Medical Committee
The University of Jordan

PHARMACOLOGY

Lecture No.: 11

Doctor Name: Malek Zihlif

Written By: Muhannad Haddadin

SHEET ■

SLIDES □

DONE BY: ISSA KHASHAN

PHARMACODYNAMICS

We ended our previous lecture by talking about enhancement of drug effects and we said there are 3 important enhancement methods:

1- Additive Drug Effect: occurs when 2 drugs with the same effect are taken together, they will produce an effect that equals the sum of the effects of the 2 drugs.

Example: an antihypertensive drug reduces BP by 10 and another drug reduces it by 30, when they are taken together they will reduce the BP by 40.

2- Synergic Drug Effect: when 2 drugs with the same effect are given together, they will produce an effect that is greater in magnitude than the sum of their effects if given individually.

Back to the previous example: the sum of the 2 antihypertensive drugs in case of synergy will be greater than 40, 50 for example (greater than the sum of both drug effects).
-Synergic drug effect is widely used in clinical practice for treatment

3- Potentiated Drug Effect: occurs when a drug has weakness in its effect (not working and not giving the desired therapeutic effect), we combine it with another drug of no effect (zero effect) to increase its activity.

Example: in order to raise the concentration of dopamine in the brain and prevent dopamine metabolism in the peripherals of the body, we give an anti-metabolizing enzyme.

-The Dynamic State of The Receptors:

-Do we really develop tolerance toward drug effects?

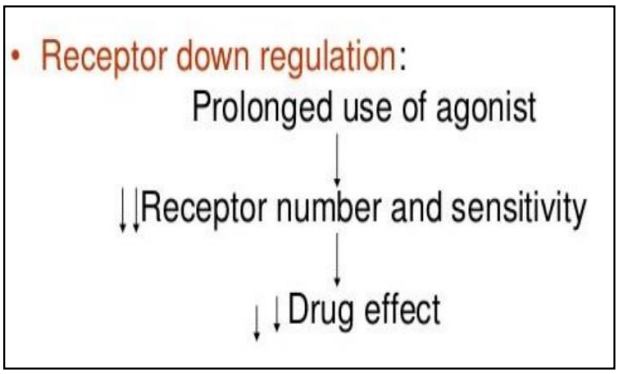
The answer is yes and no; most of the drugs that we use do not really result in tolerance (tolerance means decreasing the effect of the drug with time or with chronic use of the drug).With some drugs, there is a dynamic situation for the receptors, some of the receptors will respond to continuous inhibition and activation according to the effect we have introduced.

Receptors are in a dynamic state, what does that mean? It means that receptors can increase or decrease their numbers. Actually, our cells are in a dynamic situation and according to the condition/situation we live in, we adapt to the environment we live in. for example the protein expression/ protein levels in our cells changes according to the situation/conditions, say we have 30000 proteins in our cells, not all of them will be expressed in cells depending on the needs of the cell and the conditions, this is called adaptation not evolution. When we introduce a drug that binds to a certain receptor and keeps it activated or deactivated, the body will respond to this new condition (not in all types of drugs but certain types).

The affinity to the response to drugs is not fixed (sometimes it'll be changed); it alters according to the situation.

-Prolonged Use of Agonist:

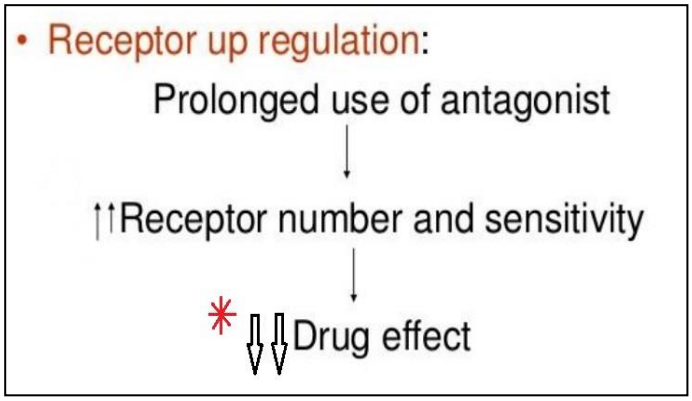
Receptors may regulate themselves down by prolonged use of agonist, the body will respond in the opposite direction; if we use an agonist, the body will reduce the number of the receptors. Simple? Very simple… (You attack the body by the drug; the body will try to defend itself by inhibiting or down regulating the receptors), after the number of the receptors decreases (and their sensitivity as well), the effect of the drug will be reduced, this is called tolerance.



Ex: Chronic use of salbutamol down regulates B2 adrenergic receptors. (Salbutamol: Common brand name: Ventolin, used for Asthma treatment). Chronic means more than usual, more than 6 months. Asthma is a chronic disease and when using sulbutamol for a long time, receptors (B2) will be down regulated. Why do we want to introduce B2 agonism? B2 agonism causes bronchodilation, but continuous use of the drug produces down regulation and in this situation you have to change your drug. As a result, efficacy and potency both change due to changing the drug, (mainly we refer to the efficacy). (*Note: Adrenaline affects B1 receptors)

-Prolonged Use of Antagonist:

Receptor up regulation is caused by prolonged use of antagonists; this prolonged use of antagonists increases the number and sensitivity of receptors and decreases the drug effect. When using an antagonist, the body responds to this by increasing the number and the sensitivity of the receptors towards the endogenous material. If you suddenly stop using the drug, there are lots of receptors to bind to the endogenous ligand, in this case the ligand will cause toxicity because the number of the receptors was too high.



Ex: Propranolol is stopped after prolong use, produces withdrawal symptoms, rise in blood pressure, induces angina. Using Propranolol -which is a stage drug; B1 antagonist- for a long time will cause the body to increase the receptors, simple?

When you stop Propranolol suddenly, the binding between adrenaline (the endogenous material) and these receptors will be exaggerated (with high affinity; avidly).

*__**Note**__: in the slide which is talking about "receptor up regulation" the arrows are going upwards (drug effect) but the doctor said that this is __wrong__, they should be downwards, make sure to correct them in the slide.

-Using an agonist →the body decreases the number and the sensitivity of receptors.
-Using an antagonist →the body increases the number and the sensitivity of receptors.
This is called Dynamic of The Receptors

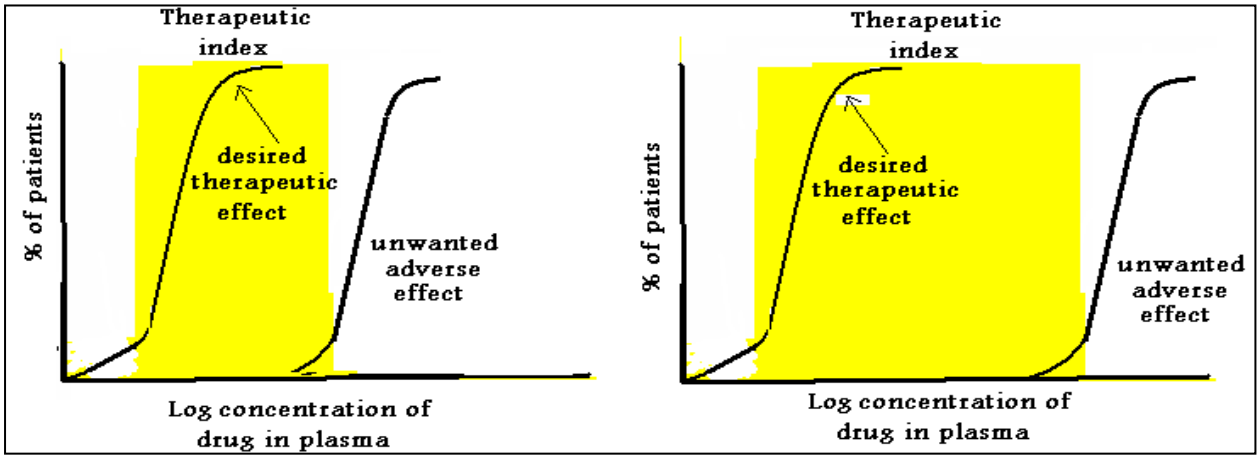
This does not apply to all drugs; just certain drugs undergo the previous condition. For example Hypnotics, they should not be used more than 2-3 weeks, after this they'll have no effect, if you want them to be effective you have to increase the dose. When using Hypnotics for more than 2 weeks, for example in the 3rd or the 4th week, they'll have no effect, so the patient will increase the dose by himself, developing tolerance after each dose change (increase), ending up with something called physical dependence. Tolerance produces either toxicity or dependence.

-Remember: Receptors are not stable, they're in a dynamic situation, they change their numbers according to the condition they face.

-Therapeutic Index/ Margin of Safety (window):

Therapeutic index or therapeutic window gives you an idea about how toxic or safe a drug is, if the window was too big that means the drug is very safe, if the window was too small, the drug is not safe, which window are we talking about? The window is the area between the therapeutic effect and the toxic effect. By increasing the dose, the therapeutic effect increases and at the same time the adverse effect also increases, the window describes how much the toxic curve is far from the therapeutic one. For some drugs, the curves are very close; for other drugs, the area between the 2 curves is very wide (here we're talking about the window).

Why do we use narrow therapeutic index drugs? Why do we have to risk our patients with these drugs? Because we have no other option, this is the only drug to treat the patient with, for example in case of heart failure; digoxin is the only drug that can treat heart failure.



-How to calculate the index (window)?

ED50 (effective dose 50): -similar to EC50- it measures the potency, what is the dose that will produce an activity in 50% of the population taking this drug.

TD50 means: what is the dose that produces toxicity in half of the population taking this drug. (You measure the adverse effect through the population, not through the receptor and the action, we'll come to this later).

When dividing TD50 over ED50 (TD50/ED50) you will have the therapeutic index, and this index is an indication of how much the drug is safe. If the therapeutic index is small (the window is small), then the drug is very toxic. If it was wide, then your drug is safe. When TD50 is too high, over ED50 which is small, that will give you a large number (wide index) that means it's a safe drug. If TD50 is small (toxicity is small, happens because of a small dose) which is close to ED50 (therapeutic dose) that means the drug is toxic.

When you compare digoxin with carbamazapine, you find that digoxin is measured in nanograms (10^-9) whereas carbamazapine is measured in micrograms (10^-6), so digoxin is more toxic. Every drug has a certain therapeutic index, the smaller the index the more toxic the drug is.

- Cyclosporine – 100-400ng/ml
- Carbamazapine- 4-10µg/ml
- Digoxin- 0.8-2ng/ml
- Phenotoin – 10-20µg/ml
- Qunindine- 2-6µg/ml

*Note: all these drugs are toxic; they have narrow therapeutic index (that means the toxicity is very close to the effectiveness). Notice the numbers, micro and nano grams, they're very toxic. So they should be measured in patients before administering any extra doses, but we don't worry about drugs with wide therapeutic index as much.

*Note: the numbers beside the names of the drugs are TD50 values (dose) and not the therapeutic index values, the index values have no units.

Panadol is a safe drug for example, another example is penicillin (amoxicillin) – antibiotic-, you can take many doses of this drug and nothing happens, why? Because the therapeutic index is very wide, it's simple. Hypnotics have two types: one type is valium (but it's not used as a hypnotic) and another type called Barbiturate. If someone took 10 tablets of valium, he can go to hospital and do stomach washing, but if he took just one extra tablet of Barbiturate he will die. Although these two drugs work on the same receptor.

**adverse effects are produced by different receptors, not the receptor the drug binds to produce the therapeutic effect.

-Drug-drug interactions:

When 2 drugs are taken together, there is a possibility for interactions between these 2 drugs to cause unwanted effects, usually an increase or a decrease in the desired therapeutic effect.

Where do drug-drug interactions happen? Interactions between drugs can occur in the following sites:

1- **At the site of absorption:** you take the drug, it goes to the duodenum, it has to be absorbed to go through the first pass metabolism or through the blood stream. At the site of absorption there might be drug-drug interactions.

Example1:
Tetracycline is not absorbed from the GI tract if calcium product is present in the stomach (it's an example on chemical antagonism). Calcium products bind to tetracycline to prevent its absorption.

Example2:

In the GI tract, mostly in the duodenum, there's a pump called p-glycoprotein (a product of MDR1 gene) it's in a dynamic state (it can be inhibited or induced by drugs). P-glycoprotein is the first line of defense in the GI tract against undesired or toxic materials like excess drugs; it prevents the GI tract from over absorption by pumping a portion of the drug out. This is taken into consideration when administering doses for patients, say you give a dose of 50mg, 10mg will be pumped out and 40mg will be absorbed and reach the circulation and that will affect the bioavailability of the drug.

If the p-glycoprotein pump is induced/ up regulated by another drug, more of the original needed drug will be pumped out and less will reach the stomach and the circulation, and so the drug may lose its therapeutic effect.

If the p-glycoprotein pump is inhibited by another drug, the absorption of the needed drug will increase in the GI tract; more drug will reach the circulation and may cause toxicity.

2- During biotransformation:

Drug metabolism (quick revision): drug metabolism has 2 phases; phase 1 which mostly depends on CYP 450. Phase 2 depends on different enzymes and those enzymes mostly add something to the drug. In some cases phase 1 is not enough to change the drug from lipophilic to lipophobic in order for the drug to be excreted in the urine, if it's not enough using phase 1 which is mostly dependant on CYP 450 isoenzymes, we have to go through phase 2 which depends on glucuronidation for example (adding a glucuronic acid because it has some polarity) so when adding a polar group to a drug, the drug's lipophobicity increases (or its hydrophilicity increases, it has the same meaning). Phase 2 depends on different types of enzymes; it's mainly needed because phase 1 may not be enough so something polar should be added to the drug whatever it is to make the drug polar enough to be excreted through the urine.

How can drug-drug interactions happen at metabolizing enzyme level?
Again, these enzymes are in a dynamic state, for example the 1st drug is metabolized by CYP2D6, the 2nd drug -your patient is taking- inhibits the CYP2D6, so drug metabolism changes (decreases). The amount of this drug in patient's body increases and with frequent doses, toxicity occurs (with accumulation) and vice versa, if the 2nd drug enhances the metabolism of the 1st drug, then the 1st drug will be under the therapeutic level.

**Note: phase 2 is required for just 10% or less of the drugs we take, 90% of the drugs will be metabolized mostly be CYP 450 but CYP 450 are inducible and it's a problem.
Drug metabolism rate (level) varies among individuals; if 4 people took the same drug their drug metabolism levels will be different because everyone has different levels of CYP 450.
So metabolizing enzymes are important (they determine the amount of active and inactive drug), when induced, they increase the drug metabolism, when inhibited, they decrease the drug metabolism, and that affects our steady state. Nice? Very nice.

3- At the site of action (drug antagonism):

Drug A binds to this receptor and drug B also binds to this receptor, either reversibly or irreversibly, antagonism happens between them (drug-drug interactions or physiological antagonism or chemical antagonism but mostly at the site of action we refer to the pharmacological antagonism and it may have physiological antagonism).

4- During excretion:

In nephrons (tubules) in the loop of Henle, there are pumps to excrete our drugs or to reabsorb them but mostly excretion. Digoxin and quinidine are both excreted from the same sites in the kidney. The quinidine will be excreted first because it is more competitive for these sites, resulting in increased serum levels of digoxin. A patient has heart failure, he takes digoxin. During heart failure there's something called Arrhythmia, we give the patient quinidine, but he already took digoxin. Quinidine inhibits digoxin excretion; remember that digoxin has a narrow therapeutic index so toxicity may occur. Drug-drug interactions are seen obviously with narrow therapeutic index drugs (because side effects for narrow therapeutic index drugs are more significant and obvious).

5- During distribution:

Free drug (unbounded drug) is active drug. Bound drug is inactive drug. By increasing the free drug you produce more effect and sometimes more side effects. If a drug is carried by Albumin for example, and another drug competes with it, then the amount of the free drug increases, and when dealing with narrow therapeutic index drugs, toxicity happens. Another example: aspirin competes with methotrexate (a drug for cancer) for protein binding sites, and because aspirine is more competitive for the sites, it results in increased release of methotrexate and so increase toxicity to tissues. Toxicity of methotrexate causes GI tract problems.

-Adverse Effects:

are undesired effects that may be unpleasant or even dangerous.

Why do we have side effects? Reasons:

1. **The drug may have other effects on the body beside the therapeutic effect:** because the receptor the drug binds to may have different effects (other than the therapeutic), in normal cases you give a drug and expect only one effect, but this receptor has many effects, this is according to the tissues (tissue specific activity); a receptor in brain cells may have a different effect from the same receptor that is found in lymphocytes for example, (cells in the body are very different, where do these differences come from despite all cells having the exact same DNA? What's different is the level of proteins and their function) the drug doesn't differentiate between receptors that are found in brain and the same receptors which are found for ex in the stomach. So production of other effects on the body besides the therapeutic effect happens because the receptors have different effects depending on what tissue they're found in.

2. **The patient is sensitive to the drug:** some patient may have allergy (hay fever for example). Some people may have it others may not because we respond to hay differently. So we may as well respond differently to drugs, some people have penicillin allergy, some are sensitive to diclofenac. Some, when taking voltaren injections, may develop bad reactions (allergic reactions – rash for example-)

3. **The patient is taking too much or too little of the drug:** when a patient takes 4 tablets instead of 2 per day, he may reach toxicity level especially if the drug is a narrow therapeutic index drug. If you take too little dose of the drug, how would this affect you? We have normal flora in our bodies, and this flora has different types of microorganisms, some of these microorganisms are resistant and some are not to the drugs (antibiotics) we use, so taking too little of an antibiotic will kill weak microorganisms and will give a chance for the strong (resistant) microorganisms to grow and produce more resistant organisms in our flora that may attack our immune system causing many infections. You should finish your antibiotic.

**Remember: no drug produces a single effect, because receptors in our body have homology, (for example alpha1 has some homology towards beta1, and alpha1 has more homology to alpha2, and beta1 has more homology to beta2, beta1 and beta2 have some homology towards muscarinic receptors). The drug that is not selective will produce more side effects and the one that is more selective and fits very well with its receptor and doesn't fit with other receptors will produce fewer side effects. In pharmacology, there are old generations and new generations of certain drugs, usually new generation drugs are more selective (have less side effects).

Example: antihistamine drugs produce hypnosis, they make you feel sleepy, they're not very selective, we call them old generation drugs. New generation drugs of antihistamine don't make you fall asleep, as they are more selective towards histamine receptors.

-Risk Factors for Adverse Drug Reactions:

• **Simultaneous use of several different drugs**: Drug-drug interactions, meaning there is more risk of adverse effects when there are drug-drug interactions

• **The patient is very young or very old in age:** a 1st week baby has different kinetics from a 2nd or 3rd week baby, also old people have different kinetics toward drugs. (Geriatric: old person, over 65 years old) (Kinetics: Different levels of fat or water, rate of excretion for example)

• **Pregnancy**: a pregnant lady is in disease state (she is not sick but she is pregnant).

• **Breast Feeding**: effects on babies.

• **Hereditary Factors**: some people are born with clotting factor deficiency, so when they're given anti-coagulants, they are more subject to adverse effects.

• **Disease states which may affect drug absorption**, metabolism, and/or elimination.