# Pharmacodynamics-2

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-we shall start talking about interactions between the drug and its Receptors

# Receptor Occupancy Theory

The "Law" of Mass Action

This theory covers the interaction of any two compounds in nature

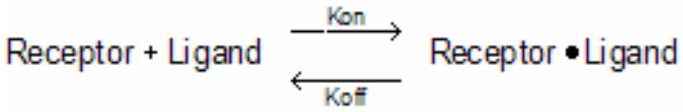
- **Activation of membrane receptors and target cell responses is *proportional to the degree of receptor occupancy.*** An important thing that determines the target cell responses is how much receptors are occupied
- Assumptions:
  - Association is limited by collision, orientation and energy
  - All receptors are equally accessible
  - All receptors are either free or bound, there is no "partial" binding
  - Neither drug or receptor are altered by binding
  - Binding is reversible

without going into details, these are the assumptions that governs our theory

# Law of Mass Action

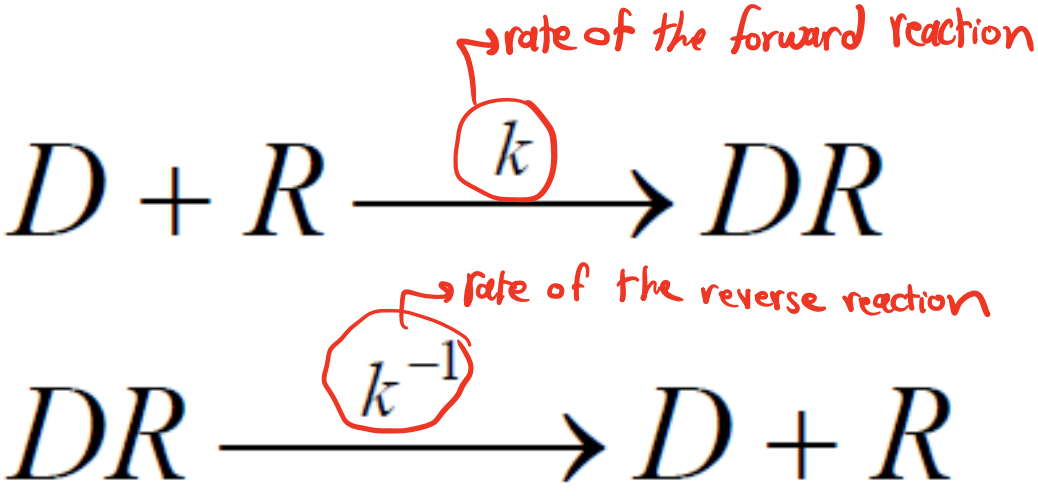
## (a model to explain ligand-receptor binding)

- 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
  - $K_d$ = Kon/Koff = [D][R]/[DR]
  - $K_a$ = 1/Kd = Koff/Kon = [DR]/[D][R]

# Drug-receptor binding



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

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

» **This ratio is the equilibrium dissociation constant or KD**

= Rate of the reverse reaction / Rate of the forward reaction

» **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** (how much of the drug will dissociate from the receptor)

(The Affinity of the drug inversely related to Kd)

# Hill-Langmuir equation

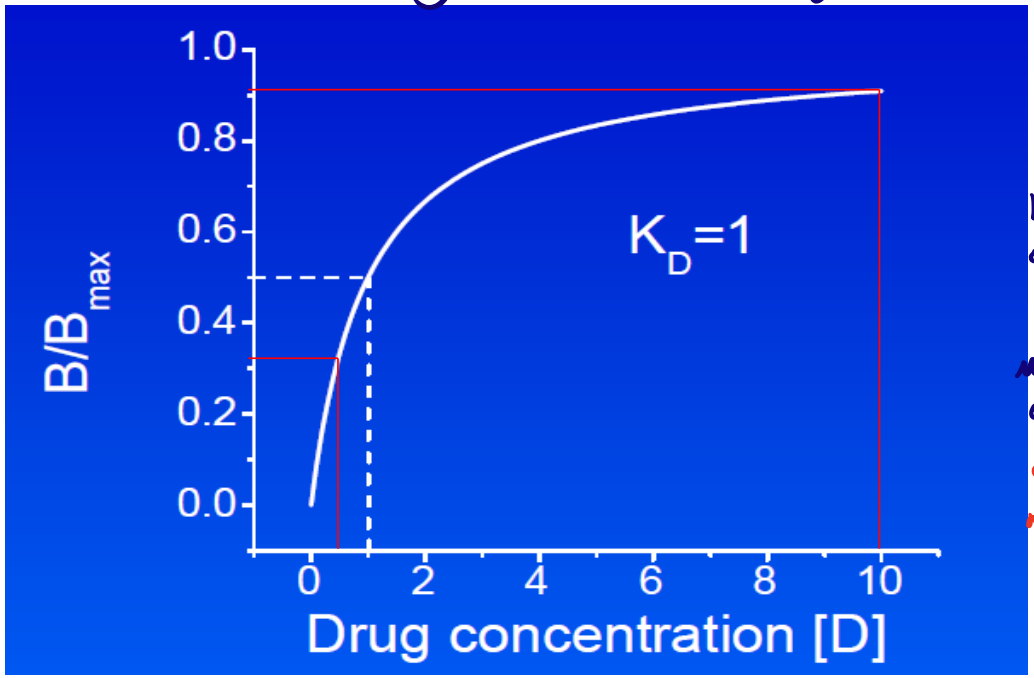
The degree of the receptor occupancy

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

- $B$: bound receptors
- $B_{max}$: maximum number of receptors in the cell. [max num of receptors that can be bound]
- $[D]$: concentration of the drug

- what determines the receptor occupancy is the affinity of the drug and the concentration of the drug.
assuming that our drug is reversible, the process is competitive, so having another compound that is able to bound the receptor will compete with the drug if it has higher concentration.

-How to calculate $K_D$ → we do an experiment where we give increasing concentrations of the drug and we look how many receptors are occupied.




-when we have increasing concentration of the drug, we have higher number of receptor occupancy until we reach the maximum value of occupancy that is determined by the number of receptors

dissociation constant

KD: concentration of the drug at which binding site is 50% occupied. (50% of the maximum occupancy)

Affinity = 1/Kd ← inversely related to Kd

ex. If the drug likes to bind to its receptor (high affinity) I need less concentration of that drug to give me that percentage of receptor occupancy and vice versa.

# 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,**
- **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.** (meaning that we're not getting all of the potential the drug can give me)

  In real life, we give much more of the drug than what actually needed to occupay all of receptors .

# Dose response relationships

There are two kinds of drug-receptor relationship: receptor occupancy
dose - response

» Graduate dose-response relations

Here we're looking at the response of the drug, not the number of receptors occupied
"how much the heart rate is increased"

As the dose administrated to single subject or isolated tissue is increased , the pharmacologic effect will also increase.

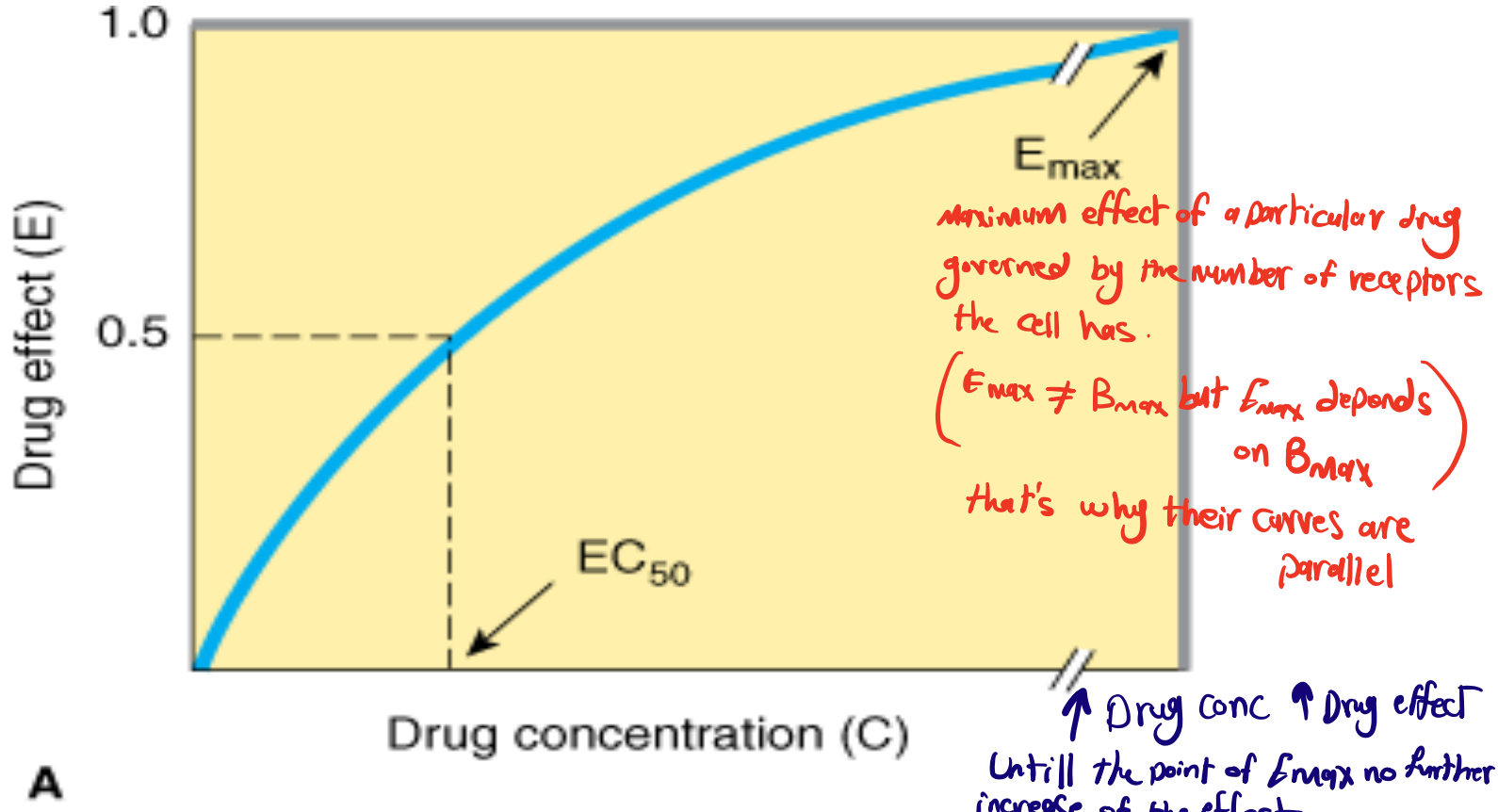
At a certain dose, the effect will reach a maximum level, which is called the ceiling effect or Emax.

After that, giving more of the drug won't lead to an increase of the effect, and that's because of the receptors saturation.

"Maximum occupancy of receptors"

So actually the dose-response relationship is related to receptors occupancy

# Relations between drug concentration and drug effect

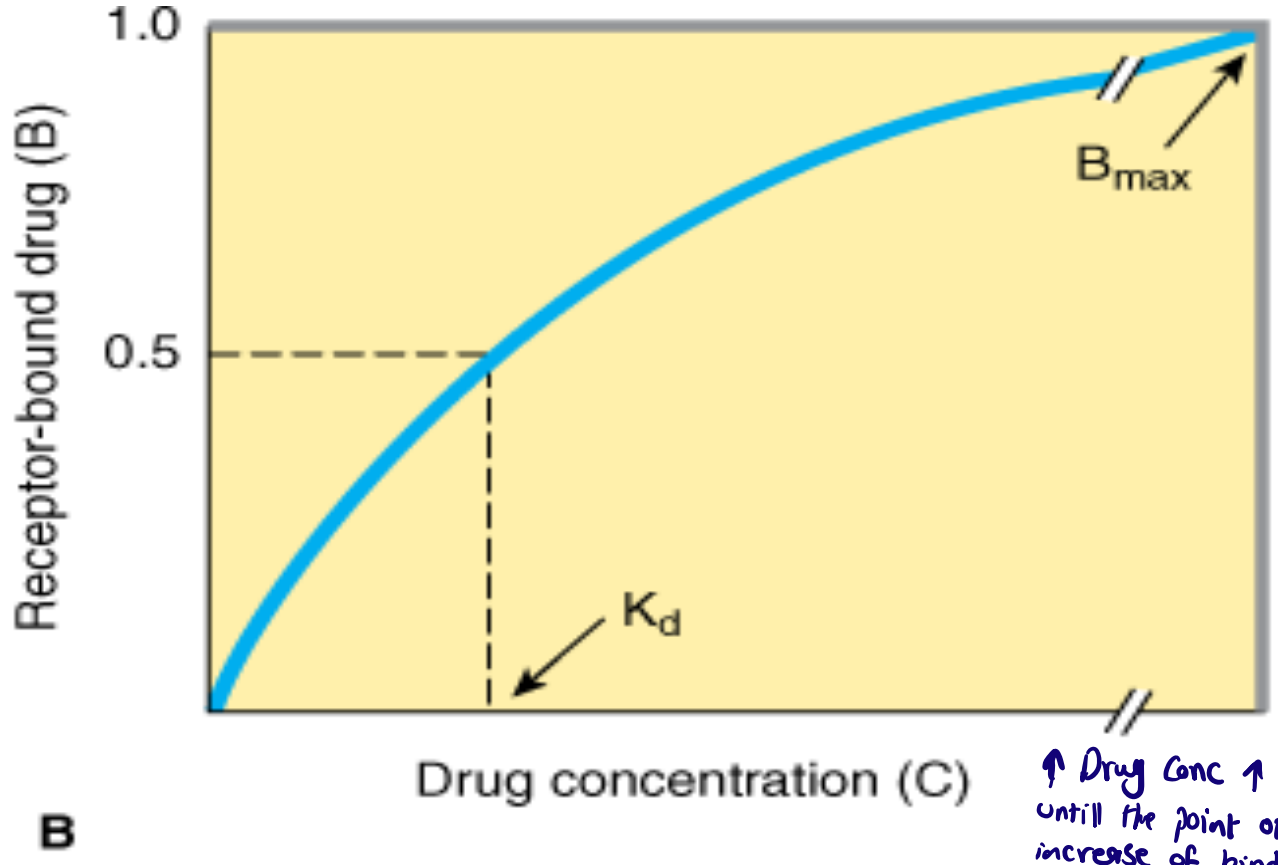



$E_{max}$
Maximum effect of a particular drug governed by the number of receptors the cell has.
($E_{max} \neq B_{max}$ but $E_{max}$ depends on $B_{max}$ that's why their curves are parallel)

↑ Drug conc ↑ Drug effect
Untill the point of $E_{max}$ no further increase of the effect

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

# Relations between drug concentration and receptor-bound drug

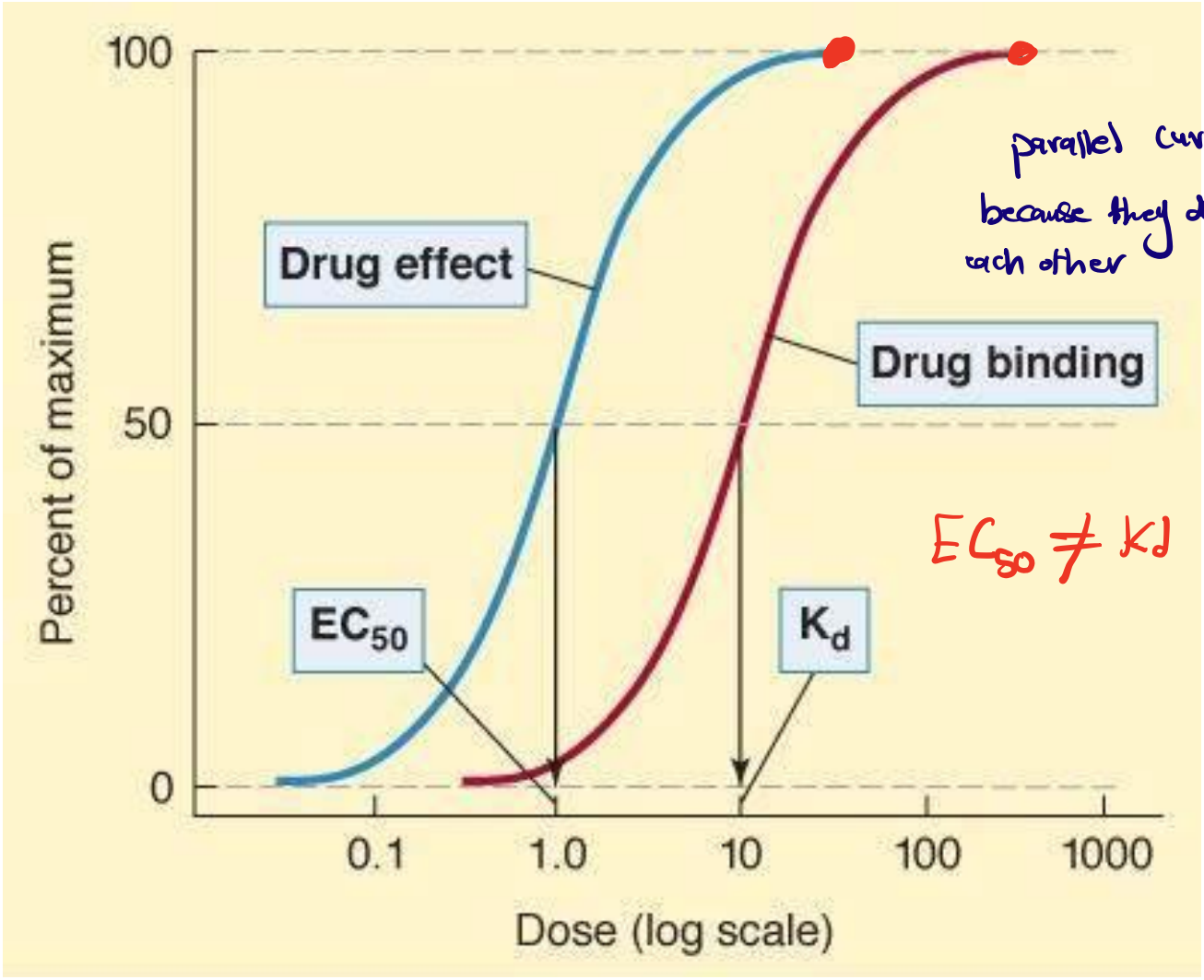



Does $F_{max} = B_{max}$ ?

No

↑ Drug Conc ↑ receptor bound drug untill the point of $B_{max}$ no further increase of binding

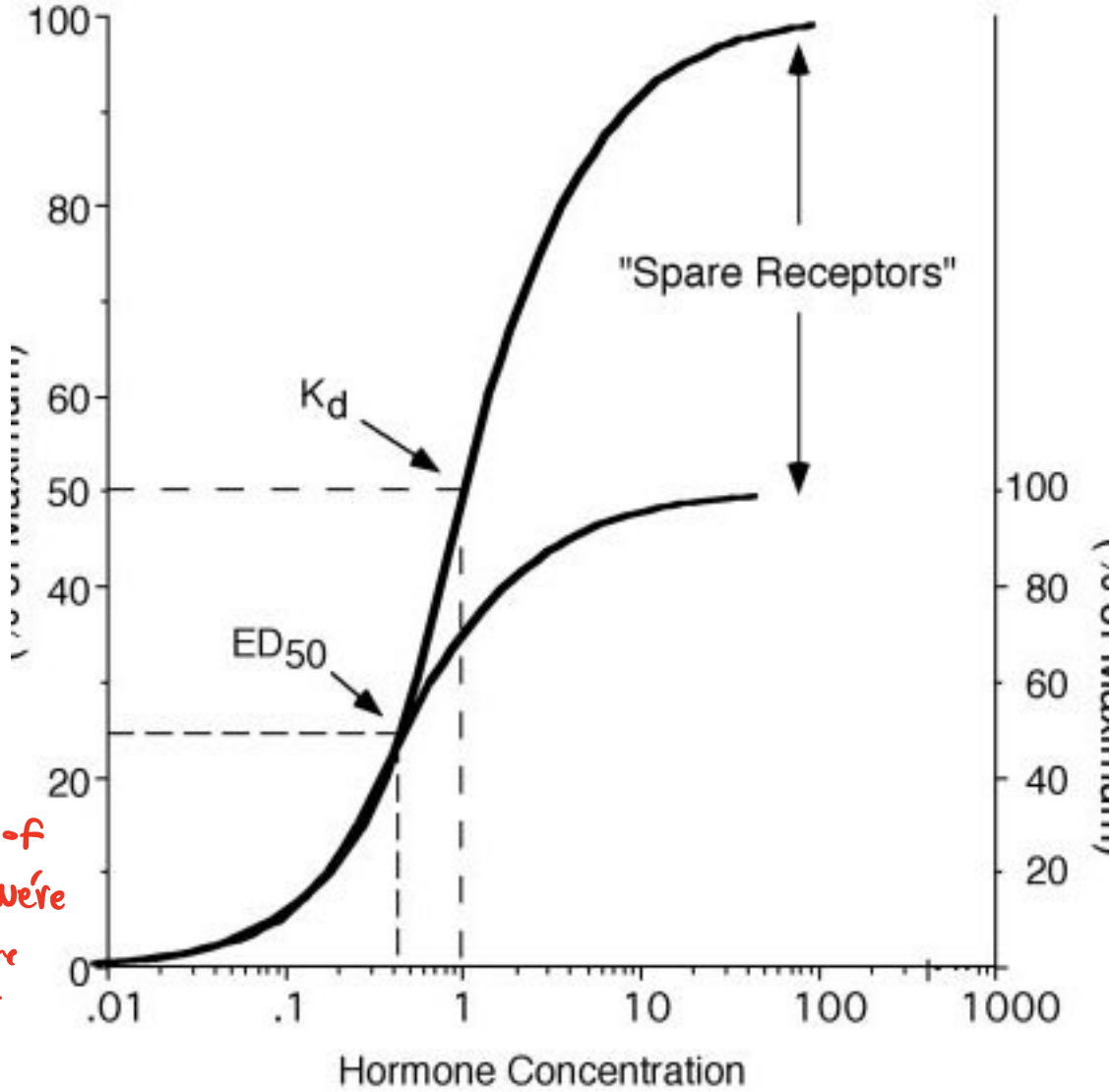
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com




parallel curves because they depend on each other

$EC_{50} \neq Kd$

$EC_{50}$: Concentration of the drug where we're getting half of the maximum effect




$ED_{50}$ = The dose of the drug where we're getting half of the maximum effect

Why does $E_{max} \neq B_{max}$ ? OR why does $ED_{50} \neq Kd$ ? Because of

# Signal Amplification

we reach the maximal effect before the saturation of receptors.

And that's because we have certain events in the cell that amplifies the signal So I don't need to activate all of receptors to get that effect.

- Receptor binding are amplification terms of duration and intensity

we have another type of amplification that occurs which is related to the Duration of the signal

- 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. More intense response

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

The drug is reversible and it takes it milliseconds to be removed from its receptor, So by activating GPCRs that presist for longer duration without the need of binding more drug particles, that will amplify the response

So what are the consequences of this amplification????

# Spare receptors

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

To obtain a maximum effect of a drug we don't need to activate all of receptors

"That doesn't apply to all receptors"

**Examples:**

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

  ↳ meaning that I only use 1% of the available receptors

  ↳ The spare receptors give

  since glucose needs high levels of regulation

- 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

here I have less capacity to cope with an ailment

# Drug Receptors & Pharmacodynamics

***Receptors are responsible for selectivity of drug action .***

- **The molecular size, shape, and electrical charge of a drug determines 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 for different classes of receptors, with resulting alterations in therapeutic and toxic effects.**

- Modifications in the chemical structure of a drug explains why we find a lot of forms of a certain drug like having lots of $\beta$ blockers that exert the same function (binding to $\beta$ receptors and blocking it) All of them have specificity for that receptor but those slight differences in their chemical structure cause differences in both pharmacodynamic parameters and pharmacokinetic ones.

- Regarding pharmacokinetics of the drug: Those modifications causes differences in the rate of absorption, excretion, time to onset of action and so on
  * For example we can change the polarity of the drug so it can be excreted faster
  * Another example is that we can make changes that would change the site of administration (IV, orally) some chemical forms of a drug can't be given orally so you will have to try another chemical form of that drug

- Regarding pharmacodynamics of the drug: Those modifications causes differences in their affinities for the receptor (having different $K_d$s, $EC_{50}$, $ED_{50}$) resulting in different chemical forms of a certain drug with different potencies and different efficacies

# Potency فعالية

- 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
- • Potency refers to the amount or concentration of drug required to produce a response. close to $ED_{50}$ / $EC_{50}$
- • On dose-response curves potency is measured on the X-axis.
- • ED50, EC50, and Kd are measures of potency.

High potency of a drug – high affinity for the receptor – requires less dose of the drug

# Potency:

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

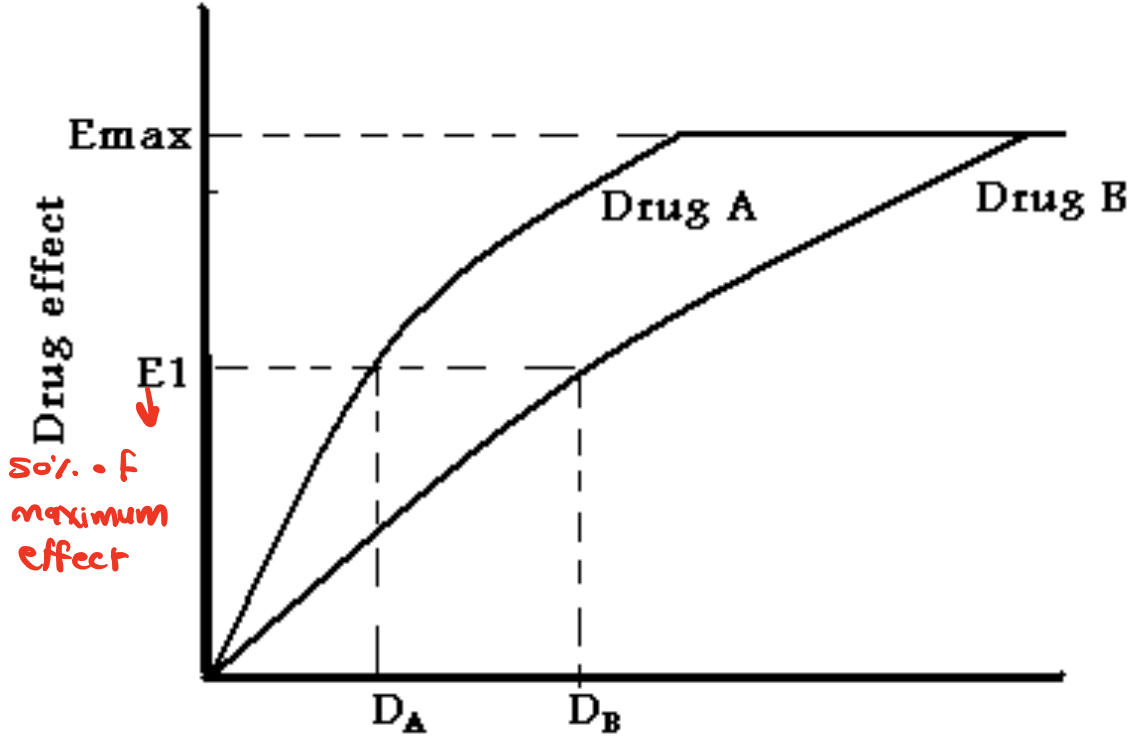
Defined as the dose of one drug necessary to produce a specific response as compared to a second drug producing the same effect

- Affinity:

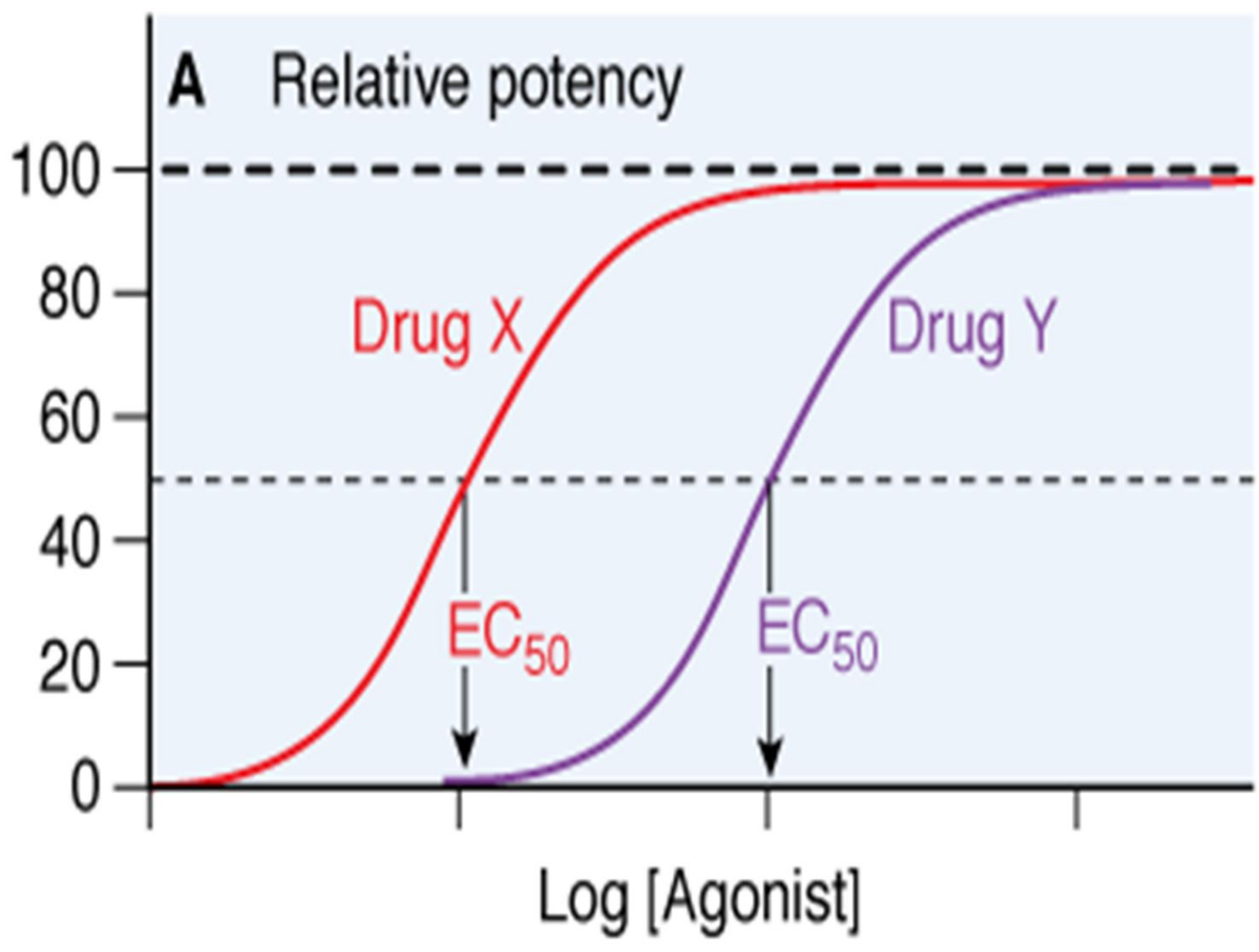
The ability of a drug to form a stable complex with the receptor

# Graduate dose-response curve

(This curve determines potency)




Which one is more potent? A, Because I needed lower amount of the drug to reach $E_{max}$


A Relative potency
100
80
60
40
20
0
Drug X
Drug Y
EC50
EC50
Log [Agonist]

Sometimes we have two drugs with the same affinity to the receptor (same chance of binding) but one of them has higher $E_{max}$, why is that?

# efficacy

Another pharmacodynamic term

"The intrinsic activity of the drug"

- Efficacy is the maximum effect of a drug, Emax, and does depend on the number of drug-receptor complexes formed, and also on the efficiency of the of coupling of receptor activation to cellular responses. How much the drug-receptor complex is capable of activating G-protein coupled Receptors to give me more or less of the response
- Aspirin and morphine produce the same pharmacologic effect (analgesia) but have very different levels of efficacy. (Their $E_{max}$ will be different)

moderate pain

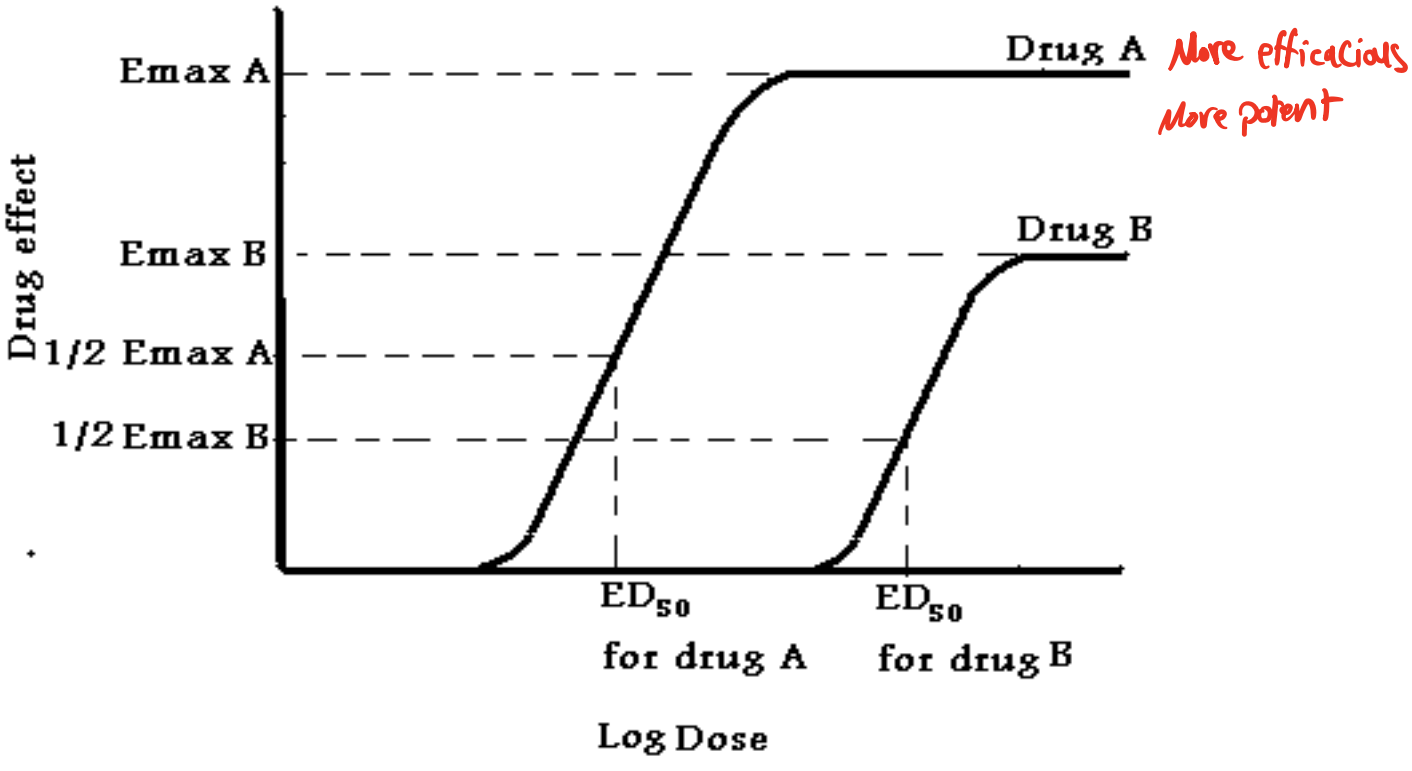
severe pain / surgeries

# efficacy

- If 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 (Efficacy of a drug depends on its intrinsic activity and the num of receptors)
- If a drug stimulates a full response, it might to said to be a full agonist and to be very efficacious.

# Log dose response curve

- efficacy is measured on the Y axis




» The smaller the EC50, the greater the potency.

» Efficacy is indicated by the height of the log dose response