Doctor 021

PHARMACOLOGY

Sheet no. 7

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RECEPTOR OCCUPANCY THEORY THE "LAW" OF MASS ACTION

» Activation of membrane receptors and target cell responses is proportional to the degree of receptor occupancy.

» Assumptions:

– Association is limited by collision, orientation and energy

– All receptors are equally accessible

– All receptors are either free or bound, there is no "partial" binding

– Neither drug nor receptor are altered by binding

– Binding is reversible

The degree of activation of membrane receptors and the resulting cellular response depends on how many of these receptors got occupied by the drug, this theory follows the "law of mass action"(the law that governs all reactions in nature)

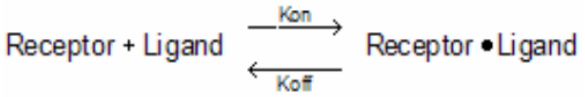
With regards to drug-receptor interaction, the reactants are drug and receptor will interact and produce drug-receptor complex, and this reaction will have a reaction rate termed **K**

There are assumptions and the important assumption we rely on is that the binding is reversible "and we prefer most of drugs bind reversibly to the receptor" this indicates that the drug-receptor complex will dissociate again to its reactants(drug and receptor) and this is the rate of the reverse reaction.

LAW OF MASS ACTION (A MODEL TO EXPLAIN LIGAND-RECEPTOR BINDING)

This slide is not required in the exam

- **When a drug combines with a receptor, it does so at a rate which is dependent on the concentration of the drug and of the receptor**
- **Assumes it's a reversible reaction**



- **Equilibrium dissociation (Kd) and association/affinity (Ka) constants**
  - **Kd = Kon/Koff = [D][R]/[DR]**
  - **Ka = 1/Kd = Koff/Kon = [DR]/[D][R]**

Kd: is the Equilibrium dissociation constant indicates how much of the drug will stay bound in the drug-receptor complex versus how much of the drug dissociate from the receptors, so the Kd gives an idea about the affinity or the strength of binding between the receptor and the drug.

The factors of formation the DR complex are:

1- Concentration of the drug, because it is a reversible reaction, drug will compete with endogenous ligands so increasing concentration, increasing the chance of binding
2- Affinity toward the drug
Note: concentration of receptors will increase maximum effect of the drug but not determine the rate at which DR complex is formed.

Drug-receptor binding

$$D + R \xrightarrow{k} DR$$

$$DR \xrightarrow{k^{-1}} D + R$$

» This ratio is the equilibrium dissociation constant or KD

» This dissociation constant, Kd, indicates the strength of binding between R and D in terms of how easy it is to separate the complex DR

$$\frac{k^{-1}}{k} = K_D$$

$$\frac{\text{sec}^{-1}}{M^{-1}\,\text{sec}^{-1}} = M$$

So we did some derivatizations on **Kd** law, and ended up by ***Hill-langmuir equation***

$$B/B_{max} = \frac{[D]}{[D]+K_D}$$

This equation similar to Michaelis-Menten Equation

B: bound receptor / Bmax: maximum number of bound receptors which depends as we mentioned on [drug] and Kd

How to determine Kd ?

By an expiremant , lets say we put an muscle in water path , and rememper there are nicotinic receptors(binds Acetyl choline) on the surface of muscles, then we add acetyl choline and mesure how many of receptors get occubied,

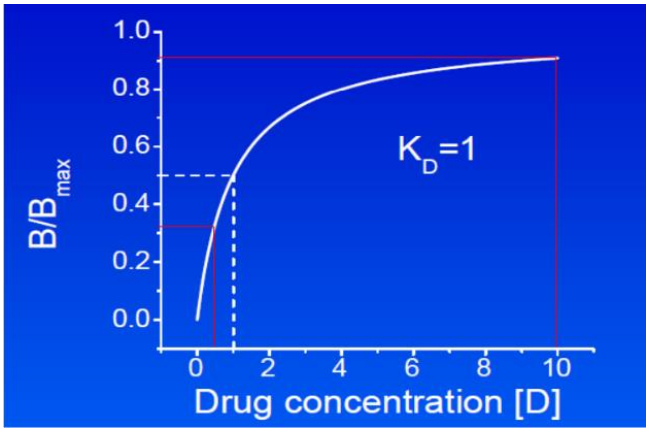
As the conc. of acetyl choline increased, more receptors will be bound to it until a certain level, the increasing in conc. doesn't effect, because of receptor's saturation.

this experiment give us indication about two things, the maximum number of receptors and the Kd.

KD: concentration at which binding site is 50% occupied.

Affinity= 1/Kd

Kd is Inversely proportional to the affinity



DRUG RECEPTORS & PHARMACODYNAMICS

Receptor interactions determine the quantitative relations between concentration of drug and pharmacologic effects.

» The receptor's affinity for binding a drug determines the concentration of the drug required to form a significant number of drug-receptor complexes.

To get a drug effect the Drug-Receptor complex should be formed and this governs by the maximum number of receptors

» The total number of receptors is usually much smaller than the number of drug molecules.

» This will limit the maximal effect a drug may produce.

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.

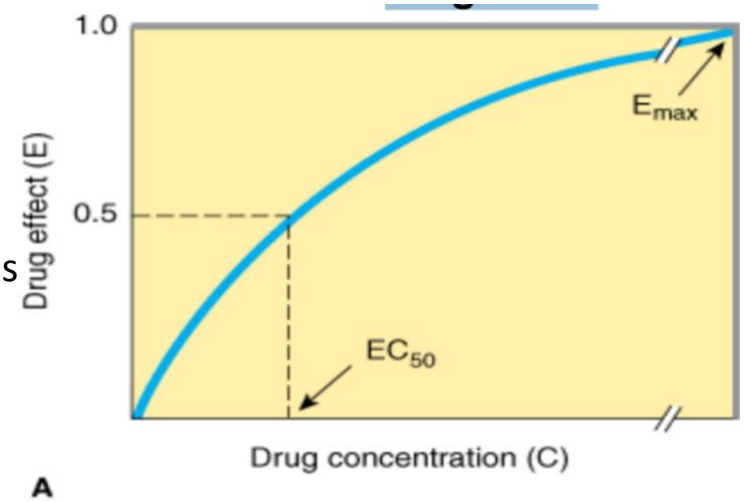
At a certain dose, the effect will reach a maximum level, which is called the ceiling effect or Emax.

Relations between drug concentration and drug effect

This curve depends on how much drug-receptor complex has been formed.

EC50: the conc. of the drug requires to reach 50% of the maximum drug's affect.

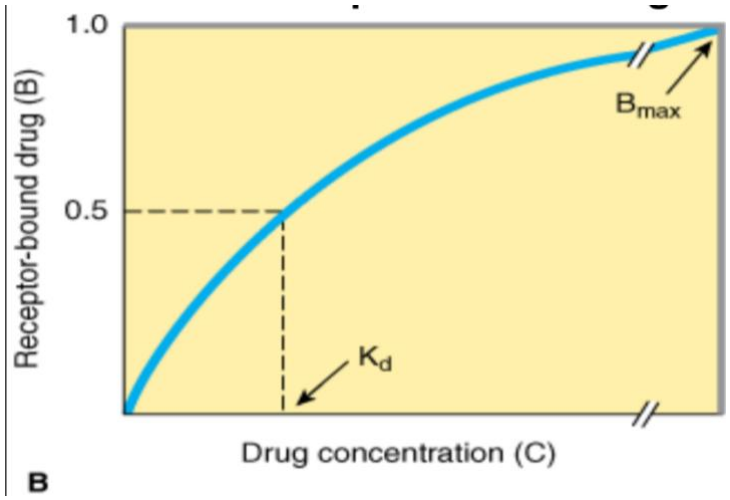
EC (effective concentration)



A

We can say ED (effective dose) dose what is taken, conc. what is really reach blood stream

Relations between drug concentration and receptor-bound drug



Both curves look similar to each other, but can we say : Bmax is same to Emax ?

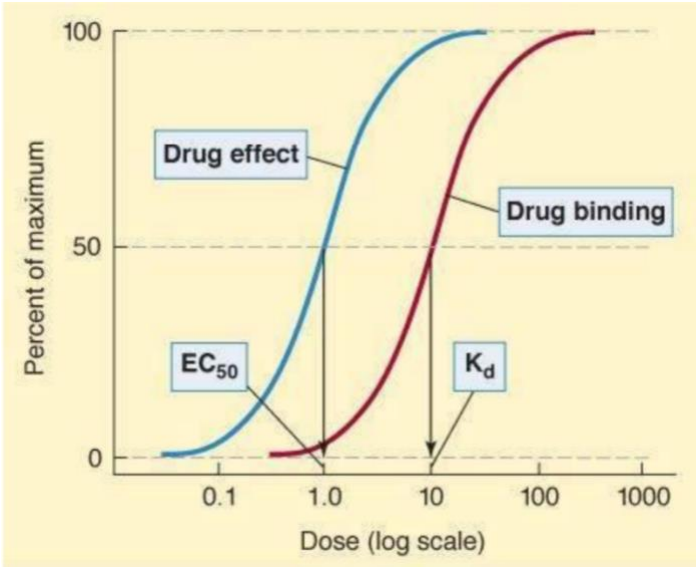
NO, because I don't need to occupy all the receptors to reach the Emax.

Kd and EC50 look similar and depend on each other , but they are not the same.

EC50 depends on Kd which indicate affintity, so if the affinity is high it will give higher affect

these two curves are parallel and depend on each other , again they are not the same, cause I don't need to occupy all receptors to get the Emax

so why is that?



Due to 2 reasons...

SPARE RECEPTORS

Only a fraction of total receptors for a specific ligand may need to be occupied to elicit a maximum response.

Examples:

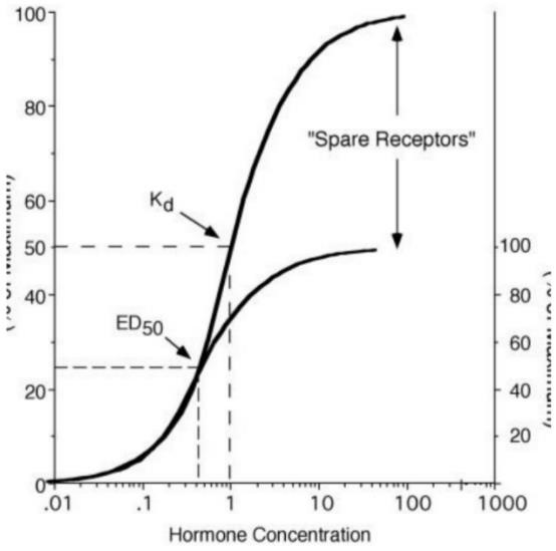
• Insulin receptors are estimated to have 99% of the receptors as spare receptors…….. large functional reserve to ensure adequate control of glucose uptake.

This main, only 1% of insulin receptors is used

• Only 5-10% of beta adrenoceptors are spare……..little functional reserve exist in the failing heart. So, most receptors need to be occupied for a maximum effect

The lower curve represents Emax

The higher one represents Bmax



SIGNAL AMPLIFICATION

• Receptor binding are amplification terms of duration and intensity

• Example: G-protein coupled receptors

• Phenomena that account for the amplification:

1. The receptor-drug complex can interact with many G proteins thereby multiplying the organ signal many folds. (intensity)

2. The activated G-protein persists for longer duration than the original receptor-drug complex. (duration)

We have said that most of drug receptor reaction are reversible, it mains it will bind and dissociate in a milli second, in this example it is GPCR, so due to this binding , a G protein will be activated and this activation take time more than that milli second, as a result if another binding happens in this period, it will not effect, the G protein is busy and still working, that's why I don't need so many receptors , there is different timing of signaling cascade events.

DRUG RECEPTORS & PHARMACODYNAMICS

Receptors are responsible for specificity of drug action.

» The molecular size, shape, and electrical charge of a drug determine how it will bind to a particular receptor.

» Accordingly, modifications in the chemical structure of a drug can dramatically increase or decrease a drug's affinities(that's why some drugs have higher affinity than other although they are working on the same receptor) **for different classes of receptors, with resulting alterations in therapeutic and toxic effects.**

As example; ibuprofen and paracetamol, both are pain killer, but…

I need 200 mg of ibuprofen to reduce pain while 500 mg of paracetamol, this is because of different affinities (Kd and EC50)

In addition, changes in chemical structure can change all of the other parameters related to the drug, like the distribution and half life of the drug.

There is another factor effect the response of the drug

Intrinsic ability(قدرة داخلية) of the drug to activate the signaling mechanisms, each drug has its own intrinsic ability.

Pharmacodynamics characteristics (concepts):

- Kd & EC
- Potency
- Efficacy

POTENCY

- **Potency refers to the affinity of a drug for its receptor or the concentration of drug required to produce a given effect. Low KD, high potency.**

  It depend on KD, but it's not the same.

- **Potency refers to the amount or concentration of drug required to produce a response**. (another definition)

The previous definition is similar to EC50 definition, but what is the difference between them?

Ans. EC50 is the half of Emax, but potency is generalized term.

- **On dose-response curves potency is measured on the X-axis.**
- **ED50, EC50, and Kd are measures of potency.**

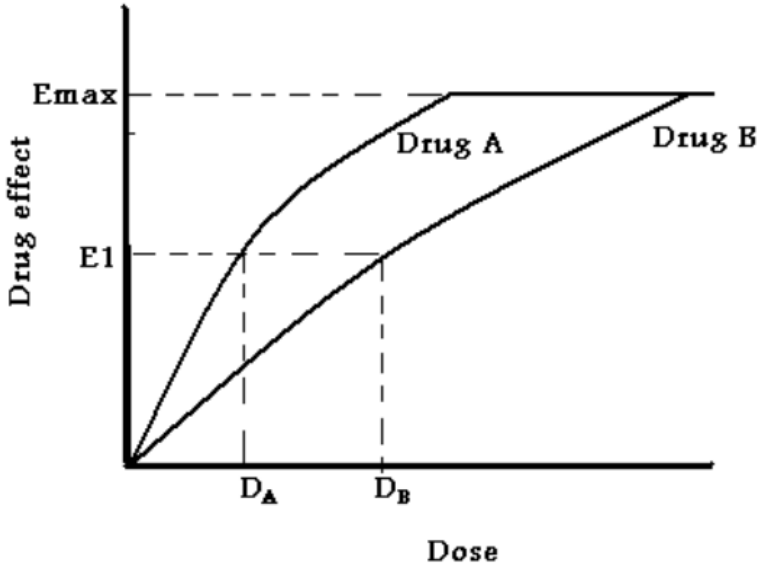
❖ **A term used whenever we compare the activity of two drugs producing the same effect.**

❖ **Defined as the dose of one drug necessary to produce a specific response as compared to a second drug producing the same effect.**

❖ **Affinity: The ability of a drug to form a stable complex with the receptor** (doctor has written it ,so we can tell the difference between potency and affinity)

GRADUATE DOSE-RESPONSE CURVE

- Dose response curve is done while doing an experiment, to monitor the increase of dose How affect the response.
- Graduate: means when we increase the dose then the effect increases.



- Responses have 2 type of curves: graduated, quantal (we will study it later)
- NOW, have a look at the curve, when you increase the dose (x axis) for different drugs (2 drugs), which one do you think is more potent (depend on EC50)?

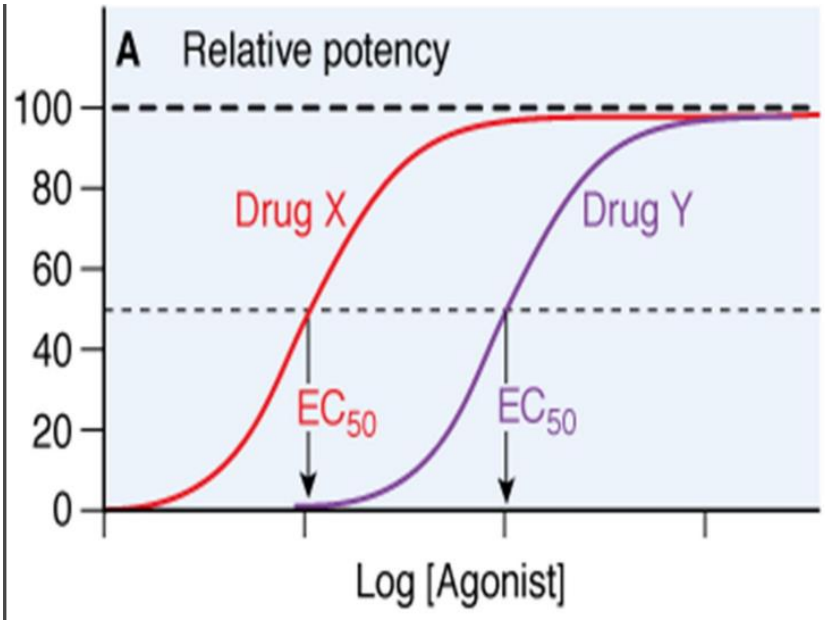
  Right! Drug A is more potent = EC50 is achieved with less amount or dose.

  In comparing drugs with potency we use any particular same point, but we use EC50 for ease.

  Note: we don't have to reach Emax while giving a patient a treatment, symptoms could be cured with less dose. Also, if we pass Emax we can see toxicity effects.

- Try again this time, which one is more potent?

  Ans: drug X



EFFICACY

- **Efficacy is the maximum effect of a drug Emax, and depends on the number of drug receptor complexes formed, and also on the efficiency of coupling of receptor activation to cellular responses.**

  The increase in total number of receptors increases the chance of binding between receptors and drug which is increases the efficiency, regardless receptors being used or not .

  Note:

  The efficacy depends on coupling receptor(when the drug binds to receptors , chemical changes happens which will change the activity of the drug in signaling, increases this will lead to higher response (higher efficacy)

- **Aspirin and morphine produce the same pharmacologic effect (analgesia) but have very different levels of efficacy.**

  Morphine is given in surgical or sever pain as cancer, due to its high Emax

  Aspirin or paracetamol are less efficacy, for headache or muscles pain

  Note: while comparing drug here, it's not necessary to work on same receptors; because we are interested in effects.

  Side note: Paracetamol toxicity can cause liver necrosis.

- **If drug can stimulate a receptor to produce a biological response it is said to have efficacy or intrinsic activit** القدرة الداخلية (cellular activities).

- **Efficacy refers to the capacity of a drug to produce an effect or the overall magnitude of the maximum response, depends on intrinsic activity.**

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

Conclusion:

- Potency is minimal dose to reach certain effects

(X axis)

(More potent= less dose)

Factor: affinity

- Efficacy is for having a great effect on reducing symptoms

Y axis

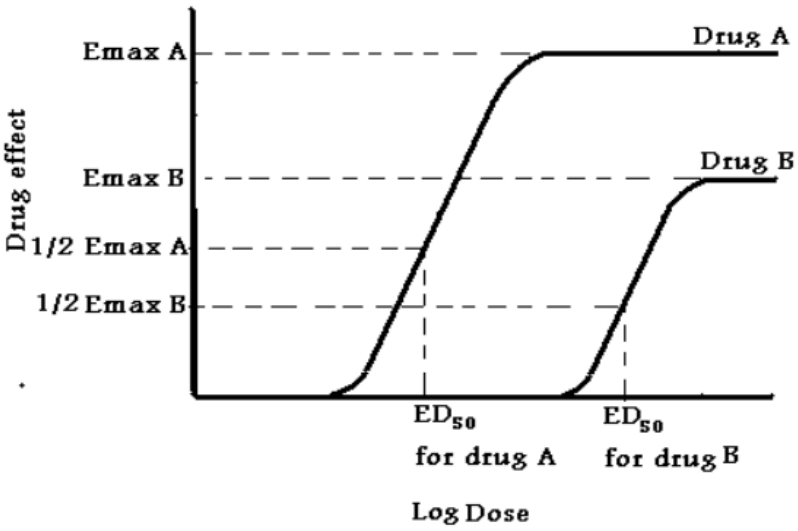
More effective= higher E max

Factors: total number of receptor, affinity of drug (but related to potency more), coupling potential.

(In clinical trials, they choose one of these, depending on research type.)

LOG DOSE RESPONSE CURVE

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



Test bank

1) Concerning drug receptor interactions, the constant Kd refers to:

A) Maximal physiological effect

B) Maximal binding

C) The drug concentration required to occupy 50% of receptors

D) Drug concentration that results in half-maximal physiological response

E) all of the above

2) EC50 mainly reflexes a drug's:

A) Maximal effect

B) Potency

C) Lethality

D) Ease of elimination

E) Safety

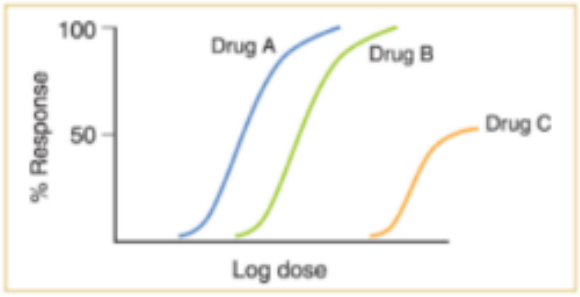
3) The data presented in the figure below show that:

A. Drugs A and B have equal efficacy

B. Drug B and C have equal efficacy

C. Drugs A and C have the same affinity and efficacy

D. Drugs A and B have equal potency



Answers:

1. C
2. B
3. A

عن أبي هريرة رضي الله عنه قال: قال رسول الله صلى الله عليه وسلم: ((المؤمن القوي خيرٌ وأحبُّ إلى الله من المؤمن الضعيف، وفي كلٍّ خير، احرص على ما ينفعك، واستعن بالله ولا تعجز، وإن أصابك شيء فلا تقل لو أنِّي فعلت كان كذا وكذا، ولكن قل قدَّر الله وما شاء فعل، فإنَّ لو تفتح عمل الشيطان))