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Pharmacology

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◉ Sheet ○ Slides

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Receptors

Most drugs are designed to work by binding to receptors, but why did we design most drugs to target receptors?

Receptors are easy to access, because most of them exist on cell membranes, so it's easy for the drug to reach them through the circulation.

Plus, to be able to bind to intracellular receptors, your drug needs to be more lipophilic to enter through the cell membrane.

Receptors mainly exists on cell membranes, and some exist intracellularly (inside cells).

Characteristics of Drug-Receptor Interactions:

1) the chemical bond:the best description of the bond between both receptors and drugs is to be easily breakable **(non-covalent)**, as drugs use our body receptors that have other substrates (we want the drug to bind to the receptor and do its effect and when its function is over to leave the receptor for other endogenous molecules to bind).

In some rare cases the drug will bind covalently to the receptor, so what will our body do to get rid of the drug effect?

Degrade the receptor by endocytosis and then recycling it,

OR

generate new receptors to replace the ones that are covalently bound.

So, in most cases our body will get rid of the drug and its effect as soon as the process is done. However, if the bond is covalent it will take more time for the body to get rid of it.

Extra information: endogenous molecules are molecules that originate from within the organism itself (our body creates it).

2) saturable: drug's binding to receptors is limited by the number of receptors in our body, so if we keep adding drug to the body, the effect will keep increasing until we saturate **(fill up)** all the receptors in our body, reaching the maximum drug effect. Adding more drug is useless because there are no more available receptors for binding.

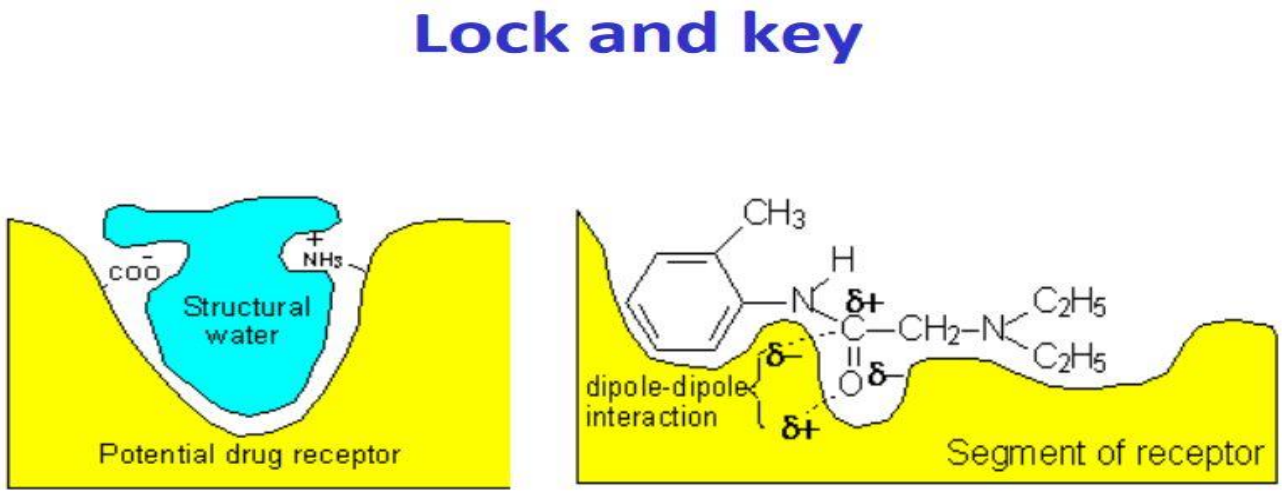
3) competitive: the drug will compete with endogenous molecules for binding.

E.g. the endogenous molecule for adrenergic receptors is **adrenaline**, and a drug was created that also binds to the adrenergic receptor, what will determine which one of those two molecules will bind to the receptor? They simply ***compete*** for it, meaning that if we have more drug than adrenaline, more drug will bind to the receptor and vice versa.

In the case of covalent bonding (irreversible), it is called **non-competitive,** because the endogenous molecule no longer competes with the drug over the receptor.

E.g. we made a drug that binds to adrenergic receptors covalently, in this case it doesn't matter how much adrenaline there is because the drug won't dissociate and allow adrenaline to bind.

4) specific and selective: specificity is that only molecules that are complement to that receptor **(fit perfectly)** bind to it, not any molecule will bind to the receptor.



Selectivity is that the effect of the drug depends on the receptor.

E.g. adrenergic receptors on **vascular** smooth muscles cause constriction of the vascular muscle (contraction of muscles). On the other hand, adrenergic receptors in our **lungs** cause bronchodilation (relaxation of muscles), even though both receptors are nearly identical, this is because the signaling pathway of the 2 receptors is **different**.

Extra information: **sensitivity is the effect that you get when a ligand binds to the receptor, and it differs between different receptors.**

E.g. binding of ligand A to receptor A will cause a stronger effect than binding of ligand B to receptor B, so we say receptor A is more sensitive than receptor B.

Sensitivity will be mentioned later in more details, but it's not required in this lecture.

5) structure-activity relationships: we already mentioned that ligands are specific for receptors, but in some cases changing the structure of the ligand a little bit can affect the activity of the receptor.

E.g. ligand A binds to receptor A with certain affinity, altering the structure of ligand A a little bit can increase the activity of the receptor **or** it can even reduce the receptors activity.

6) Transduction mechanism: each receptor has its own way of transducing a signal through its own pathway.

Now, what happens after the drug binds to the receptor?

1) antagonize receptors by binding to them without any effect.

2) activate receptors (Agonist).

Let's talk about the first case which is antagonizing the receptor, so basically the antagonist drug binds to the receptor without activating it (no response), so the drug is reducing the binding of endogenous agonists, how?

(when the drug is bound to the receptor no endogenous molecules can bind), so it did not inhibit the receptor, **all it did is reduce the binding ability of endogenous molecules to the receptor.**

Now, antagonist drugs can be **competitive or non-competitive**

- ✓ **Competitive**: It means that the drug binds to the same binding site as the endogenous molecule and competes with it for the binding site, and the determinant of the receptor's activity will be the concentration of both the drug and the endogenous agonist; if there is more drug, this means the receptor will be occupied most of the time with a ligand that does nothing (the drug), and as a result you get lower activity of the receptor.
- ✓ **Non-competitive:** there are 2 types of non-competitive antagonists, the first is when the drug binds on a regulatory site on the receptor (can be covalent or not) not allowing the receptor to bind to endogenous agonists, in this case the drug

doesn't compete with any other agonists, so increasing the concentration of agonists wont increase the activity of the receptor (in this case we call the drug an **allosteric inhibitor**)

The Second is when the drug binds irreversibly to the binding site, before it binds irreversibly the drug competes with other substrates for binding, but after this irreversible binding it doesn't matter how much endogenous agonists you have, it will not be able to bind to the receptor.

Antagonists bind to cell surface receptors most of the time, but sometimes they bind to nuclear receptors (in the cytoplasm), or even enzymes to inhibit them, or to ion channels to block them, or to different transporters to inhibit them, or some proteins to stop the signaling transduction, etc…

Now let's talk about drug agonists, they tend to act like endogenous agonists, by binding to the receptor and activating it, so the more drug agonists you have the more effect you get until you saturate all your receptors, that's when adding more drug will be useless.

So, what do agonists bind to?

1) Agonists mostly target cell surface receptors E.g. alpha-agonists, morphine agonists.

2) They can also target nuclear receptors inside the cytoplasm E.g. HRT for menopause, steroids for inflammation.

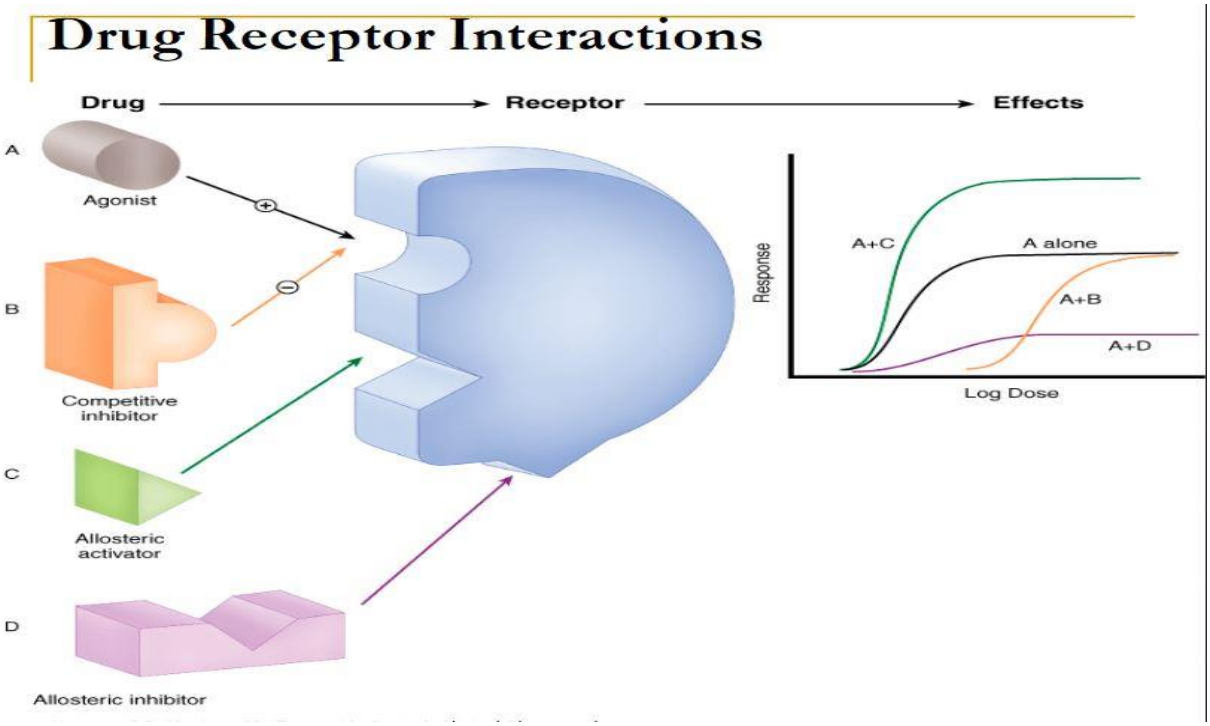
3) Another target for agonists is enzymes E.g. nitroglycerine (guanylyl cyclase), pralidoxime.

Nitroglycerine is a drug that binds to guanylyl cyclase activating it, increasing the concentration of **cGMP**, then cGMP will bind to certain channels that eventually cause relaxation of smooth muscles of vascular tissues (that cause vasodilation), which will increase blood flow to the heart, **curing angina.**

Pralidoxime is given when you have Sarin gas poisoning, Sarin gas inhibits **acetylcholinesterase**, inhibiting the breakdown of acetylcholine, leading to acetylcholine accumulation (over activation),and this leads to over contractions of muscles, which will cause paralysis of the muscles (paralysis of the respiratory muscles is the main reason of death), because the muscle will get tired eventually, so what pralidoxime does is that it reduces the energy required to destroy the covalent bond

that the Sarin gas forms **(pralidoxime reactivates the enzyme cholinesterase by cleaving the phosphate-ester bond formed between the organophosphate and acetylcholinesterase).**

4)the last target is ion channel (opening it) E.g. minoxidil (K) and alprazolam (Cl)



So, how do drugs work in unconventional ways (not by binding to receptors)?

1) Disturbing of structural proteins E.g. vinca alkaloids, colchicine for gout

Vinca alkaloids work by destroying microtubules that are important for mitosis, this will not allow cancer cells to divide.

Colchicine is used to cure gout, gout is simply the accumulation of crystals in joints, which will cause inflammations in joints, so what colchicine does is disrupting microtubules that are important for macrophage movement, so less leukocytes will get to the site of crystals, which will reduce inflammation.

2) some drugs act as enzyme themselves E.g. streptokinase for thrombolysis

3) Covalently linking to macromolecules E.g. cyclophosphamide for cancer.

Cyclophosphamide will link covalently to cancer cells DNA killing the cancer cell.

4) Reacting Chemically with Small Molecules E.g. antacids for increased acidity

Antacids are bases such as calcium carbonate or magnesium carbonate which reacts with stomach's HCL, reducing the acidity of the stomach.

5) binding of free molecules or atoms E.g. drugs for heavy metal poisoning, infliximab (anti-TNF).

Anti-TNF is an anti-inflammatory drug.

6) being nutrients E.g. vitamins, minerals.

7) Exerting Actions Due to Physical Properties E.g. mannitol (osmotic diuretic), laxatives

8) Working Via an Antisense Action E.g. formivores for CMV retinitis in AIDS

9) being antigens E.g. Vaccines

Vaccines are a weakened form of microbes, resembled by their antigens (but they're diluted and weakened so they don't cause the disease) and are given to the patient (usually by injection) to build a better immunity for that certain disease so it can fight it better the next time the cell faces it.

10) Having unknown mechanism of action E.g. general anesthetics

We know that general anesthesia works, but not how it works.

Good luck all, I hope I made everything clear, some things are clarified by me because the doctor didn't mention anything about them, don't hesitate to ask, Have a nice Day.