DOCTOR 2020 | JU

PHARMACOLOGY

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*The DOC started by revising the old material.

Now we will start talking about Efficacy : it is the maximum effect of a drug (Emax), and it depends on the number of drug-receptor complexes formed, and also on the efficiency of the coupling of receptor activation to cellular responses.

Aspirin and morphine (acts on different receptor), they produce the same pharmacologic effect (analgesia) but have very different levels of efficacy.

Efficacy also called "Emax" depends on :

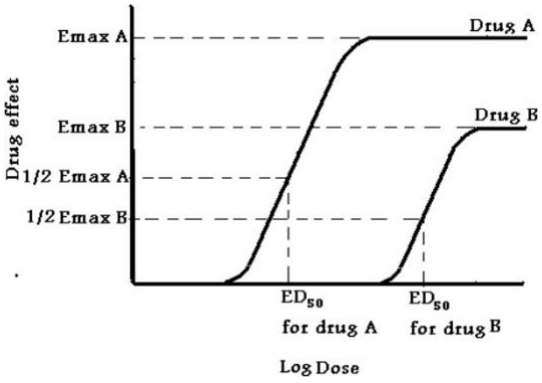
1. **Maximum number of receptors**
2. **Intrinsic activity of the drug (look down)**
3. **Affinity of binding**

If a drug can stimulate a receptor to produce a biological response, it is said to have efficacy or intrinsic activity.

» Efficacy refers to the capacity of a drug to produce an effect or the overall magnitude of the maximum response, synonymous with **intrinsic activity**.

» If a drug stimulates a full response, it might to said to be a full agonist and to be very efficacious

Drug A, has more Emax then drug B (more efficacy), also it has a smaller ED50 so its potency is greater than drug B.



- Notice that efficacy is measured in Y-axis and potency on X-axis.

The smaller the EC50, the greater the potency, while Efficacy is indicated by the **height** of the log dose response.

Adrenaline, phenylephrine, they both bind to the same receptor, but adrenaline is more effective due to its intrinsic activity.

What determines what drug we will choose, the drug that has more potency or the one with more efficacy?

It's the condition of the case, if we are using toxic drug then we try to use a small amount of it i.e we need the drug that has more potency.

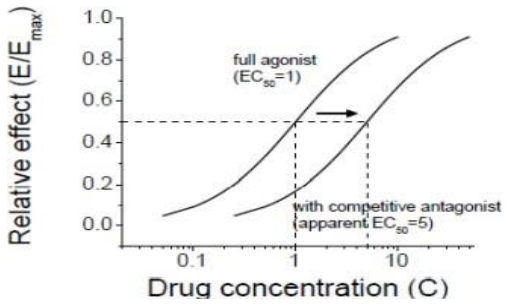
Antagonism between drugs

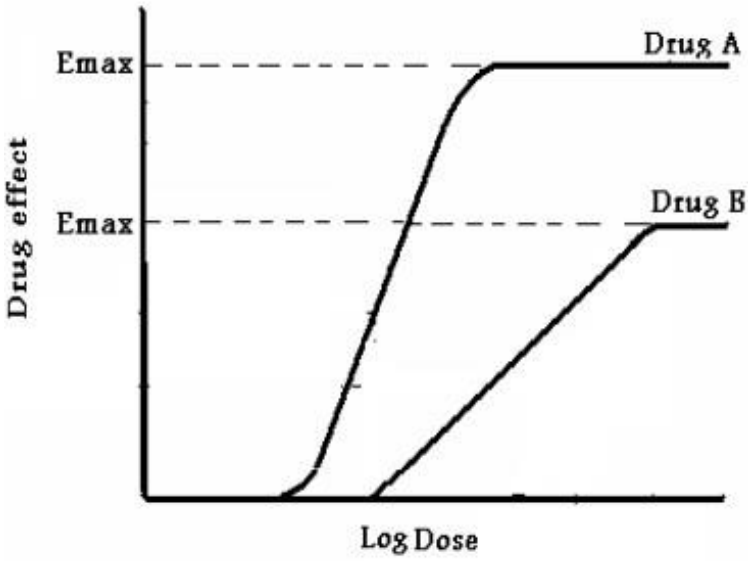
1- **Pharmacologic antagonism**: occurs when an antagonist prevent an agonist from interactingwith its receptors to produce an effect, and it can be either competitive or noncompetitive.

Competitive antagonist competes with agonist in a reversible fashion to bind the receptor. The log dose-response curve is then shifted to the right, indicating that a **higher concentration** of agonist is necessary to achieve the response
(Emax doesn't change/different E50)

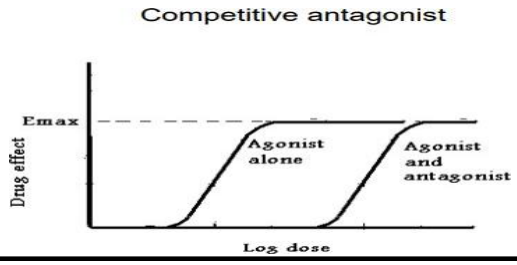
"Neutral" antagonist: they just occupy the receptor by preventing the normal ligand binding, It binds to the agonist site & do not shift equilibrium towards active or inactive conformation.

Non-competitive antagonist binds irreversibly to the receptor active site, or to another site on the same receptor, which causes conformational changes of the active site, that will inhibit the response of the agonist. And no matter how much agonist is given,the action of the antagonist can't be overcome. The shift in the log response curve in this case is a nonparallel shift (decrease of Emax).





Note that potency is dependent on the concentration of the antagonist it may change



So Pharmacologic antagonism happens when an endogenous ligand and a drug or two drugs compete on the same receptor, we also have other kinds of antagonism:

2- **Physiologic Antagonist:** here the drugs act independently **on two different receptors**, But the effect of one drug is **opposite** to the effect of the other drug and exemplified by one drug acting on the sympathetic nervous system causing the heart rate to increase and causing vasoconstriction , while another drug acting on the parasympathetic nervous system decrease the heart rate and causes vasodilation (opposite effect and different receptors) .
so for example when a drug acts on adrenergic receptors and another drug acts on muscarinic receptor independently causing the opposite effect so here we call the first drug as agonist and the other as physiological antagonist.

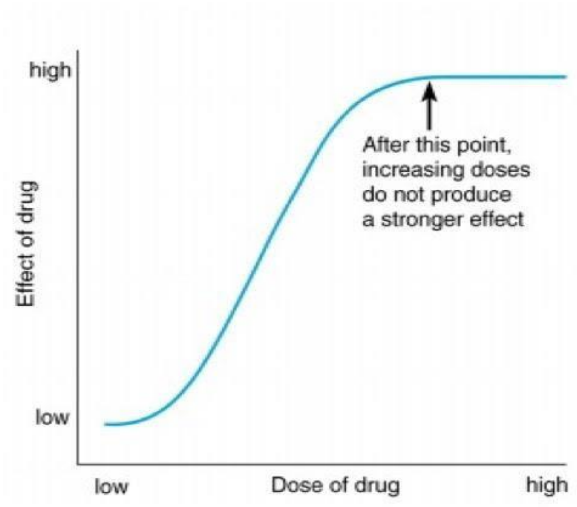
And here's another practical example:
anaphylactic shock: this happens due to excessive and exaggerated allergy to a particular substance (for example drugs , nuts …etc) and one of the symptoms of the anaphylactic shock is the throat closes up causes, swelling of the tongue , constriction of the bronchi , and falling of the blood pressure because of dilation of blood vessels and all of these symptoms are due to excessive release of histamine, so you will say that we should give the patient anti-histamine drugs but the problem here is that the patient's throat is closed and if I give him an anti-histamine drug which is taken as pills it would not save his life so instead we give the patient adrenaline or epinephrine (which are given intramuscularly) and we call this epi shot, resulting in dilation of bronchi , constriction of blood vessels and raising blood pressure by the activation of different receptors than the histamine receptor ,so it binds the adrenergic receptor and gives the opposite effect so now we treated him and this is Physiologic antagonism.

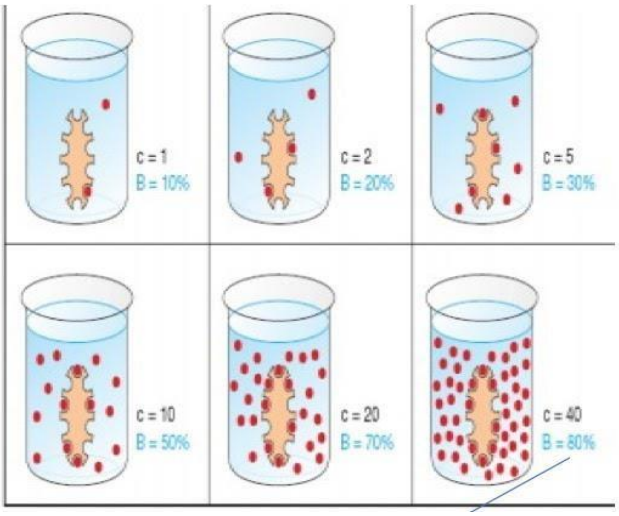
3- **Chemical antagonist (Antagonism by neutralization):** Occurs when two drugs combine with one another to form an inactive compound, and the best example being the drugs containing sulfhydryl (SH) groups, when combine with mercury or arsenic.

Another example is antacids (bases) that react with the acids of the stomach .

Graduate dose-response curve:

If we are increasing the dose or the concentration of the drug, the response of that drug will also increase.





Two-state model of drug-receptor interaction

- Full agonists shift equilibrium "fully" towards the active conformation
- Partial agonists shift equilibrium "partially" towards the active conformation
- Sub-maximal effect with receptors completely occupied .

Two-state model of drug receptor interaction

- ✓ The receptor is postulated to exist in the inactive non-functional form (Ri) and in the activated form (Ra).

- ✓ Thermodynamic considerations indicate that even in **the absence of any agonist**, some of the receptor pool must exist In the Ra state, and may produce the same physiological effect as agonist-induced activity.

This mean that the receptor can be active without an agonist being bound to it for a period of time , they are switching between active & inactive forms.

- ✓ Agonists have a much higher affinity for the Ra configuration and stabilize it, so that large percentage of the total pool resides in the Ra-D fraction and a large effect is produced.

Constitutive Activity

The effect of receptors, occurring in the absence of agonist, is termed constitutive activity.

The recognition of constitutive activity may depend on the receptor density, the concentration of coupling molecules (if a coupled system), and the number of effectors in the system.

Inverse agonists:

While antagonists are traditionally thought to have no function, shift the equilibrium towards the inactive conformation (Ri-D), it make a conformational change