Medical Committee
The University of Jordan

PHARMACOLOGY

Lecture No.: 10

SHEET

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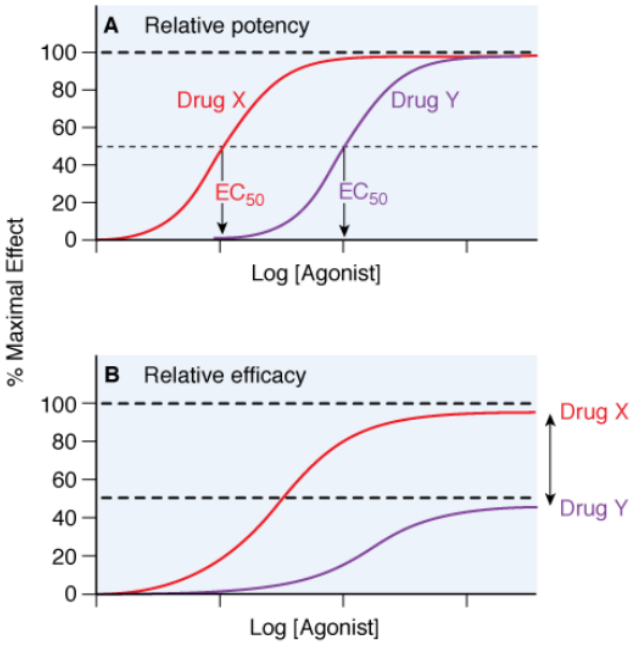
Drug response relationship 2

-I hope you all studied well in Eid and I hope you all had a blessed one ☺ , today we are going to continue our lecture about efficacy and drug-response relationship .

We talked in the previous lecture about **Efficacy which is a measure of the maximum therapeutic effect of a drug.** We said that in some cases increasing the dose of a certain drug doesn't produce any increase in the therapeutic activity, so we need to use another drug of higher efficacy or we use a combination of drugs in order to reach the desired therapeutic effect.

We talked briefly about **potency which is the concentration of the drug required to achieve half the efficacy (Emax)**, so it is a measure of the strength/power of a drug.There are different drugs that bind to the same receptor and produce the same therapeutic effect but these drugs bind to the receptor with different affinities (depending on the complementarity between the drug shape and the receptor , charges etc ..) so they will produce something called different Potency not efficacy because efficacy describes the maximum therapeutic effect but this does not describe potency of the drug which can be understood through knowing that different drugs have different affinity so they will produce different potency .

-**The figure** here talks about 2 drugs (X and Y) with the *same efficacy* which is possible, but it's not possible to have 2 drugs with the same efficacy and similar potency (there is no 2 drugs in the world with the same potency) because each drug has a unique shape which produce unique coupling and unique intrinsic activity. The drug with less EC50 is more potent.



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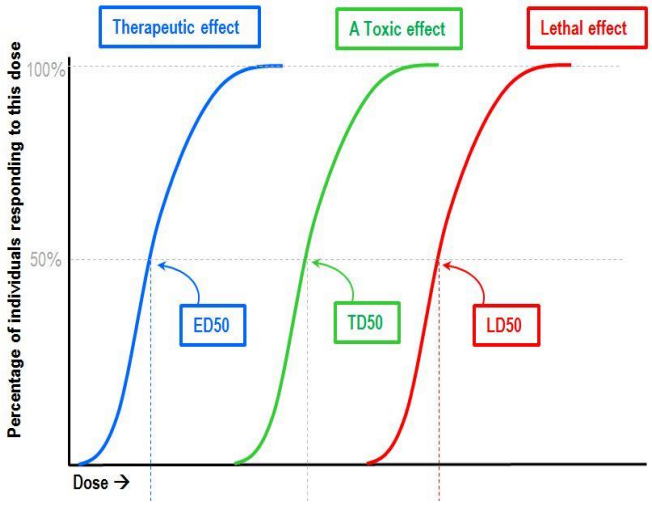
Example: Diclofenac (voltarin) and Profen both of them are analgesics for mild pain not severe pain, they have the same efficacy but different potency, when dosing your patient you give him 75 mg of Diclofenac or 400 mg of Profen so we considered that 75 mg of Diclofenac is equivalent to 400 mg of Profen, why there is difference in dosing ?

Because these 2 drugs have different potency,they both treat mild pain (same efficacy) but higher dose of Profen is needed because that receptors have lower affinity for Profen than Diclofenac (different potency).

*So which one of the 2 drugs (X and Y) represent Voltarin and which one represents Profen ? Drug X represents Voltrain and drug Y represents profen, so the more potent the drug is, the lower the dose needed to produce the therapeutic effect.

-The curve in the figure is not linear, so, where should the potency be on the curve? Scientists have used EC50 or TD50 or LD50 , anything with 50 helps to measure the potency of the drug ,so EC50 (where the curve is linear) is the dose that I need to produce 50% of the Emax , which is potency so we use EC50 to express the potency .



-Therefore, potency is a measure of the amount of drug necessary to produce an effect of a given magnitude. The concentration producing an effect that is fifty percent of the maximum is used to determine potency (EC50)

-Drugs that have the same efficacy but different potency doesn't mean much for you as a doctor, pharmacists should know more about these things. You, as doctor, must be more interested in the efficacy of the drug more than potency; because we do care about the therapeutic effect eventually.

-There are a few cases where we are interested in potency, the more potent the drug is, the less dose you give your patient. This is important in something called *accumulative dose.*

-Sometimes the drug is not completely excreted from the body, especially in patient with renal failure, sothe drug (or its metabolites) would accumulate which may result in increasing adverse effects. For example, (after 6 months) if you dose your patient with more of this drug this means that the accumulation will be higher which might be toxic and produce unwanted side effects so we try to dose this patient with the most potent drug to produce less accumulation.

-For example: In cases of hyperlipidemia, we give the patient drugs called Statin drugs, these drugs have bad side effect; called Myopathy, which is weakness in muscles. This drug , in order to work, must go to the liver. Nevertheless, part of statin would go to muscles and accumulate in myocytes resulting in myopathy with time.As you increase the use and dose of statin you will increase the accumulation of it, so more statin will go to muscles and produce Myopathy. If you use a drug called Simvastatin you have to dose the patient with 40 mg.There is another drug called Atrovastatin(which is more expensive), you have to dose the patient with 10 mg, which one of these 2 drugs have higher chance to produce Myopathy ?

Simvastatin because it is less potent than Atrovastatin .So we conclude that the more potent the drug is the less dose you will need and accumulative dose will be less so the side effect will not be so severe.

Another example is in the uses of patches that we put on the skin, the more potent the drug is the less the diameter of the patch**,** the less potent the drug is the wider the patch.

Conclusions:-

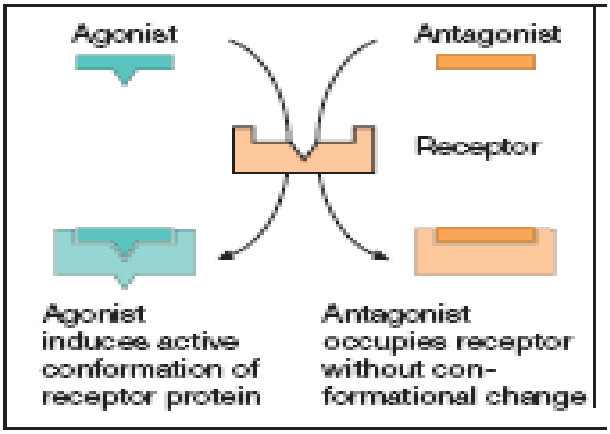
More potent → high affinity of receptors →less dose is needed .

Less potent → low affinity of receptors → more dose is needed .

Higher efficacy → higher Emax →larger therapeutic effect .

To distinguish between two drugs with the same efficacy we compare their potency (EC50) .

Receptor-Effector coupling

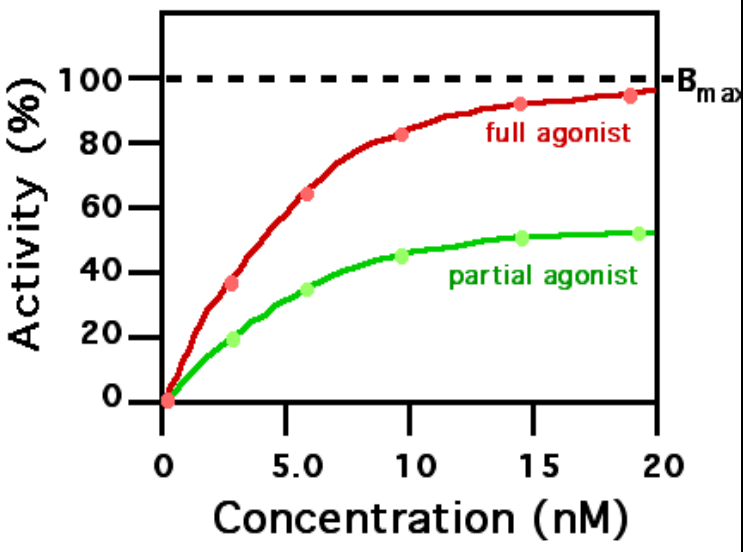


-We said that the drug molecule may either *mimic* the physiological action of endogenous ligands or molecules (**Agonist**) or *block* the physiological action/decrease the action of another drug or endogenous ligands (**Antagonist**).

The pharmacological response of agonist when a receptor is occupied can be divided into 2 classes :

1- **Full agonist .**

2- **Partial Agonist :-**binds and activates a given receptor, but have only *partial efficacy* at the receptor relative to the full agonist.This means that although this drug is bound to receptor and activates it, it cannot produce the FULL therapeutic effect even upon increasing the dose. So will never achieve the efficacy of the full of Agonist.



-For example :- Adrenaline binds normally toward Beta 1 receptor.If I gave the patient a partial agonist that binds to Beta 1 receptor, what would happen agonisim or antagonism ?

Antagonism,because the partial agonist will occupy part of the receptors and it will reduce the frequency of binding (knocking the receptor) of adrenaline/the endogenous material with Beta receptors.

To make it more simple :P if there is a receptor in the body that is normally not active and you give a partial agonist, which will bind the receptor and activate it, this will produce Agonisim. BUT if the receptor is already active (like Beta 1 receptors which are active because they bind adrenaline) and you give a partial agonist, it will inhibit it and produce Antagonism.

So the failure of partial agonist to produce full efficacy like the full agonist is actually because partial agonist sometimes competitively inhibits the response produced by full agonists actually many drugs used clinically as antagonist are actually partial agonists for example buprenorphin is a partial agonist that is safer analgesic than morphine because it produce less respiratory depression when overdosed .

Drug-drug interaction :-

Some drugs inhibit the activity of other drugs and some drugs enhance the activity of other drugs this interaction we call it drug-drug interaction . So when we want to prescribe a new drug, we have to make sure that the new drug will not affect other drugs neither activate, nor inhibit.

There are many examples of drug-drug interaction like :-

Antagonism between drugs

Drug A for example work to produce an action and drug B work against this action (decrease)

Toxicology: which is an important application of drug-drug interaction in antagonism, for example: a patient has taken an *overdose of morphine* and has signs of morphine toxicity how can I treat him ? I administrate to him a *morphine Antagonist* like Naloxone(antidote) which will bind to morphine receptor, it's called μ-receptor, and prevent morphine from binding to them to reduce the toxicity.

When antagonism comes at the receptor level we call it pharmacological antagonism, when it comes at the physiological level we call it physiological antagonism.

-In the previous example, the effect of morphine is reduced because naloxone binds to same receptors that morphine binds to. So this is at the pharmacological level.

Types of Antagonism between drugs :-

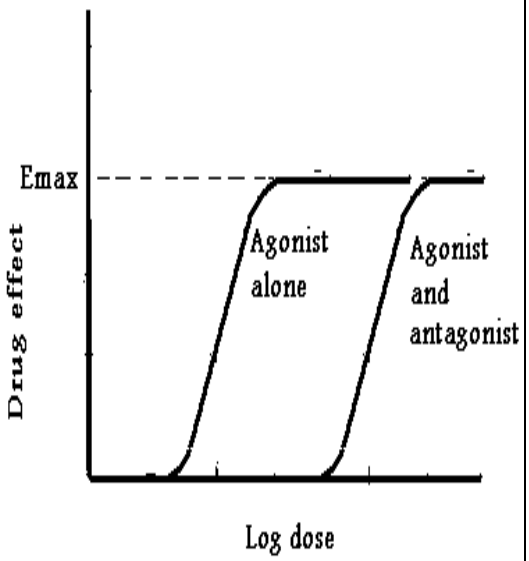
1 – **Physiological antagonism**:here the drugs act independently on two *different receptors*, and exemplified by one drug actingon the sympathetic nervous system causing the heart rate toincrease and causing vasoconstriction; while another drugacting on the parasympathetic nervous system decrease theheart rate and causes vasodilation.

If there is an increase in heart rate should we give a parasympathetic agonist or antagonist? Agonist, because the parasympathetic nervous system decreases heart rate.

-Moreover, to increase the heart rate we can either induce the sympathetic nervous system by giving adrenaline, or inhibit the parasympathetic nervous system by atropine. Atropine is an antagonist for acetyl choline, and since Ach is responsible for the parasympathetic response, antagonizing it will increase the heart rate.

In medicine you have 2 options either you activate the receptor or inhibit the receptor (pharmacological level), or you play with the physiological balance (physiological level).

2 – **Pharmacological Antagonism**: occurs when an antagonist prevents an agonist from interacting with its receptors to produce an effect, and it can be either competitive or noncompetitive.



-Competitive Antagonism :competes with the agonist in a reversible way on the same site on the receptor. An example which you know is Beta blocker drugs which block Beta

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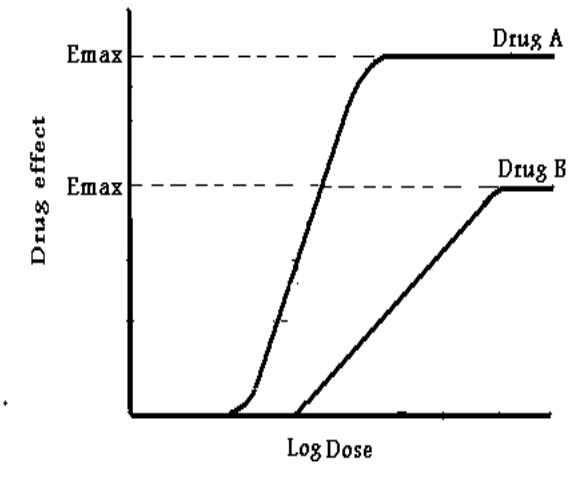
1 receptors and prevent Adrenaline from binding to decrease the heart rate.
The (log dose –response) curve is shifted to the right, which means you need higher concentration of agonist to produce the same pharmacological effect.
Another example : in the case of over production of an endogenous ligand in our body like in the case of Pheochromocytoma (PCC) which happens when the adrenal glands are producing a lot of adrenaline we must give the patient a competitive antagonist .

*the doctor corrected the curves in the figure here; drug A must be Agonist alone and Drug B must be agonist with noncompetitive Antagonist please correct it *



-Non-competitive Antagonism: when the drug binds to the receptor site or any site covalently it will bind to it irreversibly and it will not detach that will lead to the occupation of receptors so the amount of the receptors that are available will be less so the efficacy will decrease.

If my patient has been overdosed with a noncompetitive Antagonist drug how can I deal with this situation? By *physiological antagonism* ,but how?

An important example that can demonstrate this is Sarin gas which was used in Syria unfortunately ☹ it binds to the enzyme acetylcholinesterase irreversibly and block it from doing its action of breaking down Ach. That will result in more Ach, which will bind to its receptors more frequently ,so we should prevent that. What I do is that I give the patient Atropine which will bind to the receptor site of Ach (NOT THE ENZYME) and prevent it from binding so what I did is that I can't do anything about Sarin gas binding to enzyme but I can manipulate the situation by affecting the receptor.

Another example (mentioned in section 1 but not in section 3) is that Aspirin binds irreversibly to platelets to decrease blood clotting (anti-plated activity),so before surgery we prevent patients from taking aspirin to prevent heavy bleeding during surgery and if they take it, we must wait 6-7 days then do surgery, why do we wait a week? because aspirin is bound covalently to platelets and we can't get rid of it, so we wait for platelets to get recycled/regenerated in our body which takes about 7 days.

3-**Chemical Antagonism**: Occurs when two drugs combine with one another to *neutralize* it and form an inactive compound.And the best example is the drugs containing sulfhydryl (SH) groups, when combine with mercury or arsenic .
For example : heparin is an anticoagulant. If my patient has heparin overdose, I should give him an antidote called Protamine sulfate, it will bind to heparin and antagonize it preventing its toxic effects by chemical antagonism (neutralization).

Another example : In acne vulgaris we use a drug called Doxycyline which is a tetracycline. All tetracyclines if they were taken with milk they will be neutralized becausethey bind to divalent cations (have a charge of +2) and in milk there is Ca++ ,they bind calcium becoming inactive and get neutralized, this is called drug-food interaction .

Also, neutralization of tetracycline occurs if they are taken with anti-acid drugs (ex-Malox, Renin) which have aluminum hydroxide Al(OH)3 or magnesium hydroxide Mg(OH)2 .

***To sum up:**

-Antagonists are drugs that decrease or oppose the actions of another drug or endogenous ligand.

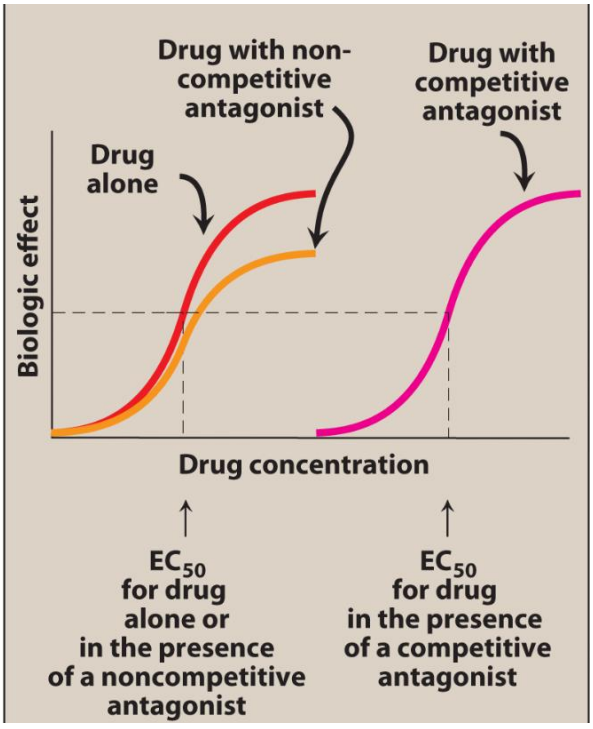
-Competitive antagonism

- When both the antagonist and the agonist bind to the same site on the receptor reversibly.
- Causes a shift of the agonist dose-response curve to the right, so the maximal response of the agonist can be obtained by increasing the amount of agonist administrated.
- Increases EC50
- The effects of it can be overcome by adding more agonist.

-Noncompetitive antagonism

- When the antagonist binds to the receptor irreversibly reducing the amount of receptors available to the agonist
- Causes a downward shift of the maximum efficacy Emax
- The maximal response is not observed even with increasing dose of the agonist

-Thus, a fundamental difference between a competitive and noncompetitive antagonist is that competitive antagonists reduce agonist potency, whereas noncompetitive antagonists reduce agonist efficacy.

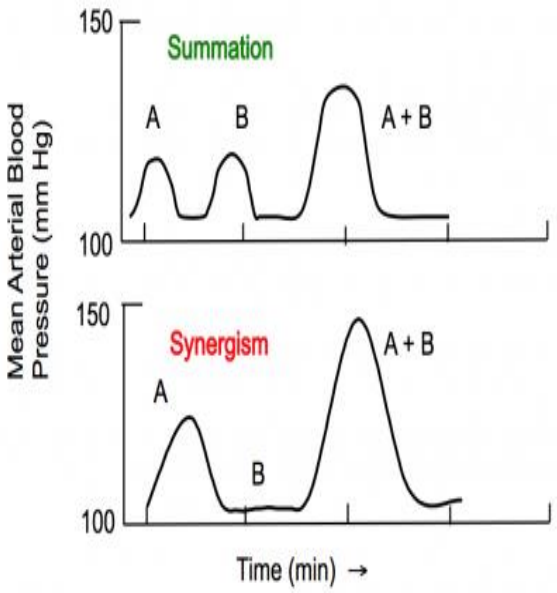


Enhancement of drug effects :-

A – **Additive drug effect** :

occurs if two drugs with the same effect, when given together produce an effect that is equal inmagnitude to the sum of the effect of the two drugs, for example if drug A reduces blood pressure by 20 and drug B reduces blood pressure by 30, when given together the blood pressure will be decreased by 50.

how is that important ? if someone has very high blood pressure (220/120) there is no drug alone in the world can reduce this pressure back to normal (*efficacy of the drug is not enough*) so we should combine drugs of different efficacies and produce an additive drug effect .



B- **Synergic drug effect** :

occurs if two drugs with the same Effect when given together, produce an effect that is greater inmagnitude than the sum of effects when the drugs are given individually. (1 + 1 >2)

for example if drug A reduce blood pressure by 20 drug B reduce it by 30 the sum of these two drugs will reduce the blood pressure by more than 100 .

3- **Potentiation drug effect**:

occurs if a drug lacking an effect of its own increase the effect of a second active drug it, means that the drug doesn't have enough activity so I use another drug to produce activity .

For example: in Parkinson disease the patient is not producing enough dopamine so we have to give him a drug called L-dopa (dopamine) but the problem is that this L-dopa is metabolized all over the body because it's a popular neurotransmitter and only little part of it will reach the blood brain barrier.So L-dopa alone is very weak, and we give with it an inhibitor of L-dopa metabolism in the periphery so more dopamine will reach the blood brain barrier to teat Parkinson disease .

-I am sorry if there is any mistake in the sheet I wish you all the best :D

Dedication to MuhannadHaddadin , Mohammad Nawaiseh, Mo'nesbadaineh, Rashid Al manaseer, Hamzeh mahaf9'a (kol wa7ad feekobdo y3zmni 3a saj bdal el dedication).

Done by : Ali Khresat