Pharmacodynamics II

PHC 721

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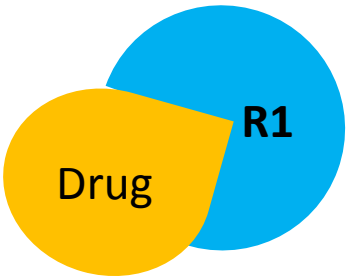
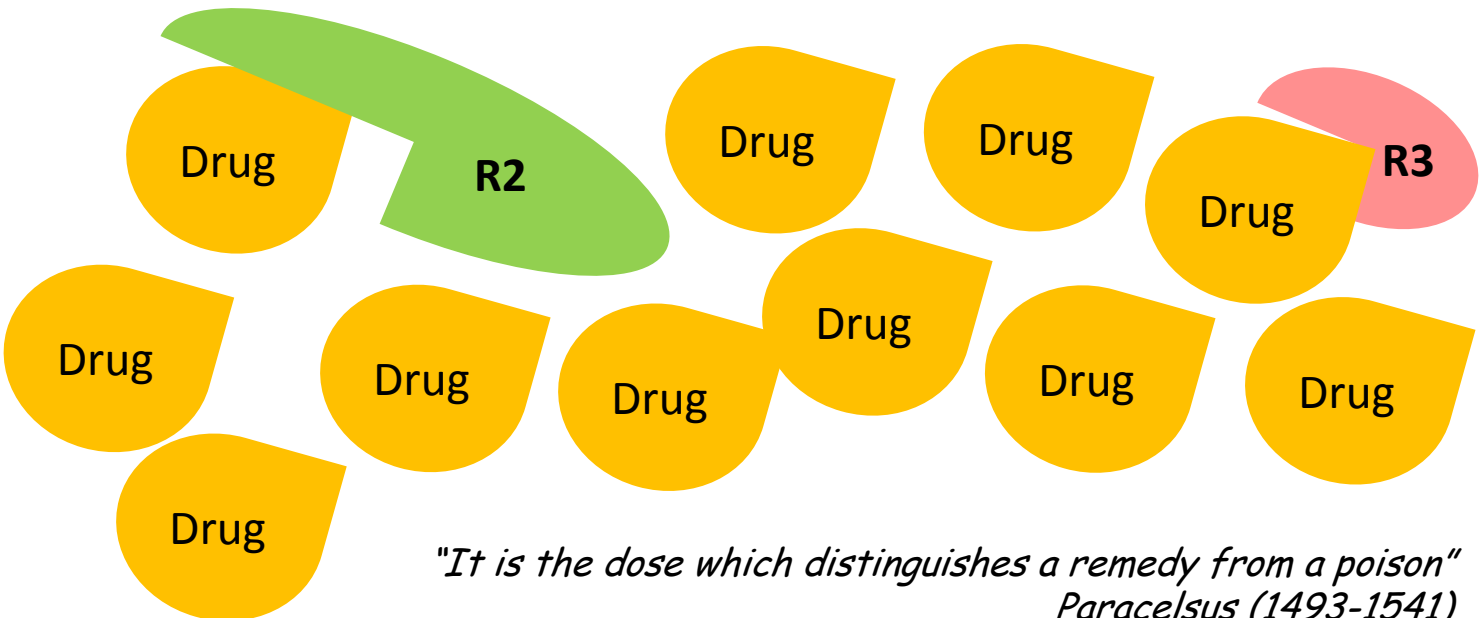
Specific or Selective?



One Receptor ⇒ One Effect ⇒ **SPECIFIC**

High Enough Concentration of the Drug:
Other Receptors ⇒ Other Effects ⇒ **SELECTIVE**



"It is the dose which distinguishes a remedy from a poison"
Paracelsus (1493-1541)

This is specific vs. selective…whether drug is Specific or selective for a given receptor.

- this is receptor R1 and the drug that bind to it. If the drug only bind to one receptor, we can say that the drug is **SPECIFIC** for this receptor. This is pretty much on theoretical concept bc there is no such drug that has only one effect and def only act to one receptor. It all matter of the dose or concentration of the drug.
- So if you put high enough concentration of the drug, the drug will now likely bind to other receptors, which might not be such high affinity as receptor R1, but it might or likely will bind to other receptors like R2 or R3. Now, binding to other receptors, even though with lower affinity will evoke other effects. So other receptor —> other potential effect now we can only say that the drug is **SELECTIVE.** *When we talk about Propranolol last time, it is a non-selective beta-blockers. So non-selective means it binds to different receptors B1 and B2. This is an example of non-selective.* Selective would be Sotalol (heart drug) that binds to B1 but if you put high enough concentration, it will also bind to B2 and block B2 receptors as well.

"It is the dose which distinguishes a remedy from a poison." The fact that if you put high enough concentration of the drug, you will get effect that could be poisonous.

NEXT PAGE:

We look at example of 2 drugs:

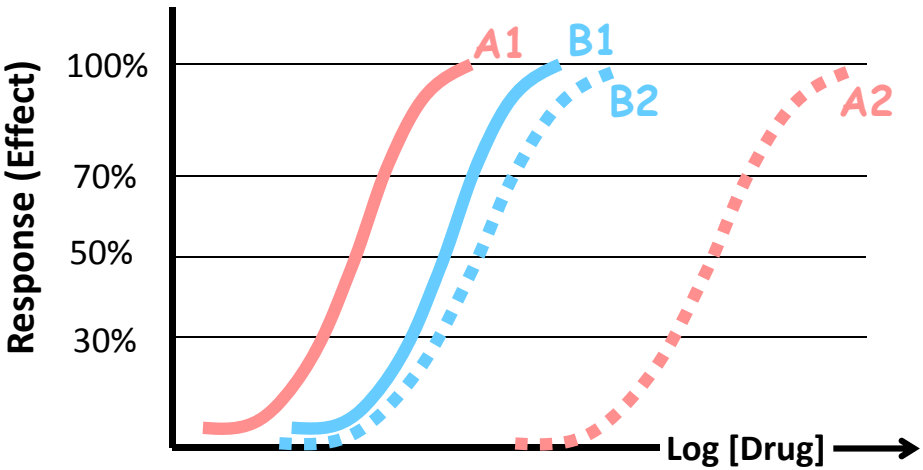
- Drug A has one response at a lower concentration of the drug. Drug A will have receptor A1 which will evoke a certain effect. Let's call the first effect, effect 1 and this is the **desired** effect of the drug that we expect it to have.
- Now, when you apply the drug at a significantly higher concentration, the drug being selective for receptor A1 but not specific for this one receptor will also have effect on receptors A2. And the effect through receptor A2 will not be desirable and we call it **adverse effect.** So a low regular concentration that the drug is supposed to be administered at, will give the effect that we expect from the drug. When we increase the concentration significantly in this case, we get that adverse effect.
- Drug B will have a certain concentration, maybe higher. I just want this to correspond to the plot being shifted to the right a little bit. So now if we shift that plot to the right, it means we need higer concentrations to obtain a given effect. Now, we have drug B acting on receptor B1 and causing the effect 1. This is the desired effect. So we can say that drug A is acting through receptor A1 and drug B is acting through receptor B1. Both are full agonists of the receptor and they cause the maximal response possible- the ceiling effect. So the Emax for them is 100% of the response. But drug A1 has a higer potency. So the efficacy of both drugs is the same, but drug A has a greater potency bc we need a lower dose to achieve the same effect as would be achieved w drug B, which requires a higher concentration. But now drug B also acts through some other receptor, and it turns out that the effect for receptor B2 is not a desirable effect, meaning it is an adverse effect. And it is actually obtained w a relatively low concentration of the drug, meaning similar concentration to the one that causes the desired effect. So we have that effect 2 which is adverse. The plot for the adverse effect is very close to the plot for the desired effect. The separation is narrow for drug B.
- For drug A, you see the difference in concentrations of the drug that caused the desired vs. adverse effect. The difference in concentrations is much greater for drug A than it is for drug B. And now the extent of the separation, when we look at drug A, we say that the drug A is more selective drug for the effect 1.

Again, we are looking at the same type of response. We have 2 drugs and drug A is more selective because when it acts through receptor A2, it requires much higher concentration of the drug.

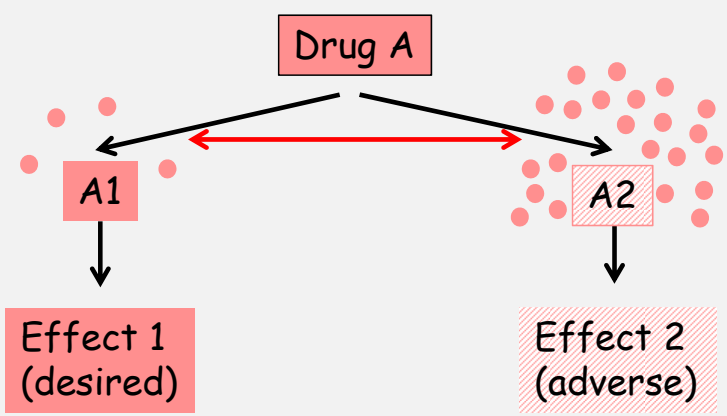
A real live pharmacological example would **beta adrenergic antagonists**. When we say the drug is a selective or non selective antagonist, Non-selective beta blocker and selective beta blocker. Propranolol is a non selective beta blocker bc it binds to both B1 and B2 receptors. You will have B1 which is a desirable blockage, but B2 blockage when you block the receptors in the respiratory system in the bronchi will cause bronchoconstriction and this is not a desirable effect. **This is why propranolol, the non-selective beta-adrenergic blocker, would be contraindicated in pt who suffer from asthma bc in addition to blocking receptors in the heart, it also blocks receptors int he bronchi.**
On the other hand, selective beta adrenergic blockers such as Sotalol and metoprolol are selective for B1 receptors, meaning you require a much higher concentration of the drug to bind to B2 receptors. So here you have A1 like adrenergic receptor 1 and adrenergic receptor 2. So in this picture, without going into details about the potency of the drug, the selective beta one adrenergic blocker would be the pink color. As an example, Sotalol would be the pink color and the propranolol would be the blue color.

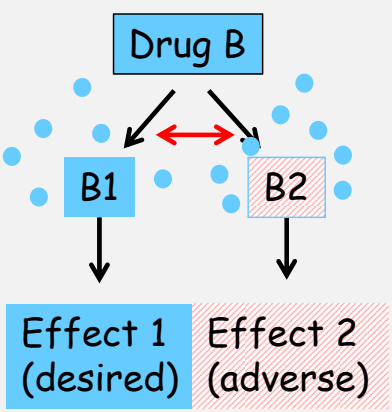
Drug 'Dose – Response' Relationship

Drug Selectivity

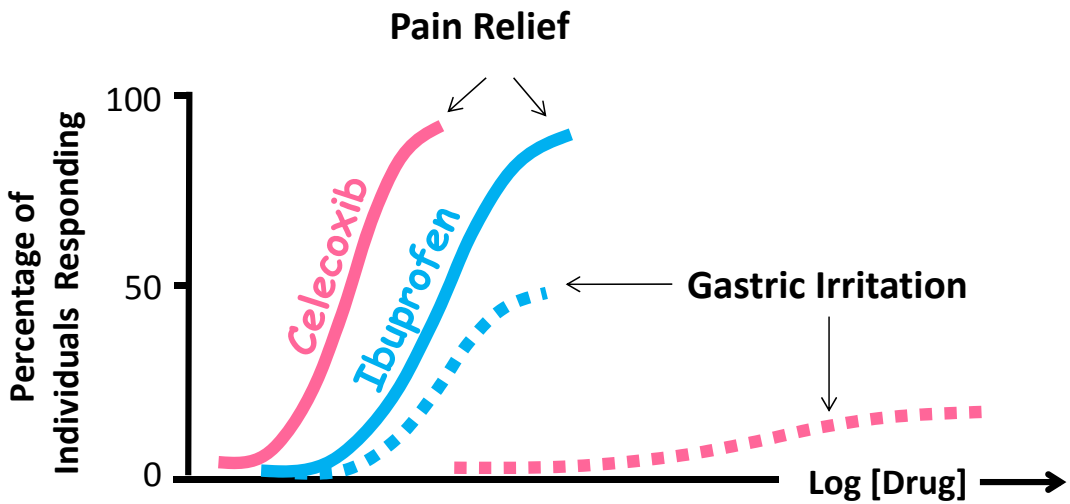


The extent of **separation of 'Dose-Response' curves (DRCs) of a drug for different effects** is a measure of its selectivity. DRCs are quite similar for Drug B, but far apart for Drug A:
Drug A is a more selective drug for the desired Effect 1.





Drug Selectivity: NSAIDs



[Celecoxib] Selective inhibitor of the inducible COX-2 isoform

[Ibuprofen] Non-Selective inhibitor of COX-1 and COX-2

Here is another example of drug selectivity. This is about nonsteroidal anti-inflammatory drugs you would be using in your practice. The difference bw previous graph and this one is on the y-axis, you see the % of individual responding to the drug. This is also the concept of quantal-dose response relationship. There are 2 NSAIDs that are compared here:

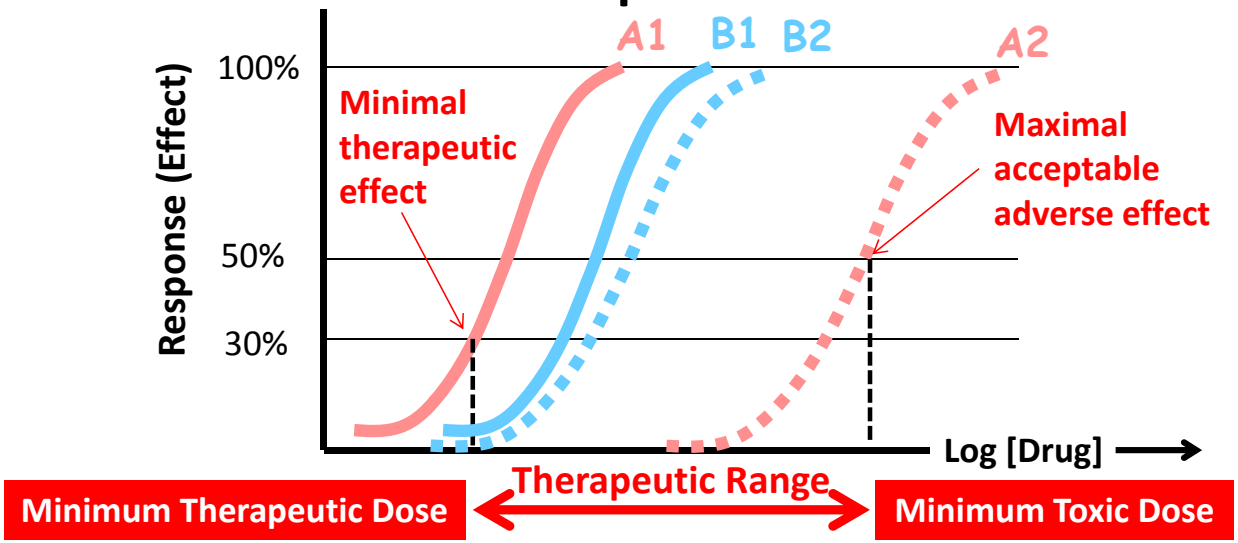
- Celecoxib is indictable COX isoform.
- Ibuprofen

When you look at side/adverse effect of those drugs, gastric irritation is mediated thru COX-1 inhibition. Notice how slowly both curves are presented here in dotted lines. For celecoxib, the gastric irritation is much lower meaning you need much higher dose to evoke any gastric irritation. Also, as % of individual that response to gastric irritation is much lower. This is bc celecoxib effect on COX-1 is very small.

Drug 'Dose – Response' Relationship

Therapeutic Range (a.k.a. Therapeutic Window)

Therapeutic Index



The safety margin of a drug is expressed as:

$$\text{Therapeutic Index} = \frac{\text{Median Toxic Dose } (TD_{50})}{\text{Median Effective Dose } (ED_{50})}$$

In experimental animals, the **Therapeutic Index** is calculated as:

$$\frac{\text{Median Lethal Dose } (\mathbf{LD_{50}})}{\text{Median Effective Dose } (\mathbf{ED_{50}})}$$

So the next and directly related concept to drug selectivity is the therapeutic range also known as therapeutic window or the therapeutic index. These are all very important terms for you to know and understand. So I'm using the plot from the previous slide, but let's get rid of drug B because it's harder to see anything with this really narrow therapeutic window and just focus on drug A.

So here we have the drug A and let's look at some more things on the plot- since we consider the **linear portion of the curve** as the part that we analyze and take into consideration. We have the 30 percent of the response maximal effect- let's say it's considered the **minimum therapeutic effect.** So there is a certain maximal response and 30 percent is the minimal therapeutic effect. So this means the minimal therapeutic effect is achieved with the **minimal therapeutic dose**.

On the other hand, we know that the drug acts through another receptor (A2) and causes some **adverse effect.** And please notice that in this case, there is a pause on the Y axis- those are two different responses. And in fact, the therapeutic dose and therapeutic effect occurs through A1, and this is a sudden therapeutic response to the drug and the adverse effect can be a completely different response because it happens through a different receptor.

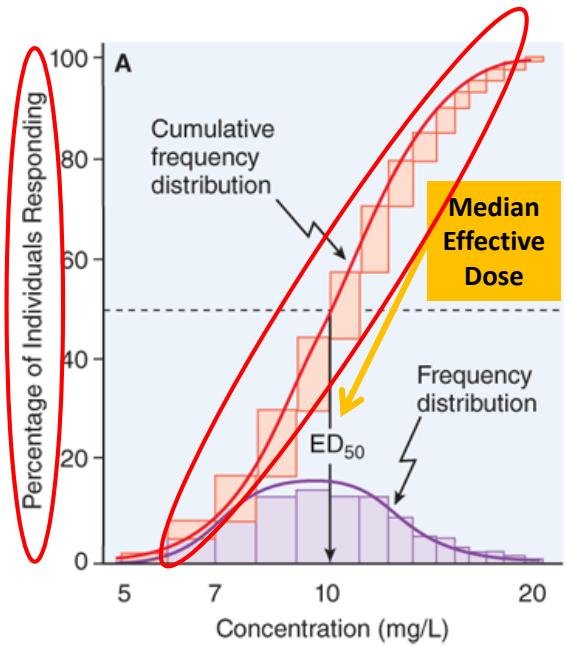
And as with all drugs, they cause some other effects. **Most drugs are only selective and not specific.** So **we have to decide what's the maximum acceptable adverse effect**. So say 50 percent of maximal response, whatever the response is, the adverse effect for a given drug- this will be the maximum acceptable adverse effect. Higher could be dangerous for the patient. So now this maximum acceptable adverse effect is obtained, we track it down to the X axis and we say that this will be the **minimum toxic dose. It's the minimum toxic dose meaning the maximum acceptable dose that is acceptable, and above this it's toxic**. So this will be the minimum toxic dose.

So between those two minimum therapeutic and minimum toxic, we have that **therapeutic range.** Lower than minimum therapeutic wouldn't be therapeutic, so it wouldn't be doing what we want the drug to do and higher than minimum toxic would be toxic for the patient (so it's bad again).

The safety margin of the drug is expressed as the **therapeutic index**. So the therapeutic index is now the medium toxic dose, TD50, to medium effective dose, ED50. So this is the therapeutic index presented for humans, for human studies, for clinical trials, for what you would see in the flyer that comes with a drug. But in fact, for **experimental pharmacology** and hardcore pharmacology, where the data come from is experimental animals first, and the therapeutic index is calculated by the **median lethal dose, LD50 and the median effective dose ED50.** So effective is fine, but the lethal dose is scary. What if you thought of this in the context of treatment patients? So this is why the therapeutic index is presented, for drugs already in clinical use as a median toxic dose over the median effective dose.

And now I want to point to the word **median** because now we will transition and we'll talk briefly about the quantum dose response, relationships that are obtained in clinical studies on patients or it can be obtained on animals as well. But you will see, what's the difference between the drug dose response relationship we've talked about so far and the quantity of those response relationships.

Quantal 'Dose – Response' Relationship in Population Studies



Goodman & Gilman's The Pharmacological Basis of Therapeutics, 13th edition, 2018

All graphs presented on previous slides show **Graded Responses**, i.e. increases with drug dose, as seen **in a single individual** (or a single experimental preparation).

In contrast, a **Quantal** 'Dose-Response Relationship describes a **binary drug effect:** either present or absent in any single individual of the tested **population**.

The plot shows the rate of positive responses to the drug at doses administered to a population. It is constructed to determine **ED_{50}**.

The slope of the cumulative frequency distribution serves as an indicator of the **population variability**.

Similar plots are constructed at higher drug doses to determine the Median Toxic Dose (TD_{50}).

Due to inter-individual variability, the effective dose for one patient may be toxic for another. A drug may have higher efficacy (induce a higher therapeutic effect), but development of intolerable adverse effects may preclude use of higher doses.

A drug should be prescribed only when the benefits outweigh the risks.

Quantal 'Dose-Response' Relationship: the relationship between the dose of the drug and the magnitude of the response that is done in population studies. So all graphs that I presented so far shown on the y-axis, the % of the maximal response. Those data come from individual pt, animals or some experimental preparation. Doses are given randomly to prevent tolerance developing and so on.

In general we construct the response to different drug doses. In contrast, the quantile dose response relationship is done a bit differently… meaning each patient or the subject in the study receives only one dose and the response to the dose is noted only as present or absent. Meaning the patient/subject responds to the given dose or doesn't respond to that dose. So this would be binary drug effect. Again, either present or absent.

And so on the Y axis here, it's the actually percentage of individuals responding to a given dose. So with smaller doses like 5 or 7 milligrams per liter, you have only small percentage of individuals responding. When you increase the dose you have a larger percentage, and then you construct from this that cumulative frequency distribution, the maximum is again 100%. But now 100% is not the 100% response maximum response, but 100% of individuals and from this you determine the ED50.

So it's median effective dose is basically the dose that's effective for 50% of the population. The similar plots are also constructed at higher drug doses. This is to determine same way you determine the median toxic dose whether the given patient shows the toxic effect or it doesn't. And the slope of this cumulative frequency distribution tells you about the variability in the population. So if the slope is more steep, you have less variability because now a large percentage of the patients response to certain range of doses. And more narrow range of doses if the slope is more flat… it means that you have basically a wider range of doses. Meaning some individuals respond already to very low dose, but for some individuals you have to have a really high dose for them to respond. So this will be higher variability.

For any medication you apply to your patients, there is variability between individuals. So as I put here, the effective dose for one patient may be toxic for another. And you may think that if you apply a higher dose then you will have a better effect, but you need to think about adverse effects that can show up. For different individuals they could be at a very different doses of the drug.

The final point I wanted to make for this is that the drug should be prescribed only when the benefits outweigh the risks because again none of the drugs on the market are specific. They're only selective meaning they have other effects and there is always a risk of those adverse.

NEXT PAGE

Now almost final topic of pharmacodynamics for us to discuss are the combined drug effects. On the following slides will focus on one specific type of drug effects = meaning antagonism.
But before we get to antagonism, I wanted to provide meaning receptor based antagonism. I wanted to give you an overview of our combined drug effects. Two major groups:

1. Synergism: when the action of one drug is increased by another drug with another drug is called synergistic partner (this is probably less important for you) and what is important there are two types of synergies:
a. Additive (A+B): that if you have two drugs one drug has it's a fact another drug has its effect when you combine the two to drugs you get basically the fact that it's of the magnitude of combined effect of both drugs
b. Supra additive or potentiating effect: when you combine the drugs the effect of combining is actually greater than simply addition of the two effects of the drugs. And interestingly one component alone may not even have any effec, but enhance the other effect. So then you would also call it potentiation because one is 0, and when you add to some effect you will get a greater effect.
2. Antagonism: Many different types of antagonism but basically antagonism is when the effect of combined drugs is less than the drugs alone. And same as for the synergism one component could be not having any effect, and the classic example this will be the receptor mediated antagonism selected for non selective antagonists as we already said at the beginning. They don't have any efficacy. Meaning you don't expect any effect from them, but they can bind to the receptor and can block another drug from acting.
a. physical antagonism: Physical property of the drug. Example: charcoal and absorbs alkaloids, prevents layer absorption, decreases by if you block drug absorption. We can't talk about pharmacokinetics yet, but basically you prevent the drug from working from acting on the body.
b. chemical antagonism: we'll talk about this later talk with other give other examples but here is just one that combine drugs form the inactive products, such as for thiopental sodium. That could be important for you although this is more in the surgical context when you need to evoke muscle paralysis, because sectional choline is substance drug that causes muscle paralysis so this will be the chemical interaction.
c. physiological antagonism: physiological meaning that they antagonize the effect but they don't act through the same receptor.
d. receptor based: competitive and noncompetitive…two types of receptor based antagonism with different

pharmacodynamic properties.

Combined Drug Effects

I. Synergism (Greek: *syn*-together; *ergon*-work), when the action of one drug is increased by another drug (synergistic partner):

A. **Additive -** effect of drugs A+B = effect of drug A + effect of drug B
B. **Supra-Additive (Potentiation) -** effect of drugs A+B > effect of drug A + effect of drug B*

**one component given alone may produce no effect, but enhance the effect of the other*

II. Antagonism, when one drug decreases or abolishes the action of another:

effect of drugs A+B < effect of drug A + effect of drug B**

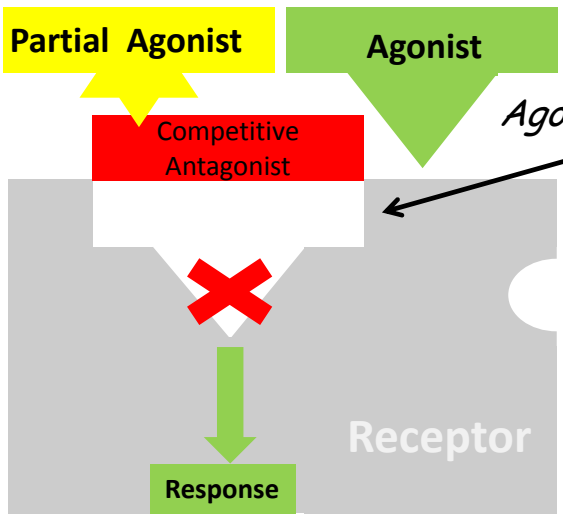
A. **Physical –** based on the physical property of the drugs (e.g., charcoal adsorbs alkaloids, preventing their absorption – used in alkaloidal poisoning),
B. **Chemical –** two drugs react chemically, forming an inactive product (e.g. when mixed in the same syringe: *Succinylcholine Chloride + Thiopental Sodium*),
C. **Functional (Physiological) –** two drugs act on different receptors (by different mechanisms), but have opposite overt effects on the same physiological function, i.e. pharmacological effects in opposite directions (e.g., *Glucagon* and *Insulin* on blood sugar levels).
D. **Receptor-Based –** one drug (Antagonist) blocks the receptor action of the other (Agonist):
   (a) Competitive
   (b) Non-competitive

***usually, one drug (Antagonist) is inactive alone, but decreases the response to the other.*

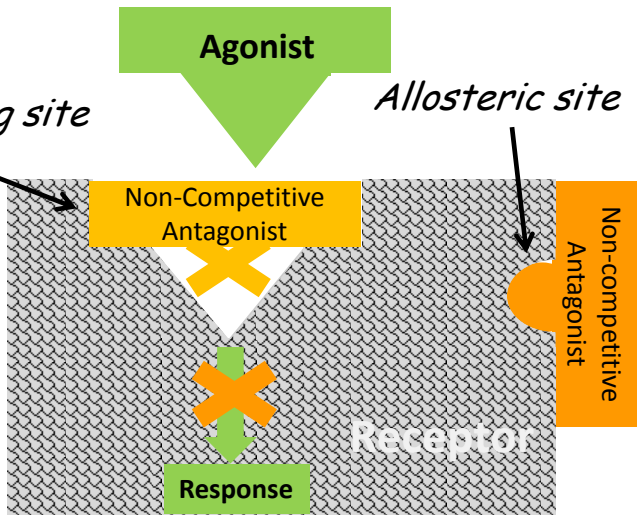
Combined Drug Effects

Receptor-Based Antagonism

Competitive Inhibition



Non-Competitive Inhibition



Competitive Antagonist:

- is chemically **similar** to Agonist;
- competes with Agonist;
- binds **reversibly** to the same site (exclusion of Agonist molecules)
- prevents conformational changes/ signal transduction
- **the majority of antagonists in clinical use**

Non-Competitive (Irreversible) Antagonist:

- is chemically **unrelated** to Agonist;
- does not compete with Agonist;
- binds **irreversibly** (it need not be a covalent modification of the receptor) to the same site or a different (allosteric) site;
- **alters the receptor** such that it is unable to bind the agonist or transduce the response

COMPETITIVE INHIBITION

We have a receptor. It has binding site for agonists. Now we are talking about the partial agonists and full agonist.

- Full agonist has much higher affinity for the receptor so the response is much stronger so we get the maximal efficacy
- Partial agonist doesn't give the same response. The magnitude of the response is smaller and and basically because of the intrinsic activity of the Agonist is lower. This is because the binding to the receptor is (based on the cartoon) imperfect. It doesn't fit perfectly.

Once The Agonist binds to the binding partial agonist, they evoke the response.

In the competitive inhibition scenario, the competitive antagonist is chemically similar to The Agonist. Chemically similar structure and has affinity for the same receptor for the same binding site. Affinity meaning is able to bind antagonist, meaning it doesn't have any efficacy so it's not able to evoke the response. So once the competitive antagonism binds to the site where normally agonist binds, the Agonist cannot bind, so it prevents The Agonist from making the changes to the receptor that would result in the response… whatever the response is. So that competitive antagonist competes with The Agonist for the binding site.

So this is all a matter of drug concentration, both The Agonist and the antagonist. First, because this is a competition, here in order for the competitive antagonist to be effective in blocking the effect of agonist, usually you need to have the concentration of the antagonist several times the concentration of The Agonist. The antagonist is going to push away from the binding side, so it's sometimes 5,10 times even 20 times higher concentration of the antagonist. But the binding is reversible. So now if you put the antagonist and put high enough concentration of The Agonist, The Agonist can push away the antagonist and bind.

Push away is basically is not one permanent binding. The drug and the receptor constantly bind and unbind, detach and attach. Basically, you can think about this as the competitive antagonist waiting for the moment when agonist is not there and getting to the binding site. If you have high enough concentration of agonist, the probability that this is the antagonist that occupies the side and not The Agonist increases. So it competes with The Agonist, but reversible.

As you will see on the next slide, we discussed the effect on the dose response curve. I want you to keep in mind that for competitive inhibition this is all the matter concentration that you can achieve the effect of both antagonist and agonist. If you put high enough concentration of one of those. But once the competitive antagonist binds again, because it doesn't have any efficacy, it prevents the signal transduction conformational changes of the receptor and so on.

The majority of antagonists that are used in clinically are competitive inhibitors/competitive antagonists. Although there are a few examples of non competitive antagonists, and one of them is actually very prominent example for because aspirin binds noncompetitively to Cox and enzymes.

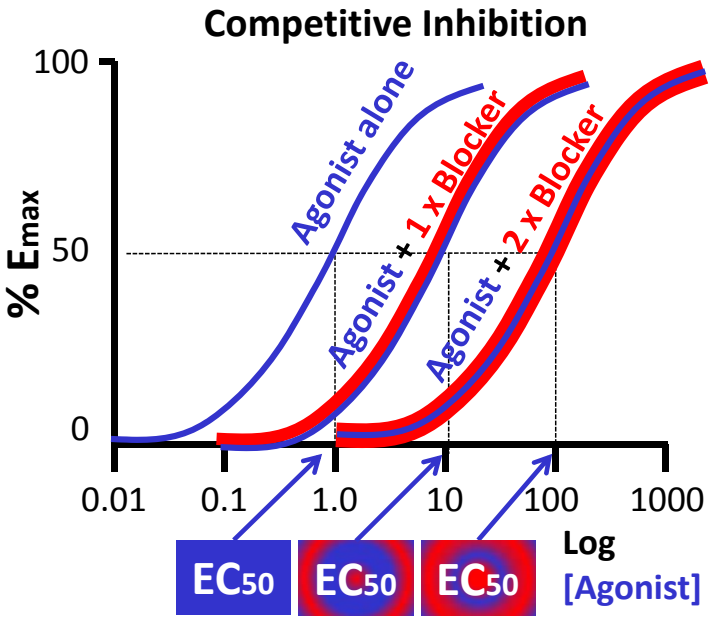
NONCOMPETITIVE INHIBITION

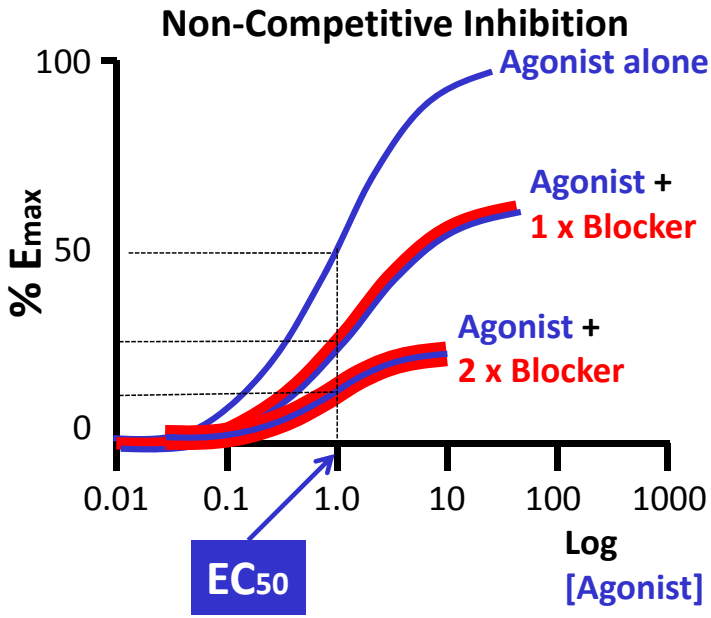
Non competitive inhibition the concept is the same of binding, but there are different things going on with noncompetitive inhibitors. Noncompetitive inhibitors combined for either the side where normally The Agonist binds or to a different side of the receptor. In either case, they prevent the signal transduction. They basically change their receptor in the way that's not able to transfer information. And noncompetitive antagonist is not usually related chemically, unrelated to agonist because it's not about competing with The Agonist, but making changes in the receptor. It does not compete and it binds irreversibly, so the name even non-competitive are also sometimes called irreversible antagonists. Those interactions are irreversible, but not necessarily covalent. As you know the covalent bonds are the strongest ones, but those changes don't need to be covalent bonds. BUT those are still irreversible interactions. So again the noncompetitive inhibitor can bind to The Agonist binding side, but more frequently, it actually combines towards allosteric site, which is a different side on the receptor.

Noncompetitive changed their receptor. It's not about blocking the site for agonist binding, but about changing the receptors so even if the noncompetitive inhibitor binds to a different side and agonist can occupy its normal binding site, the receptor cannot transduce the information.

Combined Drug Effects

Agonist 'Dose – Response' Relationship





Effects of Competitive Antagonists (Blockers):

1. Parallel rightward shift of Dose-Response Curve (↑Concentration of Antagonist ⇒↑EC50 of Agonist, i.e., an apparent reduction in affinity of Agonist)
2. The same Emax by increasing dose of Agonist (**surmountable antagonism**)
3. Emax depends on **[Agonist] & [Antagonist]**

Effects of Non-Competitive Antagonists (Blockers):

1. Downward displacement of Dose-Response Curve (↓ Emax and **no change in EC50** for Agonist)
2. Emax is suppressed (**unsurmountable antagonism**)
3. Emax depends only on **[Antagonist]**

And finally they're super plot that we will discuss now the effects of The Agonist dose response relationship. Agonist will be like any drug that we gave given examples before. After those response relationship, and then on top of that, we are adding and what is the effect of antagonist on The Agonist.

COMPETITIVE INHIBITION

Competitive inhibition: (left graph) agonist has the shape of the curve. When you apply antagonist, the plot shifted to the right. So agonist and one time blocker at a certain concentration shifts the plot to the right. Now when you double the concentration of the blocker, the block shifts even farther towards right, so it's rightward shift. Characteristic feature of this type of inhibition is that the plot shape doesn't change, the height is the same. What it means is that when you apply the blocker, you are able to obtain the same efficacy And the same maximal response, the same Emax, but what it looks like is that the blocker causes the loss in the potency. Loss of potency = you need higher concentration of The Agonist to obtain the same level of response the effect.

How do we judge the concentration that we need for a given response EC50? Let's look at that. Effect of the competitive blockers and as I put here is the parallel rightward shift. And now when you look at the Emax 50% effect of response Because all curves have the same height meaning courage the same maximal point will be the same and actually the maximum we are shown here that the Emax is 100%. So 50% of the effect will be 50% of the Emax in this case. When you look at what the concentration of The Agonist is required, to obtain the 50% of the maximal response to reach the 50%, for agonist alone, the value is certain value~ 14 agonist, and one time blocker the value is 10, or agonist and two times longer the value is 100= meaning you need 100 times more higher concentration of the other. When you apply it with a blocker at the two times of its concentration. Those are arbitrary units here, but one time blocker and two time blocker, 50 increases dramatically, but you can put a positive spin on it and say that despite the presence of the blocker, you can obtain the same maximal effect or the same 50% effect, you just need to increase the concentration of the drug.

Please remember this and keep this in mind when we compare it it with noncompetitive inhibition. What happens first feature here is the parallel rightward shift of the dose response curve if you have the competitive antagonist present. There's no real reduction in affinity of The Agonist. This is because The Agonist can still bind to the receptor with the same strength as long as it can get there right. As I already said, that Emax is the same. It's by increasing the dose of agonists you will get the same response.

NON-COMPETITIVE INHIBITION

In the non competitive inhibition scenario, we have again that agonist alone and look what happens when we add the block. When we add one time blocker, again the some arbitrary unit of blocker, you don't reach the same Emax. A plot flattens downward shift. When you put agonist and two times blocker, you get even further reduction in efficacy. (for competitive inhibition the efficacy is not affected, potency is affected). For noncompetitive inhibition, the efficacy is affected, potency is NOT affected. So basically for non competitive information no matter what amount of the drug you put it simply cannot evoke its effect because the noncompetitive inhibitor made changes to the receptor.

Non-competitive antagonist: downward displacement, it's got flatten and interestingly look the pattern EC50 does not change here. The concentration required to obtain the 50% of the maximum response does not change.

One thing to remind you that if you calculate the EC50, you need to take the 50% of the maximum for a given condition for a given drug. If you look at The Agonist plus one time blocker, this is like a different drug with lower efficacy, so the lower efficacy that the maximum efficacy bold the drug. The maximum efficacy for agonist with blocker is the reference point when you calculate the 50%. This is why the 50% for the 1xblocker were blocked is at lower levels than the 50% for The Agonist alone. We have that three levels of 50% for each of the plots. Now you see that all have the same EC50, so the part EC doesn't change, but the efficacy decreases.

Emax decrease is a no change in EC50 for agonist.

The Emax is suppressed and cannot be overcome by increasing the concentration of the agonist. And the Emax depends only on antagonist because the antagonist makes structural conformational changes to the receptor. Add agonist cannot bind anymore no matter what concentration you put. So the Emax depends only on [Antagonist].

Regulation of Receptors

In tonically active receptor systems,
prolonged receptor inhibition (e.g. denervation/agonist deprivation, use of an antagonist)
⇓
1) Receptor Upregulation (recruitment of internalized receptors, *de novo* synthesis)
2) Amplification of signal transduction
⇓
SENSITIZATION
super-sensitivity of the receptor and effector system to the agonist
CLINICAL EXAMPLES: sudden discontinuation of *Propranolol* in Angina Pectoris

Continued intense receptor stimulation (e.g., by the agonist)
⇓
1) Receptor Downregulation (internalization, ↓ synthesis, ↑degradation)
2) Attenuation of signal transduction (e.g., phosphorylation of amino acid constituents)
⇓
Desensitization (refractoriness) of the receptor to the agonist (becomes less sensitive)
⇓
Loss of drug action / Decrease in drug response
PHARMACODYNAMIC TOLERANCE
CLINICAL EXAMPLES: Bronchial Asthma treated with *Albuterol*;
Parkinson's Disease treated with high doses of *Levodopa;*
Chronic Pain treated with *Morphine*

Regulation of Receptors: Think about the system that will discuss as homeostatic system so that two concepts and two effects.

1. One is about what happens when you inhibit it is helpful for a prolonged period of time you inhibit the receptors. You decrease the signaling through the receptors. How the body responds it up regulates the receptor and amplifies the signal transduction? So what you get as a result is what we call sensitization to the given drug or to the given agonist. There will be basically stronger response if The Agonist is applied after the period of prolonged receptor inhibition.
    A. One clinical example here is when the patient who is chronically treated with again propranolol beta blocker. When the patient suddenly discontinues use of Propranolol, during the treatment with Propranolol because there is receptors are blocked, there will be up-regulation of the receptor the body is defending against the blockade of the receptors. So there is a risk of cardiac ischaemia so angina pectoris meaning chest pain in a patient. In this situation because now you have a lot of receptors beta-1 receptors in the heart are available for epinephrine norepinephrine binding and this would lead to dangerous increase in the heart rate and basically life threatening situation. Beta blockers shouldn't be discontinuous suddenly. It can be removed slowly if you decrease a dose, then the mechanism of receptor will be winding down basically.
2. The opposite situation where you have the prolonged activation of the reset prolonged intense receptor activation. How does the body respond down regulates the receptors have fewer receptors available for the drug to basically minimize again the fact of The Agonist? The concept of homeostasis bring the system to some basal level and not only down-regulation of the receptors, but now attenuation of the signal transduction. So this would be opposite to sensitization, desensitization of the receptor to The Agonist. There will be less response to The Agonist and we call it pharmacodynamic tolerance.
   When we get to pharmacokinetics we'll actually learn drug action modifiers in the subsequent session. Then, we'll talk about pharmacokinetic tolerance, also mechanisms of tolerance based on the drug metabolism and so on. BUT here is pharmacodynamic tolerance = meaning that tolerance developed with receptor based, so tolerance meaning now you apply the drug but the body doesn't respond as well because there is a betters are down regulated.
    A. Clinical examples: The patient is no longer responding to albuterol which is beta2 agonist. If the patient is chronically treated beta-2 agonist longer acting agonist, so basically the patient has asthma attack, and one users arbitral and arbitral is not working.
    B. Parkinson's disease treated with levodopa is another example. we'll talk about Parkinson's disease and and actually also treatment of asthma in the summer course
    C. Opioids: so tolerance to opioids that the patient who is chronically treated with opioids. For example terminally ill patients with cancer, you need to increase the dose of morphine. Why is that? because the body is trying to defend itself from the increased effects of morphine and down regulates the receptors.