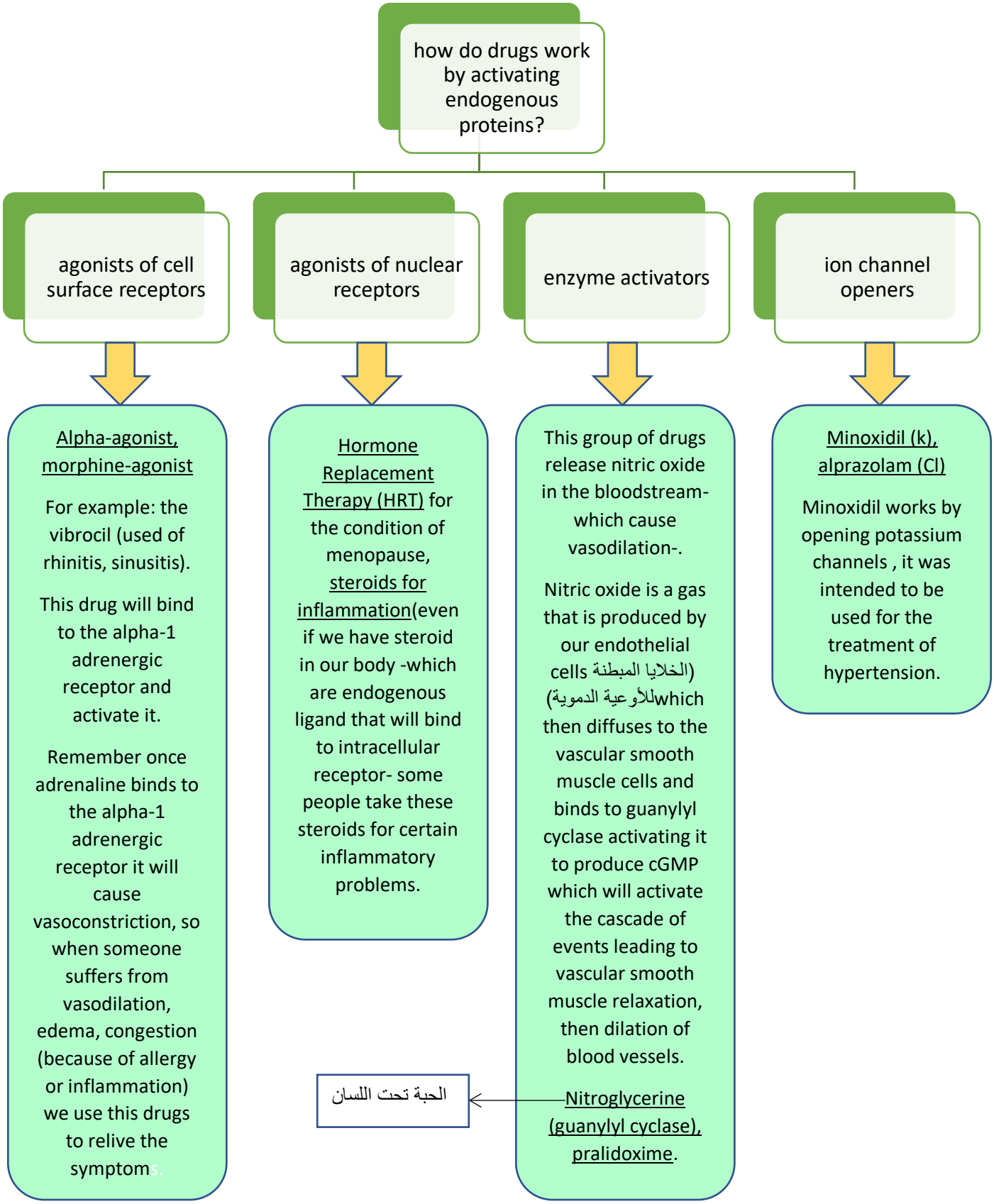
Nowadays, because we have technologies to be able to sequence the proteins in our bodies, we were able to identify these second messengers or small enzymes that are present inside the cell. Most of the drug discovery now start with the molecular target. So we start with these small proteins or enzymes (intracellular)

We develop the drug that can target this enzyme.

Remember:

Penicillin was discovered by coincidence, and we started with the drug then we saw what physiological effect we had. It kills microorganisms, so treats infection. And we needed about 30 years later to know about its mechanism which is preventing the cell wall synthesis of bacteria.

After talking about antagonist, but also there are some drugs that utilize the receptors to activate them.



HOW DO CHEMICALS WORK BY ACTIVATING CELL SURFACE RECEPTORS? KEY CONCEPTS:

•Cell surface receptors exist to transmit chemical signals from the outside to the inside of the cell.

• Some chemicals bind to cell surface receptors and trigger a response.

• Chemicals in this group are called receptor agonists.

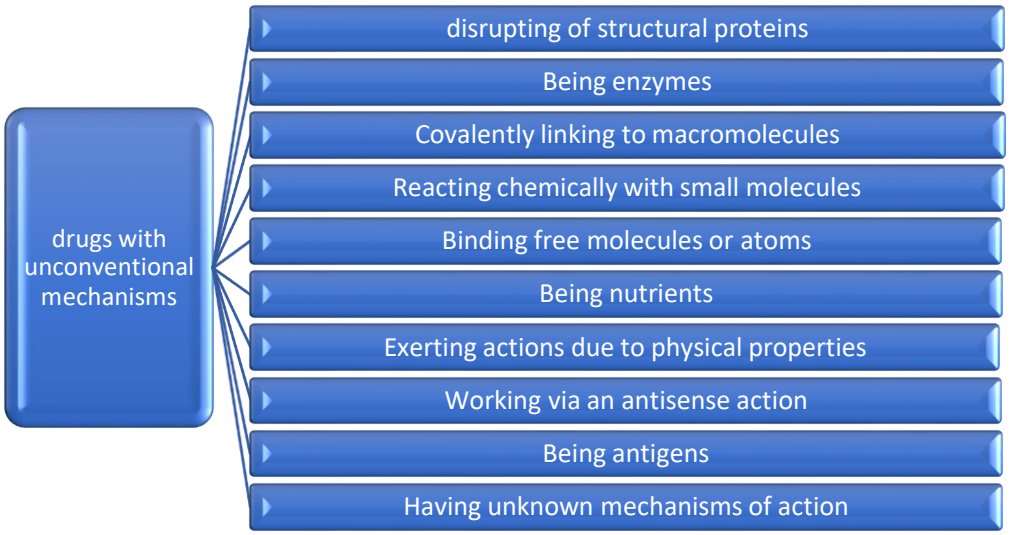
• Some agonists are actually the endogenous chemical signal, whereas other agonists mimic endogenous chemical signals.

They are either the endogenous ligand itself we give if from an extragenous source, or they are drugs thar mimic it and can bind in the same place and then activate that receptor.

ممكن استعمله كدواء agonistبعض ال
و الانسولين. steroidsزي ال

أو بعض اللأدوية مثل alpha-1 agonist
بيشبه شكل phenylephrineالي هو
الأدرينالين فبقدر يربط على alpha-1
receptor and activate it.

After we talked about the general way of drug working, now we will talk about some unconventional mechanisms



Disrupting of Structural Proteins

Some examples:

- Vinca alkaloids for cancer
- Colchicine for gout, this drug prevents the polymerization of a part of the cytoskeleton of the cell which is the Tubulin polymers into microtubules.

Microtubules are necessary for the inflammatory cell function (macrophage engulfing), so colchicine prevents the formation of these microtubules by disrupting the process of their synthesis.

So, we utilize them in the treatment of that inflammatory disorder (gout), and another potential use for it is for the treatment of cancer. How??????

Microtubules are also necessary in the division process of the cell because (remember: when the chromosomes are in the middle of the cell, the microtubules bind to these chromosomes to separate the different chromatid), so by disrupting that process of the formation of the microtubules, we can prevent the cell from dividing.

Colchicine is used as chemotherapeutic agent

Being Enzymes

Some drugs are enzymes by themselves. It might be taken from animal source (nowadays we take it by the use of recombinant DNA technology named streptokinase).

Streptokinase can be taken from bacteria that can make lysis for thrombi (clots), so we can use it for any condition where we have thrombotic event for thrombolysis, especially for stroke patients.

Covalently Linking to Macromolecules

Some of the chemotherapeutic agents can bind to the DNA and cause disruption of the structure of the DNA.

Ex. Cyclophosphamide **for cancer**

Reacting Chemically with small Molecules

These drugs are bases that interact chemically with the acid of my stomach.

(so it is just a reaction between base -my drug- which is called antacid and the HCl acid in my stomach producing salt and water.

Ex. **Antacids for increased acidity**

Binding Free Molecules or Atoms

- Some drugs we use them to attach with heavy metals especially in cases of poisoning and they help the body to excrete those heavy metals.

Ex. Metal poisoning, lithium poisoning

- Another group that are considered as new drugs are the monoclonal antibodies that can be used for certain inflammatory conditions or for autoimmune disease, they also combine to a certain molecule in the body like TNF (tumor necrosis factors).So I can give the patient extragenous antibodies which will bind to these factors that are found in our blood and then inhibits the inflammatory process. **Infliximab**

Being Nutrients

Someone who suffers from vitamin C deficiency I will give him vitamin C. So the drug is a supplement or a nutrient to fix a deficiency in the body.

Ex. Vitamins, minerals

Exerting Actions Due to Physical Properties

These drugs have physical properties help it for example in absorpting water like Laxatives ⟶ drugs used for the treatment of constipation. So it has a hygroscopic(محب للماء) physical property. It is like fibers which attach to water and make a big bulk in the intestine that will help the body get rid of the constipation.

Another ex. Mannitol (osmotic diuretic)

Working Via an Antisense Action

This is some of the antiviral drugs ex. Fomivirsen that can bind to the DNA or the RNA of the virus and prevent its transcription. So the target here is either a DNA or RNA.

Ex. Fomivirsen for CMV retininitis in AIDS

Being Antigens

Vaccines

Having Unknown Mechanisms of Action

Ex. General anesthetics, usually these are old drugs , we don't have a lot of alternatives to them and they are potentially save and their side effects are bearable

So we still use them even if we don't know how they work.

What are the characteristics of Drug- Receptor interactions??????

Very important characteristic

*Remember: we said that we want most of our drugs to be able to bind reversibly.

But at the same time some drugs bind with a different bond type like hydrogen, hydrophobic, or covalent(the irreversible inhibition) bonds.

*Saturable ⟶ it means that I have a limited number of receptors on the cell surface, once this number is all filled up with a drug **I reached the staturation**, so no matter how much more I increase the concentration of my drug or endogenous ligand I'm not gonna get more Drug-Receptor binding.

*Competitive ⟶ when it is reversible binding

*Specificity and selectivity ⟶ we talked about it in the last lecture

*Structure-activity relationships ⟶ the relationship between the shape of the drug -this is more related to designing certain drugs- and the activity of them.so sometimes the structure of the drug itself can dictate how much activity of the signaling cascade would I get,not only how much of that drug will bind with the receptor. (كمية الدواء الي بترتبط بال receptor عندي كم راح يصير بتحدد response) but also the structure of the drug itself sometimes it might affect how much this drug is able to activate.

*Transduction mechanisms

We talked about this slide last lecture

Receptors are an Excellent Drug Target

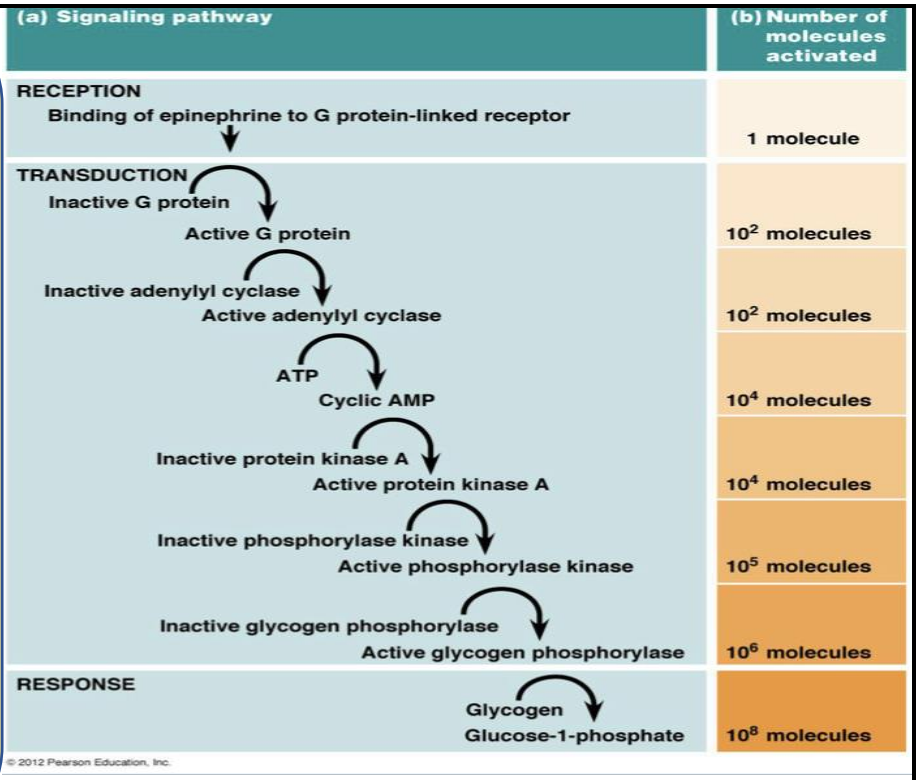
- Activated receptors directly, or indirectly, regulate cellular biochemical processes within and between cells to change cell function.
- Recognition sites are precise molecular regions of receptor macromolecules to which the ligand binds providing:
- Specificity
- Selectivity
- Sensitivity

Here we are going to explain the sensitivity of G protein coupled receptor:

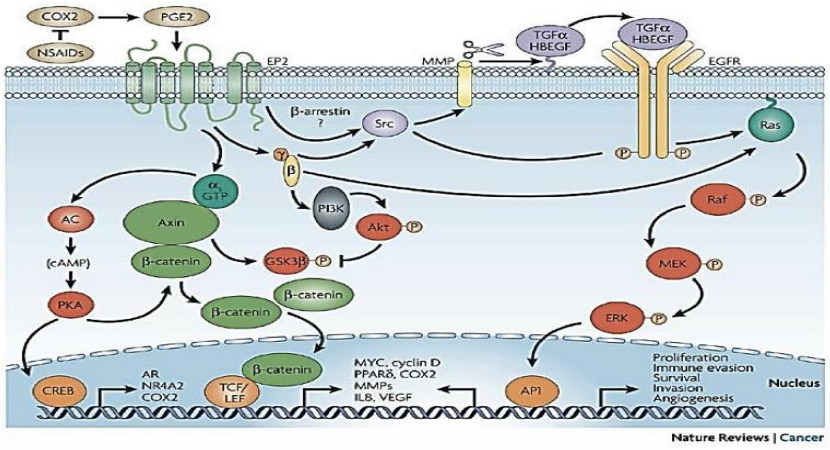
Sensitivity: it is related to the amplification of the signal

You can note here epinephrine (adrenaline)binding to a G protein coupled receptor, Note that one molecule of epinephrine can result in 100 molecules of active G protein resulting in activation of 100 molecule of Adenylyl cyclasem this gives me 10^4 (10000) molecule of cyclic AMP, activating another 10000 of protein kinase A.

So the net effect (all the amplification signals) 1 epinephrine gives me 10^8 molecules of the effect (here Glucose-1-phosphate).



This slide shows signal transduction cascade



How do we measure the relationship between the drug and the receptor and what does this relationship indicates????

Receptor Occupacy Theory (the Law of Mass Action)

» **Activation of membrane receptors and target cell responses is *proportional to the degree of receptor occupancy.***

» Assumptions:

- Association is limited by collision, orientation and energy
- All receptors are equally accessible مافي اشي مخفي
- All receptors are either free or bound, there is no "partial" binding
- Neither drug or receptor are altered by binding
- Binding is reversible

ما بغير شكل الروابط

In a muscular cell for example, it has a certain number of receptors (100) when the acetylcholine bind to it, if 1 acetylcholine binds to it I will get the response that is equivalent to 1, if 10 acetylcholine binds I will get the response that is equivalent to 10, if it bind to 100 so I have completely occupied all of these receptors I will get a response that is equivalent to 100. Now if I increase the acetylcholine concentration more and more I will not see more of a response.

But, if we go back before reaching the saturation, the relationship tells us that I increase the conc. of a drug I will increase the receptor complex formation leading me to get more of a response.

So activation of membrane receptor and target cell response (يعني عدد الactive receptors و الresponse الي بشوفها من هاي الخلية أو النسيج) is propotional to the degree of receptor occupancy.

First reaction: If a drug is gonna be bound to my receptor, we have formation of drug receptor complex.

Second reaction: Drug receptor complex will dissociate at a certain stage. Why???? Because we said that the binding is reversible (usually the bind stays for milliseconds).

The mathematic details are not required

Why are these important????

Because it give me important term named KD.

What is KD????

KD: dissociation constant, and this is the ratio of the equilibrium reaction.

KD determines how much affinity between my drug and that receptor, if there is a high affinity no quick rate breaking in bonds will occur and the drug receptor complex will stay for a longer period of time or a higher concentration.

» **This ratio is the equilibrium dissociation constant or KD**

» **This dissociation constant, Kd, indicates the strength of binding between R and D in terms of how strong that binding is.**

Drug-receptor binding

$$D + R \xrightarrow{k} DR$$
$$DR \xrightarrow{k^{-1}} D + R$$

$$\frac{k^{-1}}{k} = K_D$$
$$\frac{\text{sec}^{-1}}{M^{-1}\,\text{sec}^{-1}} = M$$

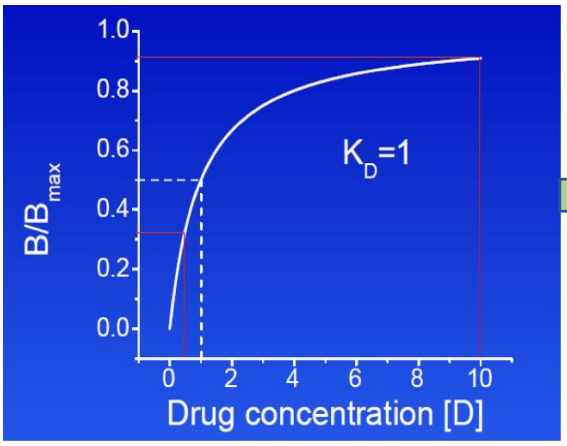
Hill-Langmuir equation

$$B/B_{max} = \frac{[D]}{[D]+K_D}$$

Bound Drug ← B/B_{max} ; $[D]$ → Drug ; K_D → affinity

Bmax: the maximum amount of drug bound to a receptor

Between the drug and the receptor



KD: concentration at which binding site is 50% occupied.

Affinity 1/Kd

KD mathematical definition: the concentration of the drug that will give me 50% of the maximum binding.

In an experiment we gave increasing concentration of the drug and we saw how much of these receptors gets occupied.

KD is reversely propotional to the affinity.

This is important to understand what is the relationship between KD and the response of the drugs.

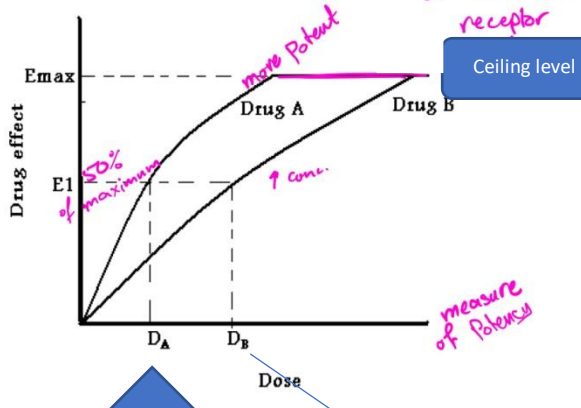
One important factor that determines KD is the concentration of the drug that is available and also the degree of affinity.

What does this dictate in relation to response?????

*if I have a drug receptor complex formed then I will have activating of signaling cascade, I will see a cellular response, so KD is also a measure of how much response I did.

Graduate dose-response curve

both working on the same receptor



Ceiling level

Drug A is more potent because I need less conc.

For drug B I need much more conc. to reach the same maximum response.

So, if we look again at the relationship between the drug dose and the response we gonna note it follows the same kinetics or dynamics .So, when we increase the dose of the drug we're gonna see more of the response, and this is again related to how much of the drug is bound to its receptor.

We give this the name as graduate dose response curve, so with increased doses of the drug we see more of the response.

Ex.I give more acetylcholine, so there is more contraction until I reach a plateu, So I'm giving more and more of acetylcholine but I'm not getting more contraction than a 100 for example. Why???? Because of the saturation.

The relationship between the affinity of the drug and the potency of the drug are very much related.

Potency: refers to the amount or concentration of drug required to produce a response. If I specified this response to 50% of the maximum response, in this case I refer to this as EC50 or ED50.

What do you mean by EC50 (ED50)?????

EC50 means effective concentration 50, we can define it as: the concentration of the drug that is giving me 50% of the maximum effect.

What can we define ED50????

ED50 is the dose of the drug that is giving me 50% of the maximum effect.

** ED50, EC50, KD all of them give me indication about the affinity of the drug and they are all measures of potency.

When we say about a drug potent if I needed a less concentration of it I can say this is more potent drug than if I have a drug that I need high concentration of it to give me the same effect.

**I don't have to give that high dose of the drug for me to see the therapeutic effect (I don't reach the maximum effect when using drugs).

In the figure above I can say that drug A is better than drug B because I need less concentration of A to reach E1 with is EC50 (ED50), with is the concentration I need to give me my particular therapeutic effect.(drug A is more potent than drug B)

E1 is enough to treat the problem that I have.

Potency is measured in the x axis while efficacy is measured in the y axis.

Ceiling level is determined by the maximum number of receptors that are being present on that tissue, also intrinsic activity of the drug.

Dose response relationships

» Graduate dose-response relations

As the dose administrated to single subject or isolated tissue is increased , the pharmacologic effect will also increase.

At a certain dose, the effect will reach a maximum level, which is called the ceiling effect or Emax.

Potency كفاءة الدواء

» Potency refers to the affinity of a drug for its receptor or the concentration of drug required to produce a given effect. Low KD, high potency

» • Potency refers to the amount or concentration of drug required to produce a response.

» • On dose-response curves potency is measured on the X-axis.

» • ED50, EC50, and Kd are measures of potency.

Some drugs have the ability to give me a response more than others.

Because they gonna be able to activate the signal transduction pathway more than other drug, and this is related to the intrinsic ability of that drug to activate the signal transduction cascade (it doesn't only depend on the maximum number of receptors).

When comparing about two drugs that work on the same receptor (same mechanism) ex. Morphine and codeine both are pain relievers and both work on the same receptor (morphine receptors), but the effect of the morphine is much higher that codeine because of the intrinsic ability to activate the receptor is higher than that of codeine.

ملاحظات:

الشيت شامل السلايدات وكلام الدكتورة لمحاضرة سكشن 7/3

الشيت طويل شوي لكن خفيف ان شاء الله

لا تنسونا بدعوة في ظهر الغيب

Good luck