PHARMACOLOGY

◉ Sheets ○ Slides

Number: 2

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Subject: Pharmacodynamics/Pharmacokinetics

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Enhancement:

- Using antagonism is great for treatment of toxic materials that you just want the body to get rid of
- However, there is a method called enhancement which is good for treatment

Why is enhancement important?

- Drugs don't usually have high efficacy (high capacity for producing the desired result)
- So sometimes multiple drugs need to be used to treat a patient
- **For example, Diabetes Mellitus (DM):** An early patient who was just diagnosed with DM will have few amounts of functioning insulin. Pharmacists depend on the functioning insulin, so they will give the patient Glucophage (metformin), an oral drug used to help control glucose levels in the blood. But after some time this functioning insulin will disappear, so this Glucophage will not treat the patient. So now another medication needs to be introduced to add with the Glucophage. And the reason for this is to enhance the first drug.

In order to understand enhancement, we need to understand the relationships between drugs:

- **ADDITIVE:** both drugs have the same effect, but when given together the effect will be equal to the sum of the two drugs.
  - Example: Drug A decreases blood pressure by 10, Drug B decreases blood pressure by 10, and when used together they reduce blood pressure by 20 (1+1=2)
- **SYNYRGIC:** Two drugs when put together will not work to the sum of their effects, the effect will be greater in magnitude than the sum
  - Example: Drug A decreases blood pressure by 10, Drug B decreases blood pressure by 10, and when used together they can reduce the blood pressure by 25, 30, 40 (any number greater than the sum)
  - This relationship is great because it increases the efficacy, but this comes with a cost!
  - When drugs are combined it is important to focus on the side effects, because synergism is occurring to them as well (but not always)
  - In situations like this, you need to be the judge. Look at the risks, benefits, and the situation of the patient. If the risk outweighs the benefit then you shouldn't give the patient the drug, and vice versa.
- **POTENTIATION:** Some drugs can be metabolized very quickly before taking effect (short half-life). So another drug is given to enhance the effect of the first drug. This drug can inhibit an enzyme in the

metabolization process of the first drug and not let it get metabolized so quickly.

Receptors:

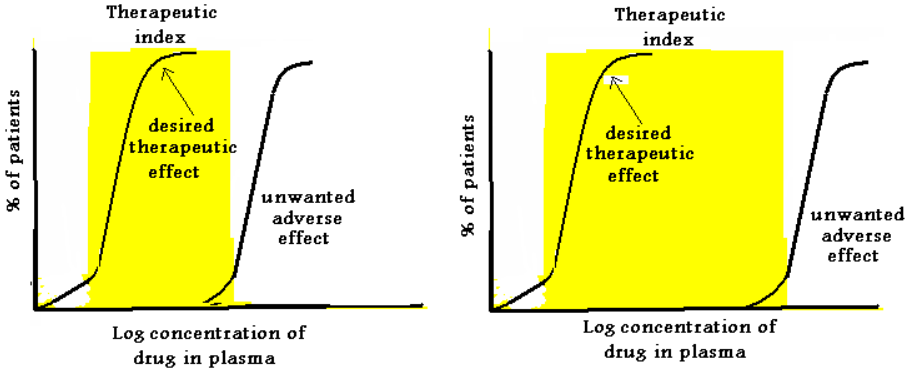
- Receptors are **dynamic**
- The affinity of the response to drugs is not fixed. It alters according to the situation
- So this statement is important for understanding **tolerance**→ the loss of the effect of the drug with the time of dosing
- **RECEPTOR DOWN REGULATION:** There is prolonged use of **agonist**, there will be a **decrease** in the number of receptors and sensitivity, therefore **reducing** the drug effect
  - This is important with addiction
  - So this is why you see people die from heroin overdose. The person was so addicted to it, that in order to get the feeling/effect they wanted, they increased the dose so much that the side effects increase→unable to breath→resulting in death

But why did the side effects increase?

  - In down-regulation, the receptors that are supposed to signal the effect have decreased. But there are open receptors that are involved with other effects, so the drug/substance will bind to the other receptors (the drug has to go somewhere!)
- **RECEPTOR UP REGULATION:** There is a prolonged use of **antagonist**; there will be an **increase** in the number of receptors and sensitivity, therefore **changing** the drug effect.
  - An antagonist will be inhibiting a receptor, so the body responds by increasing the number of receptors
  - <u>Example:</u> Propranolol inhibits β-1 receptors, so in response the body increases the number of β-1 receptors. The endogenous substance that binds with β-1 receptors is adrenaline. So when propranolol is stopped after prolonged use, the adrenaline effect increases and there is a hypertension crisis. So when the use of propranolol needs to be stopped, it needs to be stopped at a slow rate so the body can adapt without it.

Note: not all drugs affect the number of receptors

Therapeutic Index:



- When you look at both of the curves you will see a line for the percentage of patients that benefited, usually by increasing the dose
- There is another line with the percentage of patients with unwanted side effects, and that occurred with increasing the dose to a greater magnitude
- Between the two lines there is a window→**margin of safety** or **therapeutic window**
- The dose of the drug can be increased only so much before it causes some dangerous effects for the patient→this is the purpose of the window: it's a range for giving an appropriate dose for a drug to give the desired therapeutic effect
- There is a difference between the two curves you see above, and that is the therapeutic window
- The first curve has a narrow therapeutic window so a small dose can cause an adverse effect
- The second curve has a large therapeutic window, so it would take a large dose to cause an adverse effect
- The safety of drugs is determined by this curve: **therapeutic index curve**

How can we calculate this curve?

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

TI= Therapeutic index

TD50= minimum dose that is TOXIC for 50% of population

ED50= minimum dose that is EFFECTIVE for 50% of population

- The larger the toxic dose (TD50), the wider the curve

- The smaller the toxic dose (TD50), the narrower the curve
- The smaller the therapeutic index, the LESS safe the drug will be
- Ideally the TD50 should be a higher dose than ED50 so the therapeutic index will be large
- Drugs with a narrow therapeutic index are usually given in hospitals because they need monitoring → narrow therapeutic drugs (the effective dose is so close to the toxic dose)
- Drugs with a narrow TI are used because sometimes there are no other drugs that serve the same purpose.

END OF PHARMACODYNAMICS

REFER TO LIPPINCOTT PHARMACOLOGY FOR EXAM

Pharmacokinetics:

- **Pharmacokinetics:** following the movement of the drug in the body→what the body does to the drug
- Absorption, distribution, metabolism, and elimination
- This "pathway" can be altered by the medical condition of the patient or with the drugs the patient is using

Drug Transport:

- There are transporters that transport drugs out of the body and into it
- So let's say a drug was taken and it reached the duodenum (main site of absorption), in the duodenum there are transporters
- On the membrane of the duodenum there are active pumps (need ATP) and solute carriers (depend on concentration)
- **ABC Family:** pumps that need ATP
- **SLC family:** depend on osmolarity
- The duodenum has transporters that do not allow the drug to pass→**Expelling transporters** [P-glycoprotein (P-gp), MDR1]
- The purpose of expelling transporters is to eliminate the drug from the body, it protects (remember drugs are "toxins")
- So it's important if you need the drug to stay in the body to not allow it to be a substrate to expelling transporters that don't allow drugs to pass → increasing the concentration of the drug will eventually allow it to bind to other transporters
- Expelling inhibitors can sometimes be inhibited

- MDR1 can be inhibited by grapefruit juice. So if a person where to take a drug with grapefruit juice, the MDR1 would be inhibited and that means ALL of the drug will be absorbed and there will be an increase in toxicity. There will not be an efficient protective mechanism.

❖ All transporters can be effected by drugs
❖ So it's important when you want to prescribe a drug to know what transporters are effected so when you prescribe a second drug there is no problem with the absorption→ drug-drug interactions

Route of Administration

❖ Most drugs absorbed by the duodenum will go to the liver and will be metabolized there
❖ The amount of drug that will be present in the blood depends on the dose administered
❖ **First-pass metabolism:** process in which a drug is administered by the mouth and absorbed by the GI tract and transported to the liver to be metabolized. Only a small amount of active drug will reach the circulation.
❖ Some drugs have high first-pass metabolism (a lot of the drug will be metabolized and won't reach the target)
❖ So when those drugs are taken orally it all goes to the liver and not much goes to the blood stream
❖ Some drugs are given by injections to avoid the first-pass metabolism and to give a rapid response
❖ Injections can cause cellulitis (needles and skin need to be sterilized)
❖ **Intravenous injection:** the drug concentration is high at the beginning for the rapid effect, then it will decrease rapidly
❖ **Intramuscular injection:** the drug concentration will decrease very slowly because the intent is for the drug to stay for a long period of time in the body
❖ **Subcutaneous injection:** used when the drug needs to stay in the body for a very long time (insulin)
❖ Oral is safe, but it takes a while for there to be an effect