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number : 3

doctor : malek

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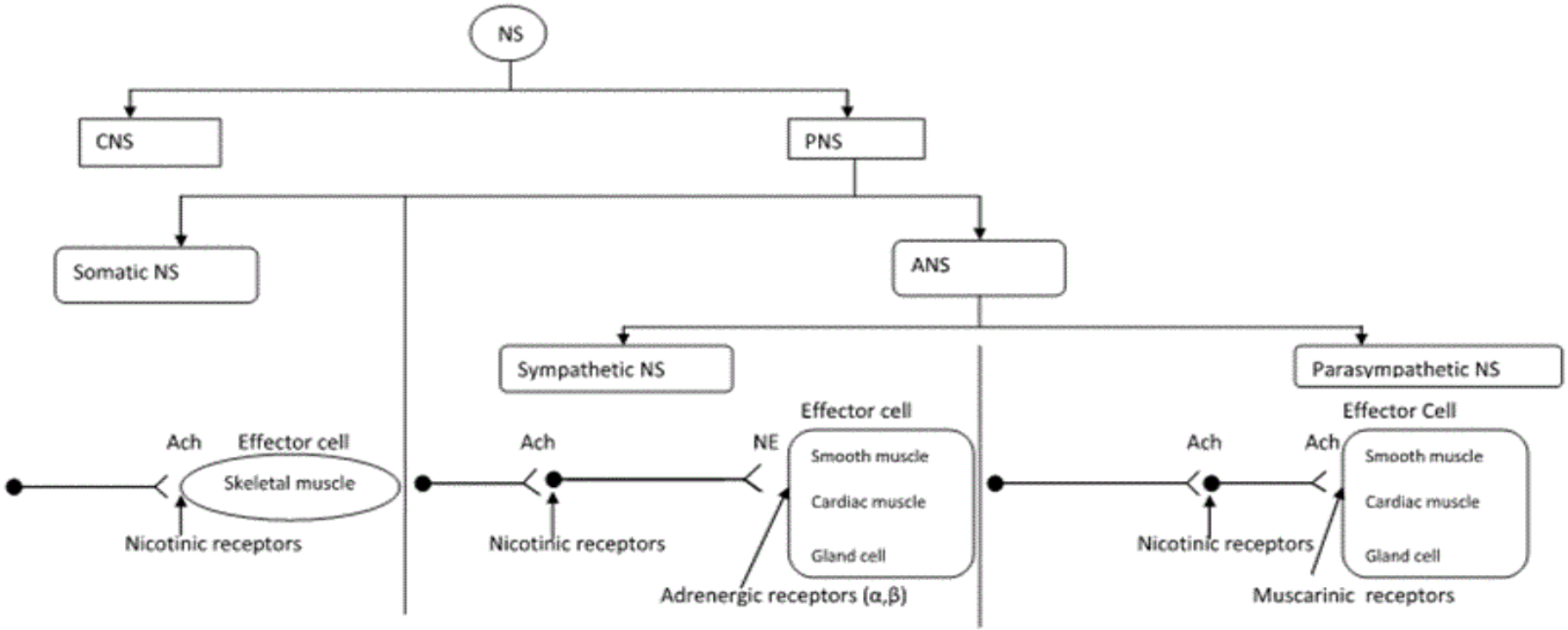
correction : moh'd abu jubba



Locations of Receptors for Acetylcholine, Norepinephrine, and Epinephrine

I. Receptors for acetylcholine

A. Nicotinic receptors

1. On postganglionic neurons in the autonomic ganglia
2. At neuromuscular junctions of skeletal muscle
3. On some CNS neurons

B. Muscarinic receptors

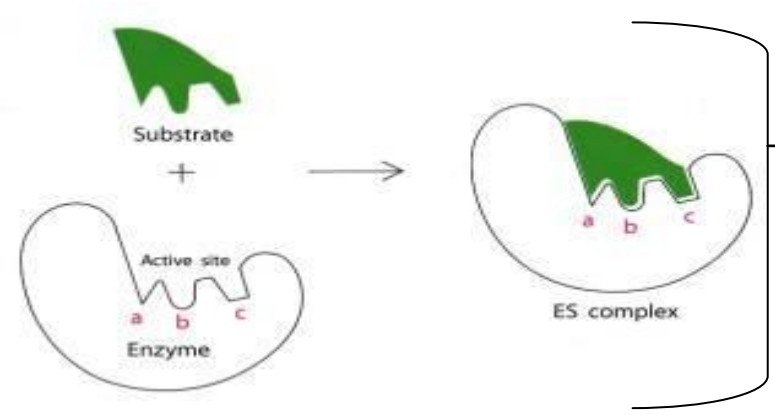
1. On smooth muscle
2. On cardiac muscle
3. On gland cells
4. On some CNS neurons
5. On some neurons of autonomic ganglia (although the great majority of receptors at this site are nicotinic)

II. Receptors for norepinephrine and epinephrine

A. On smooth muscle
B. On cardiac muscle
C. On gland cells
D. On other tissue cells (e.g., adipose, bone, renal tubules)
E. On some CNS neurons

Model of Drug / receptor binding

99% of drugs prescribed to patients go toward the body and find the receptor and produce therapeutic effect, the rest 1% don't use receptors and we will take about them later.



Model of drug receptos binding Which is mostly lock and key model Promoted by

the 3-D structure of the receptors where the drug-receptor interactions are complementarity of shape between drug and receptor.

Our bodies have different properties . Two different important properties you should know.

١-Tissue specific receptor activity: the same receptor is found in different part of the body, and in each place it has specific action(activity). So the same effector(drug) will bind to the receptors at different sites on the body and we will have different activities. For example beta-2 is found in the lungs in the muscles of bronchi, and it is found in the liver, as well as it is found in the heart and other parts of the body. So when you give a drug for example for a patient that has asthma(beta-2 agonist drug), it will bind to beta-2 receptors. Beta-2 receptors will bronchodilate muscles of bronchi, at the same time it will work on glucose metabolism. So if I want to bronchodilate my patient, I am gonna to affect his glucose metabolism , and that is because beta-2 receptors are found in different part of the body and at every single part this beta-2 receptor has different activity, this is first factor for the side effects. But in the case of asthma to avoid the side effect of beta-2 agonist, we can give the patient Ventolin spray Inhaler (not oral). so it 90 percent will just bind to beta-2 receptors in the lungs because it mostly will not go to the blood circulations and will not bind to receptors other than that present in the lungs, so we treat asthma with about no side effects. Another example is the steroid receptors (like estrogen receptors) which increase the growth of the breast cancer in other hand they decrease the growth of cancer in endometrium of uterus due to different activities they have.

So why drugs produce side effects? Simply speaking because they gonna bind to the receptor(All the receptors) and the receptor itself has tissue specific activity, means in each tissue it will produce different activity.

2-Receptors homology: receptors in the body are made up of amino acids and they have some similarities to each other which referred to as **homology.** Homology : receptors look like, for example alpha-1 receptor is homology (similar) to alpha-2, it also has some similarities to beta-1 receptor but to a lesser extent than to alpha-2. Also beta-1 receptor is homology to beta-2 , and it has some similarities to alpha-1 but to a lesser extent than to beta-2 .

And as you know that the binding of the drug toward the receptor depends on affinity. So if I'm targeting my drug toward beta-1 receptors it is going to bind beta-1 mostly, but this drug will also bind, to a lesser extent, to beta-2 receptors→lesser extent to alpha-1→lesser extent to alpha-2 receptors and so forth. This homology between receptors is the second factor for side effects.

There is no drug 100 % specific, which means that there is no drug with a single effect.

Major receptors families

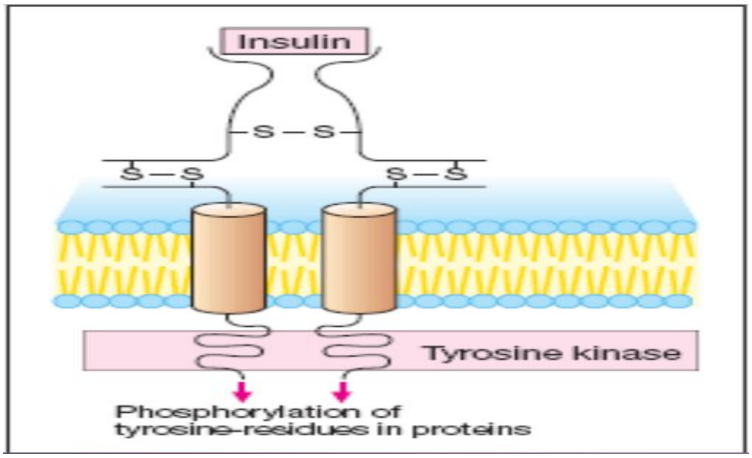
1- Ligand-gated ion channels: Ach will bind nicotinic receptors then Na^+-channels open, then producing action potential which leads to muscle contraction . for a patient with its muscle contracted, we give antagonism (muscle relaxant) which reduce contraction leading to muscle relaxation.

ex: to treat Myasthenia gravis patients we give them agonist drugs to increase the activation of their nicotinic receptors but as we know in the body we already have nicotinic receptors and Ach so where is the problem? What really is happening that their immune system attack their receptors so they decrease in number so the frequency of activation of receptors to contract the muscle will be lesser than usual and can't contract.

2- G protein-Coupled receptors: Such as adrenergic receptors(control heart rate and contraction of vessels …etc) and moscarinic receptors (m1-m5) .

G-Protein-Coupled receptors are seven transmembrane segments that loop in and out of the cell membrane, so they have an outer-face and inner-face (extracellular domain and intracellular domain(cytoplasmic domain).The cytoplasmic domain(inner-face) is coupled to G proteins that include three (i.e., trimeric) parts—the α, β, and γ subunits. When the ligand (Endogenous ligand or the drug) binds to the extracellular part of the receptor, a conformational change occurs in the receptor that activates the G proteins by binding to guanosine triphosphate (GTP) then induces intracellular signals .ex: increasing the ATP which leads to increase the secretion of ca++ from ER and then increasing the heart rate (the drug here is adrenaline).

3- Enzyme-linked receptors: The common example is insulin. Insulin binds with its receptor and phosphorylates tyrosine kinase which causes a sequence of reactions which leads then to the therapeutic activity by The addition of phosphate group which modify the three dimensional structure of the target protein, and so resulting in molecular switch.

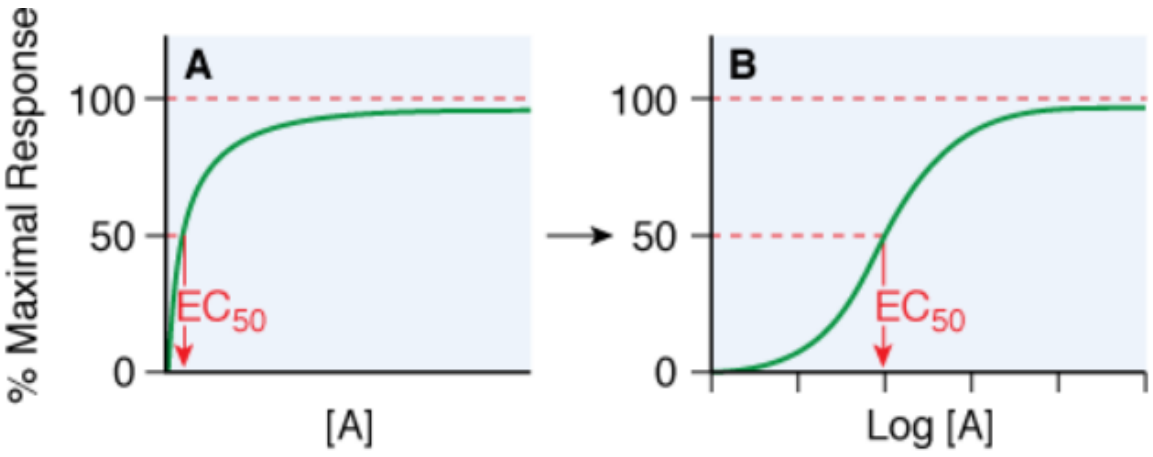


4- Intracellular receptors: In this family the ligand must diffuse into the cell to interact with the receptors. Therefore the ligand must have sufficient lipid solubilities (they are lipophilic)to be able to move across the target cell membranes. The best example being the steroids hormones. In which the activated ligand-receptor complex migrate to the nucleus, where it bind to a specific DNA sequences, resulting in regulation of the gene expression.

Dose response relationships

❖ Graduate dose-response relations:

As the dose administrated to single subject or isolated tissue is increased, the pharmacologic effect will also increase. At a certain dose, the effect will reach a maximum level, which is called the ceiling effect or E_{max}(Efficacy). This means that at first I give drug with low concentration, then I gain low response, and as I increase the concentration of my drug, I gain more effect until I reach the maximum effect and then there is no more effect but only increase the probability of causing side effects, but if I give the drug with very low concentration there will be no effect and the patient is not does not

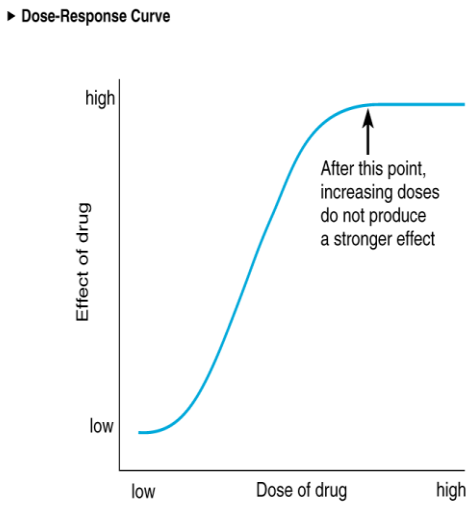


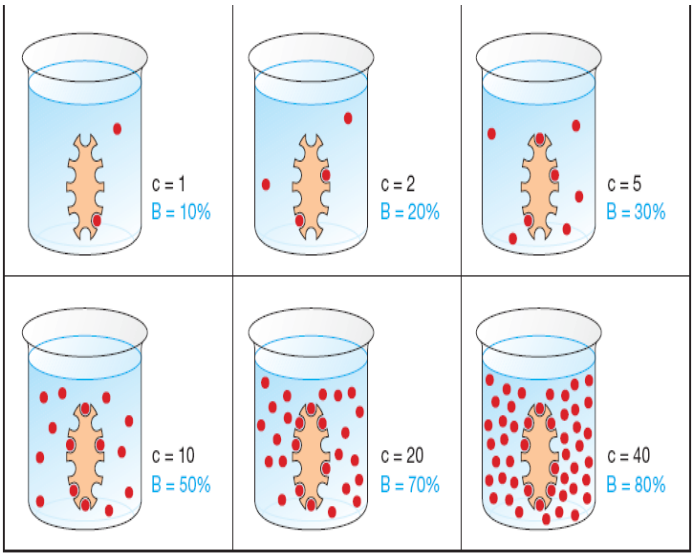
respond. Here we call it sub-therapeutic effect

When you have headache you go to the pharmacy and you ask the pharmacist to give you profen. So the pharmacist the 200mg profen. So -1-why are there many concentrations of profen(200, 400, 600)mg? -2-why did not he give you the 400mg or 600mg profen?

1-There are more concentrations of profen because there are different levels of pain. Some patients might have mild pain(ex:headache→200mg profen), some have moderate pain(ex:dental pain→400mg profen), and some have moderate to severe pain(Sprained ankle or Rheumatic arthritis →600mg). So patients with mild pain will be given 200mg profen, patients with moderate pain will be given 400mg profen, and patients with moderate to severe pain will be given 600mg profen. But if the pain is too severe and not responding to this 600mg profen, I have to prescribe another drug to this patient.

2-As I increase the dose, the effectiveness is increasing until I reach saturation-point or E_{max} (ceiling effect)(Efficacy) where there are no more receptors to occupy, so I should not ever get drug more than this saturation because all receptors are already occupied. If I get drugs more than this, the drug that didn't find sites for binding is now free so it will miss its specificity and will bind with other receptors. So side effects will appear more clear as I'm increasing the drugs.





So that: **<u>Don't</u> give drugs over the ceiling effect(E_{max}) to avoid side effects.**

Now the question is: why don't we prescribe 600mg profen from the beginning for all patients with all levels of pain?

Simply, if we increase the dose, free drug will be a lot, and side effects will be subsequently a lot. So you do not have to have side effects unless there is a reason.

Patients with mild pain like headache→ we give him 200mg profen

Patient with moderate pain like toothache→ we give him 400mg profen

Patient with severe pain like Rheumatic arthritis →we give him 600mg profen.

why can not paracetamol relieve a tooth pain(dental pain) which is a moderate pain?

Because the paracetamol's E_{max} is at mild pain, so it can't relieve a tooth pain which is moderate pain.

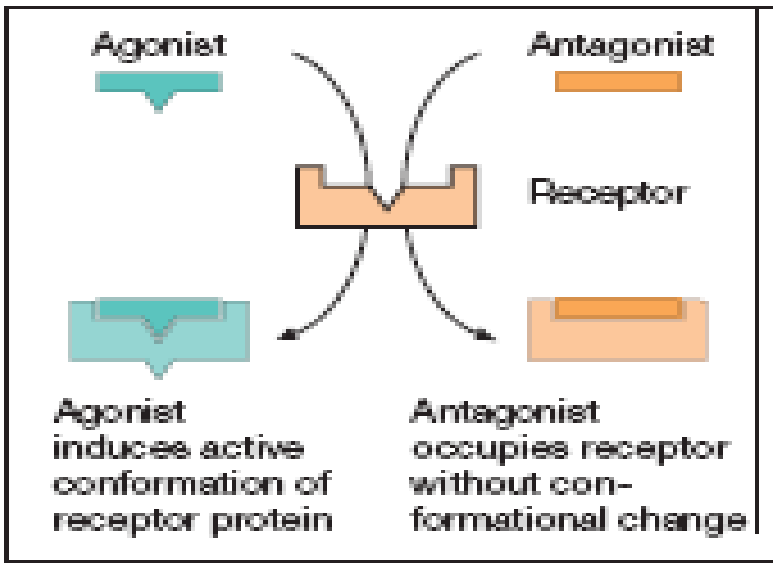
Agonist and antagonist

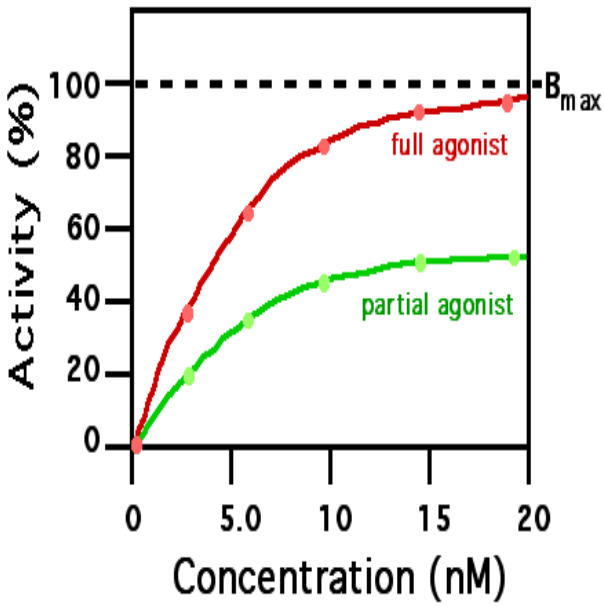
الدكتور تكلم عن هذا الموضوع في بداية المحاضرة لكن تم وضعها هنا حسب الترتيب في السلايدز

Drugs can either mimic physiological activity of the body's own molecules or block the physiological activity of the body's own molecules. If the drug bind to a receptor and produces a physiological effect (produce intrinsic activity) that mimics the response to the endogenous ligand (hormone) it is known as an **agonist**. But if the drug decreases the action of the another drug or endogenous ligand (does not produce intrinsic activity) by either binding to its receptor or by binding to the endogenous ligand itself (or other drug) it is known as an **antagonist**. Each receptor has something to bind to, which is called endogenous ligand. These endogenous ligands are naturally existed inside our bodies. For instance morphine receptors have its own ligands which are endorphins and enkephalins. These endorphins and enkephalins bind toward the receptors and activate the receptors. When we give a drug like morphine. If it was morphine agonist, it will activate the morphine receptors, but if it was morphine antagonist, it will not.

Often the agonist has the intrinsic activity as the endogenous ligand. But sometimes the agonist has opposite activity to the endogenous ligand. This agonist which binds to the same receptor as the endogenous ligand but induces a pharmacological response opposite to this endogenous ligand, is called **Inverse agonist.** It is theoretical and does not exist actually. **Inverse agonist**...not important **(just for your knowledge)**

Not all agonist have full efficacy at the receptor. So when this agonist bind and activate a given receptor , but have only partial efficacy at the receptor relative to a full agonist it is called **partial agonist.**



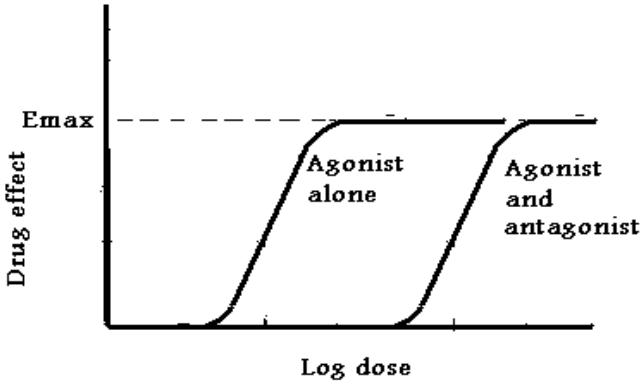


Affinity: there is something called affinity between the drug and the receptor. This affinity tell us the time of binding (Kd). Simply speaking, the drug binds toward the receptor and then come out. How long it binds and how long it come out depends on affinity.

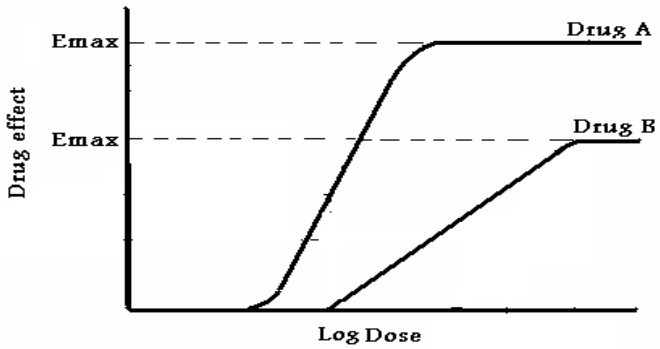
Antagonism between drugs :-

- **Pharmacologic antagonism:** Occurs when an antagonist prevent an agonist from interacting with its receptors to preduce an effect, and it can be either competitive or noncompetitive.

➢ **Competitive antagonism→** compete with agonist in a reversible fashion in the receptors. The log dose-response curve is shifted to the right, indicating that a higher concentration of agonist is necessary to achieve the E_{max} and response(as in the case of competitive inhibitors in the biochemistry when the competitive inhibitors compete the substrate and decrease its affinity '' K_m increase'' to the enzyme, so we need more concentration of the substrate to achieve the V_{max}→ the V_{max} is not affected in this case)



➢ **Noncompetitive antagonism→** binds irreversible to the receptors site or to another side that inhibit the response to the agonist. And no matter how much agonist is given, the action of the antagonist can not be overcome. The shift in the log log response curve in this case is a nonparallel shift(as in the case of noncompetitive inhibitors in the biochemistry when the noncompetitive inhibitor bind to the enzyme and decrease its V_{max} but do not affect its affinity)



- **Physiologic antagonism:** Here the drug act independently on two different receptors, and exemplified by one drug acting on sympathetic nervous system causing the heart rate to increase and causing vasoconstruction; while another drug acting on the parasympathetic nervous system decrease the heart rate and causes vasodilatio.

- **Chemical antagonist (Antagonism by neutralization):** Occurs when two drugs combine with one another to form an inactive compound, and the best example being the drugs containing sulfhydryl (SH) groups, when combine with mercury or arsenic.

    - You can see this video in the youtube for more understanding

https://youtu.be/z_R-A0_aRBE

- appendix link :

https://drive.google.com/file/d/0B7_HurnNvwCzbHE1Mkp0bURESzA/view?usp=sharing