◉ Sheet ○ Slides

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Antagonism between drugs

***Note**: you don't need to memorize any name of the drugs that will mention in this lecture for now . You will memorize them in the coming lectures.

* In the previous lecture, we talked about antagonism between drugs and its types and here is **quick revision** :

>>Antagonism between drugs is three types:

1) **Pharmacological Antagonism** : we have two drugs work on the same receptors and they compete to bind the receptor reversibly and we called this **: competitive antagonism** . We have another type which is **noncompetitive antagonist** which occur when the drug binds irreversibly to the receptor or bind to site which inhibit the response to the agonist.
   >>**We said that we can overcome the problem of the noncompetitive antagonism by using physiological antagonism to reverse the effect of the drug like we mentioned before , the sympathetic and parasympathetic activity as example.**

2) **Chemical Antagonism** : in many cases we need to act fast so we use for example antidotes which go toward the drug and bind to it (here we don't have any actions of the receptor in this type . It's more about the reaction between two drugs).

   Antidote is a drug or agent that counteracts the effects of poison or over dosage by another drug. It neutralizes the harmful effects of a poison.

3) **Physiological Antagonism** :Here the two drugs have opposite effects on the body and each one of them acts on different receptor .(We mentioned an example in the previous lecture.)

So , let's start with our topic today. Let's start with enhancement of drug effects ...

*** Enhancement** means increase the effect of the drug . We used this method in many cases especially when the effect of one drug is not enough .

For example : diabetes mellitus and hypertension patients have a lot of prescribed drugs , and each drug of them have the same effect. Hypertension patients , for example , take 3-4 drugs to get to normal situation . There is no anti hypertensive drug that lower the pressure more than 40 mmHg because the maximum efficacy of the drug is only 40. Imagine a hypertension patient come to your clinic with blood pressure 210/140 . If you give him a drug that reduce the pressure toward 170/110 you will find that this is not good enough and it is not acceptable , so you need to combine drugs together to have the wanted effect to reach the optimum pressure.

> **Note :** when we talked about drug antagonism , we used this method to get rid of side effects ,poisoning and when a wrong drug prescribe or drug given overdose . But enhancement of drug used when the efficacy of the drug is not enough .

For diabetic patient , at first they take a drug named Glucophage (supporting drug) . After moment , the **β cells** in pancreas will decrease in number , so there will be not enough insulin in the body , and so we have to give insulin (we need to combine things together) .

> β cell : is type of cell that found in pancreas . Its primary function is to store and release insulin . Insulin is a hormone that brings about effects which reduce blood glucose concentration .

For **enhancement** of drug effect , we have three types:

1- **Additive** drug effect.

2- **Synergic** drug effect.

3- **Potentiation** drug effect .

>>Let's explain each one of them ……

1- **<u>Additive effect</u>** : You add the effect of the first drug to the effect of second drug , and then you will have a total activity of both of them . For example , if we have drug A that lower the blood pressure by 10 and drug B lower it by 30 the summation of the effect of these two drugs is 40 , so when you give the two drugs together , you will have a total effect equal 40.

>>Look at this equation : **EAB = EA + EB** 1+1=2

* So if we , for example , have a drug has in its name plus (+) like : Blopress plus , plus here mean plus of diuretic drug like hydrochlorothiazide (the drug that combine with Blopress) , so plus in general means that this drug must take with another drug to give additive effect.

Blopress plus is a drug and it's the commercial name for Candesartan drug.

2- **<u>Synergic drug effect</u>** : In Arabic mean (تفعيل قياسي), two drug with same effect when given together they produce greater effect than the summation of the two drugs (1+ 1>2).

*** For example** you have an antibiotic drug called trimethoprim (it's a bactriostatic drug) and other drug name sulfamethoxazole (and it's also bactrisatatic drug) , so when we combine these two drugs together , the combination will produce an effect not equal their summation , but greater than it . It actually gives a big jump that convert the drug from bacteriostatic function to bactericidal , and the name of drug will be Co- trimoxazole .(This is the most example that explain the synergic effect , convert from bacteriostatic to bactericidal (big jump))

Bacteriostatic : is a biological or chemical agent that stops bacteria from reproducing, while not necessarily killing them.

Bactericidal: is a substance or agent that kill Bactria .

>>Another example (but it's not real) , if we have drug A that lower the pressure by 10 and drug B that lower it by 10 , it will give a total effect more than 20 (maybe 30 , 40 …).

****Note :** When combine two drug in this type , they don't produce additive effect . Instead , they produce more than the sum . You can call the synergetic effect **abnormal additive effect** (We don't understand how it happens , but it happens .)

>> The synergistic effect has a problem related to side effects (exaggeration). This will appear clearly when we combine two drugs with same side effect. The end point is very bad side effect , so as primary rule in pharmacology never combine two drugs with same side effect because we afraid at synergistic effect that the two drugs will produce more side effect than their effect . (the main purpose to give the drugs !!) As the doctor said , it's a stupidity treatment to give diclofenac with profen because they make ulceration in the stomach as a side effect .

Look at this equation : EAB > EA + EB 1+1>2

3- **Potentiation drug effect** : the doctor start explain it with an example. We have augmentin (antibiotic drug) . It's a drug made of combination of two amoxicillin and clavulanic acid . Let's take clavulanic acid . It's not an antibiotic . It doesn't act on bacteria . It has an action on an enzyme (inhibitor for it) that secreted by staph aureus for example, which break amoxicillin , so amoxicillin can't kill these bacteria alone , so it needs calvulanic acid to inhibit these enzymes and complete its job as antibiotic .

Look at this equation : EAB > EA + EB 0+1>2

>> In the previous equation , we consider clavulanic acid as zero because it does not have any effect on the bacteria . It's just inhibit enzyme and notice that it gives total effect same to synergistic , so don't jumble between the two.

It's the common type and the ideal way to take care of breaking down drugs in the body . For example , Parkinson's patient has shortage of dopamine , so he needs dopamine but when dopamine enter the body there are a lot of enzyme that break it down , so to overcome this problem we give levodopa and carbidopa .(Carbidopa is also zero . It's just inhibit the enzyme that break dopamine).

Parkinson : is a long term disorder of the central nervous system that mainly affects the motor system .

*** <u>Receptors are in dynamic state</u>:-**

Q: Are the receptors stable/static or dynamic ?

We as human beings adapt because of variable factors leading to variable changing in humans . This is controlled by gene expression . As we say he drugs are toxic materials , and we don't have them naturally . So when we take drugs , our body adapt to it .

The first adaptation we will discuss is: When we give antagonist drug , we block the receptor , so the body adapt to it by increase the number of receptor through gene expression.

The second one is : When we give agonist drug , the number of receptor decrease.

<u>* Note:</u> the adaptation in the receptor can be through two ways : **gene expression** (<u>decrease</u> or <u>increase</u>) or by sensitization of the receptor, but the doctor said that gene expression occur more strongly than sensitization and he repeated that he strongly favor it.

The affinity or the receptor not always fixed . It changes according to two ways :

A-Receptor down regulation : If there was prolonged used of agonist , the body will adapt to turn to its normal state by reduction of receptor number and sensitivity , so the drug effect will decrease ,,,,,,this way is the mechanism of two thing : 1- tolerance 2- drug resistance

****Drug resistance**: the patient not responding to the drug , which means there is no receptor for this drug or the number of receptors is low.

****Tolerance** : the doctor explain it with examples, a patient with asthma has a sprayer contain ventolin (its scientific name is salbutamol or albuterol). It's binding to beta 2 receptors , stimulate them and causing bronchodilation . Now , if he used it a lot , when he needed or not , this called **chronic use** (It's a rescue drug , not for treatment or chronic use) . This make the number of receptors decrease , so when the patient has asthmatic attack , he will not respond to it because of decreasing number of receptors (it may be sensitivity) , and that's what we called the tolerance (reduce the efficacy of the drug due to prolonged and chronic use).

>> Another example , patient with insomnia (lack of sleep) . We give him hypnogenic , and we warn him from using it more than two weeks because if he use it more than 2 weeks , it will lead to tolerance . He will take two tablets instead of one after two weeks , and this will lead to more side effects .

* **Note:** Not all of the drugs produce tolerance **.** For example , when some people drinks coffee they may sleep , and so some drugs .

A student ask a question: if we stop taking the drug can it be back to tolerance? If we stop the drug , the body will adapt as it does not exist , so that we make what we call **tapering** to let the body adapt with the non existing of the drug.

There was a question about how we reduce the receptors ?

The number of receptor not reduced . It's in dynamic state and they exist with their half lives, but we decrease their production by gene expression that affected by something called growth factors that control the production of these receptors . Remember that receptors are not stable in their position . They change continuously with cell division and other factors,, It is related to E max , but it has a strong relation with efficacy because it will decrease if the number of receptors decreases.

If you want to know more about gene expression you can read this article

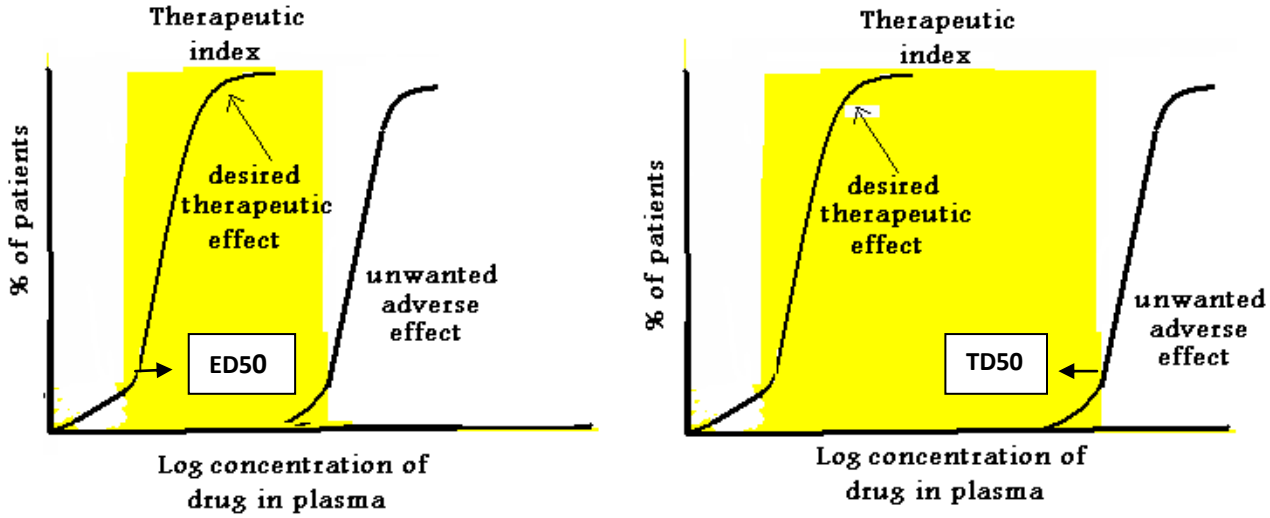
https://en.wikipedia.org/wiki/Gene_expression

B-Receptor up regulation : prolonged use of **antagonist** lead to increase number of receptor but it not always increase drug effect . The body actually increase number of receptor that bind to the drug, so the drug effect look like it increases . Let's see this example . Propranolol is stopped after prolonged use . We know that it prevent adrenaline to bind with beta 1 receptor. It's identified as antagonist , so number of receptor increases , so when we stop propranolol , adrenaline will face a lot of receptors then a lot of adrenaline will bind to them , so the heart will palpate very tightly and rapidly causing arrhythmia . This happen because we stop the drug suddenly , so to avoid that we make tapering (lower the dose of propranol slowly) , and so the number of receptors come back to normal.(This isn't tolerance . This is exaggeration.)

So , the drugs are not simple to deal with . They are complex things and this come also from that the receptors are not static . Instead , they are **Dynamic .**

*** <u>Therapeutic index and margin of safety:-</u>**

It is a ratio of the dose that produces toxicity to the dose that produces a clinically desired or effective response in a population individuals. (The range that we can give a dose of drug without side effect or mild.)



**The colored area is the range of therapeutic index

We set the dose of drug that can be taken in the previous lecture with efficacy and E max and sub therapeutic level . But in this lecture we will take another factor that determine the dose that we give which is the **side effect** .

>>To determine it we use the same **log dose response** with a few differences (here we use log concentration of drug in plasma with percentages of patients) **.** We increase the dose and we check the patients with side effects and then draw the curve . From the curve we can know TD50 and ED50 to calculate TI(therapeutic index).

>>We can calculate it by this equation :-

$$TI = \frac{TD_{50}}{ED_{50}}$$

>>Where : **TD50** is the minimum dose that is **toxic** for 50% of the population.

ED50 is the minimum dose that is **effective** for 50% of the population .

>>Ideally the TD50 Should be a much higher dose than the ED50 so that the therapeutic index would be large.

* Some drugs if you take it more and more and more there will be no side effects . For example , the antibiotics . If we increase the dose any time there will be no side effects . The range between TD50 and ED50 is too large , and so we call this **wide therapeutic index .**

* According to this , there are two types of therapeutic effect :

1-Wide **2-Narrow**

****Wide therapeutic** which means that any increase in the dose , there will be very low toxicity . The ED50 is far away from TD50 , and so it is easy to use and kind of safe (we can use it in the house).

****Narrow therapeutic effect** means that if we increase the dose a little amount , it will lead to toxicity and they are danger drug taken in the hospitals . The ED50 is so close to TD50 .(low increase in dose , high increase in toxicity)

Therapeutic effect depend on the drug and the body of the patient. Normal body variation between population (individual variation) will discuss later .

In slide 34 the drugs and their doses not for memorize . This is only to show the difference of doses between drugs (Just to understand the concept).

The doctor talk about very danger drug like digoxin . It's present in the blood and we have to maintain its rate in the blood . The TD50 is very close to ED50 for the digoxin (0.8 – 2ng/ml) . Just to know , Digoxin has killed many people all over the world , so why not choose another drug ? Because it's the **only** and the most effective drug that treat the heart failure , so we make monitoring to it to avoid its high toxicity , and so other toxic drugs .

>>Be confident . Believe in yourself that you can reach the top and just do what you want not other people want you to do <<

Sorry for any mistakes . GOOD LUCK