بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pharmacology | Lecture #5

Pharmacodynamics

pt.3

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ARE DRUGS THAT INHIBIT SIGNAL TRANSDUCTION PROTEINS CLINICALLY USEFUL?

Some important examples:

Tyrosine Kinase Inhibitors for chronic myelocytic leukemia

)imatinib [Gleevec(]®

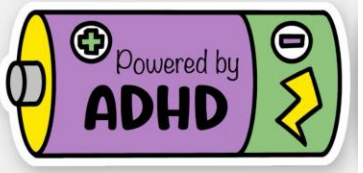
Tyrosine kinase is active in several cancers so we traveled that enzyme and we created a targeting drug for certain cancers

For blood cancer

Type 5 Phosphodiesterase Inhibitors for erectile dysfunction

)sildenafil [Viagra(]®

- This is a major focus of drug development



HOW DO DRUGS WORK BY ACTIVATING ENDOGENOUS PROTEINS?

Agonists of Cell Surface Receptors

)*e.g.* alpha-agonists, morphine agonists(

- Agonists of Nuclear Receptors

)*e.g.* HRT for menopause, steroids for inflammation(

- Enzyme Activators

)*e.g.* nitroglycerine (guanylyl cyclase), pralidoxime(

- Ion Channel Openers

)*e.g.* minoxidil (K) and alprazolam (Cl((

K+ channels-> vasodilation

Revision: an agonist is a molecule that is going to bind to the target

Agonists of Cell Surface Receptors

)*e.g.* alpha-agonists, morphine agonists(

Adrenergic receptors → Alpha → Present in blood vessels-> activation-> constriction of vessels

Beta

Otrivin for eg is a drug that has alpha agonist-> vasoconstriction-> shrinkage of swollen blood vessels-> breathing

So this is an example of drug that mimics the action of endogenous ligand which is adrenaline/noradrenaline

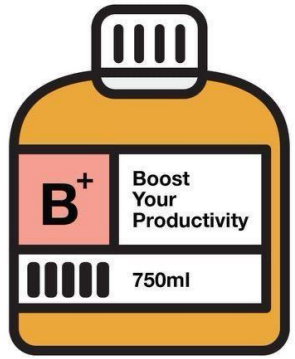
So the reason I use a drug and not adrenaline is for the effect on the heart an it's selectivity . We use alpha-1 agonist and activate the receptor so I don't worry about activating other adrenergic receptors

زي مثال الاوتريفين السابق؛ بس ضيقنا الأوعية الدمويه المراد معالجتها مو كلهم

- Agonists of Nuclear Receptors

)*e.g.* HRT for menopause, steroids for inflammation(

Example of intracellular receptors. Some times we need to take steroids exogenously eg: cortisone (same as the endogenous; it is going to bind to the receptor that's intracellular and activate post transaction of gene transcription and then doing its effect – reducing inflammation)



- Enzyme Activators

)*e.g*. nitroglycerine (guanylyl cyclase), pralidoxime(

Guanylyl cyclase
Is the target and second messenger that is present inside the cell. It's an enzyme (Cyclase) that produces cyclic GMP .
Another example is nitric oxide (which is a vasodilator produced in our body) I sometimes give drugs that releases nitric oxide -> drug called nitroglycerin used in cases of Angina (الذبحات الصدرية)

Remember: Nitric oxide (NO) directly activates guanylyl cyclase.

HOW DO CHEMICALS WORK BY ACTIVATING CELL SURFACE RECEPTORS?

KEY CONCEPTS:

- Cell surface receptors exist to transmit chemical signals from the outside to the inside of the cell.

- Some chemicals bind to cell surface receptors and trigger a response. (Opposite to antagonists)

- Chemicals in this group are called receptor agonists.

Eg: adrenaline

- Some agonists are actually the endogenous chemical signal, whereas other agonists mimic endogenous chemical signals.

Some times I use phenylephrine to mimic adrenaline but sometimes I use steroids or corticosteroids or cortisone itself (the cortisone pills I give to my patient is very similar to the cortisone in our body

There is a difference in the quantity of the response:
1: full agonist -> maximum effect
2: partial agonist -> triggers a response but not the maximum limit

HOW DO CHEMICALS WORK BY UNCONVENTIONAL MECHANISMS OF ACTION?

Don't follow the sub groups in the previous pie chart

- Disrupting of Structural Proteins

e.g. vinca alkaloids for cancer, colchicine for gout

- Being Enzymes

e.g. streptokinase for thrombolysis

- Covalently Linking to Macromolecules

e.g. cyclophosphamide for cancer

- Reacting Chemically with Small Molecules

e.g. antacids for increased acidity

- Binding Free Molecules or Atoms

e.g. drugs for heavy metal poisoning, infliximab (anti-TNF(

(No names just know the mechanism of action)

- Disrupting of Structural Proteins

e.g. vinca alkaloids for cancer, colchicine for gout

Colchicine in muscoskeletal system disrupts the polymerization of tubular into microtubules , this disrupts cell division and could be used as a treatment for cancerous cells.....Also, vinca alkaloids (which are natural source of drug) are used for treatment of cancer by disrupting the formation of microtubules -> prevent the replication of cells

- Being Enzymes

e.g. streptokinase for thrombolysis

Streptokinase is a fibrinolysis of blood clots (dissolve clots), can be used in brain strokes.

- Covalently Linking to Macromolecules

e.g. cyclophosphamide for cancer

Here we target the DNA and bind to it , this causes cross linking of DNA (alkylating agents) -> disrupting the structure of DNA -> cell death/ kills cancer cells

- Reacting Chemically with Small Molecules

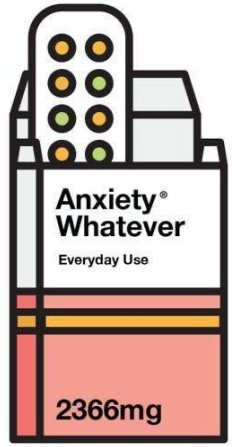
e.g. antacids for increased acidity

Eg : Gaviscon ; when acidity in the stomach increases the calcium carbonate in the drug will not be absorbed , but it interacts chemically with HCl and give salt and water as products. . (No receptors/ no enzyme)

- Binding Free Molecules or Atoms

e.g. drugs for heavy metal poisoning, infliximab (anti-TNF(

We give activated charcoal (scavengers) that binds to these metals (eg:mercury/lead) and helps get rid of poisoning



HOW DO DRUGS WORK BY UNCONVENTIONAL MECHANISMS OF ACTION (Continued?(

- Being Nutrients

e.g. vitamins, minerals

For eg :vitamin D deficiency

- Exerting Actions Due to Physical Properties

e.g. mannitol (osmotic diuretic), laxatives

For constipation , is a colloid material that attracts water (absorbs water) ; so it become bigger and bulky and this forms pressure on the intestine's wall->peristaltic movement (just a physical property)

- Working Via an Antisense Action

e.g. fomivirsen for CMV retininitis in AIDS

For eg : siRNA (small interfering RNA) that knocks out some genes ; and inhibit the function of the gene/protein

- Being Antigens

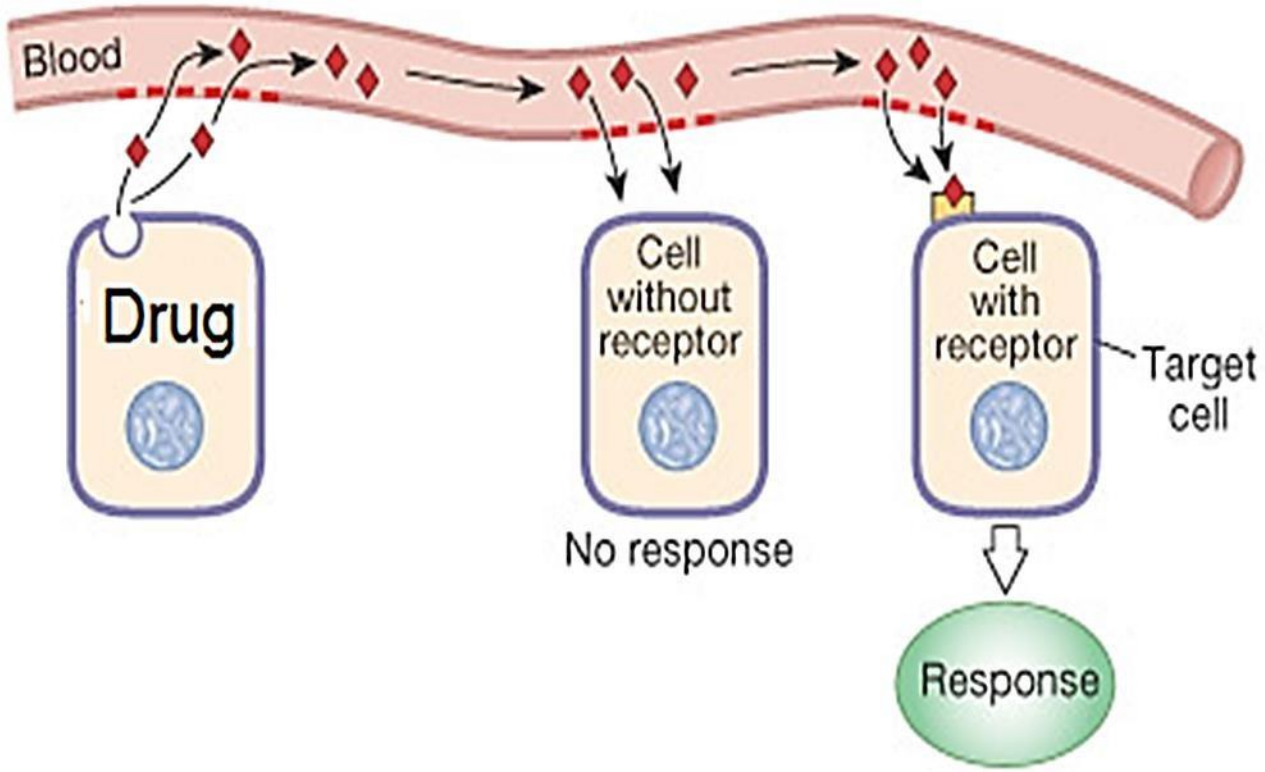
e.g. vaccines :An antigen that's produced outside the human body (from another species)

- Having Unknown Mechanisms of Action

e.g. general anesthetics

Pharmacodynamics-2

Dr. Alia Shatanawi



Receptor Occupancy Theory

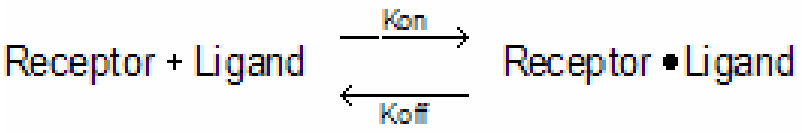
- **Activation of membrane receptors and target cell responses is *proportional to the degree of receptor occupancy*.**

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 <u>reversible</u> 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]

If I have one molecule of that drug and 100 receptors, that one molecule will bind to one receptor and give an response . And if I give more molecules I will see more response, until I occupy all receptors-> I get maximum response

Rate is dependent on drug concentration and on receptors' concentration

This is wrong ,it is
Kd = Koff / Kon
But we are not focusing on equations

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**

Receptor Drug

Kd is a measure of how well the drug-receptor complex stays together. It reflects the affinity of the drug for its receptor. The higher the Kd, the lower the affinity.

Hill-Langmuir equation

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

The calculations and numbers are not required in the exam.
You only need to know from this slide that receptor occupancy depends on drug concentration:
The higher the drug concentration, the greater the chance for binding and the higher the receptor occupancy.
Receptor occupancy is inversely proportional to Kd, which is the dissociation constant measuring how tightly the drug binds to the receptor.

B represents the bound drug, and Bmax represents the maximum number of drug-receptor complexes. Therefore, B divided by Bmax represents the receptor occupancy percentage.

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.**

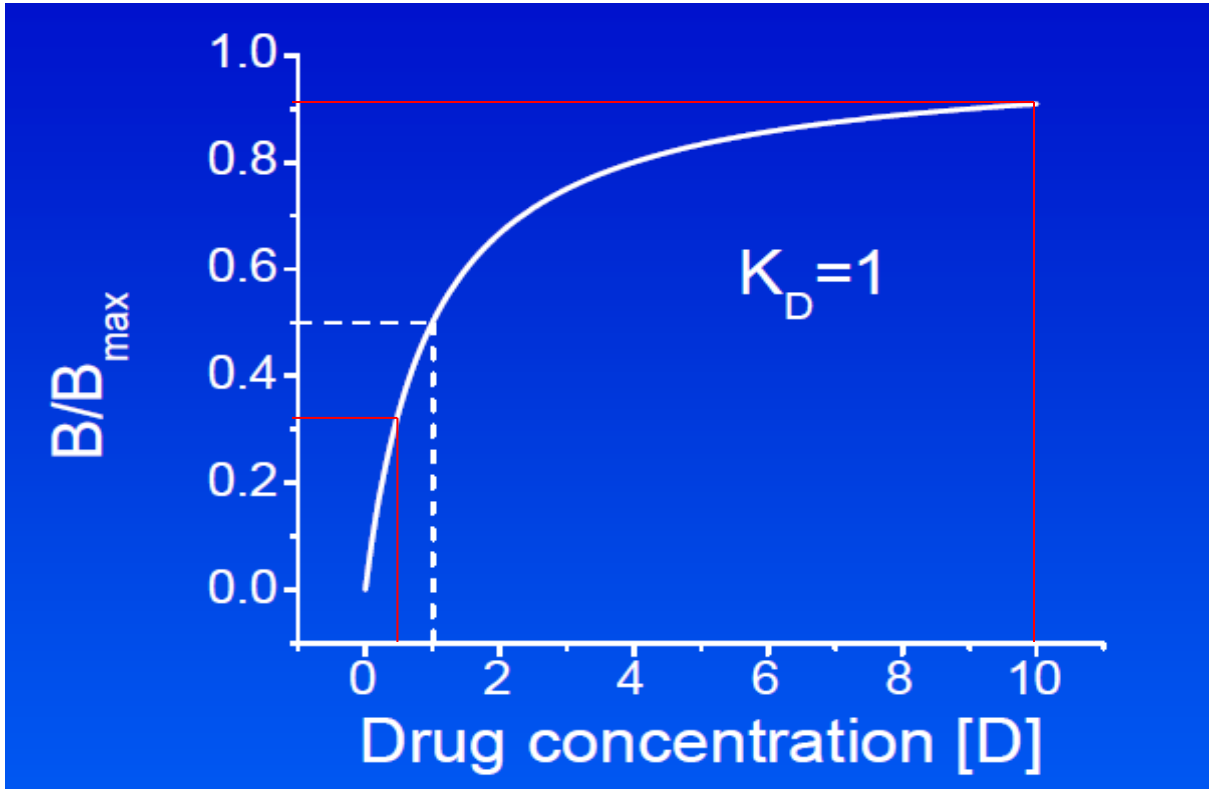
B represents the bound drug, and Bmax represents the maximum number of drug-receptor complexes. Therefore, B divided by Bmax represents the receptor occupancy percentage.

The total number of receptors determines Bmax.

Kd and affinity have an inverse relationship.

If a high concentration of a drug is needed to occupy 50% of the receptors, it has a high Kd, which means it has low affinity.

Conversely, if a small concentration of a drug can occupy 50% of the receptors, it has a low Kd, which indicates high affinity.



Of the drug

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

Affinity 1/Kd

Dose response relationships

The Dose-Response Relationship represents the relationship between the concentration (or dose) of a drug and the effect it produces, specifically the therapeutic effect.

» Graduate dose-response relations

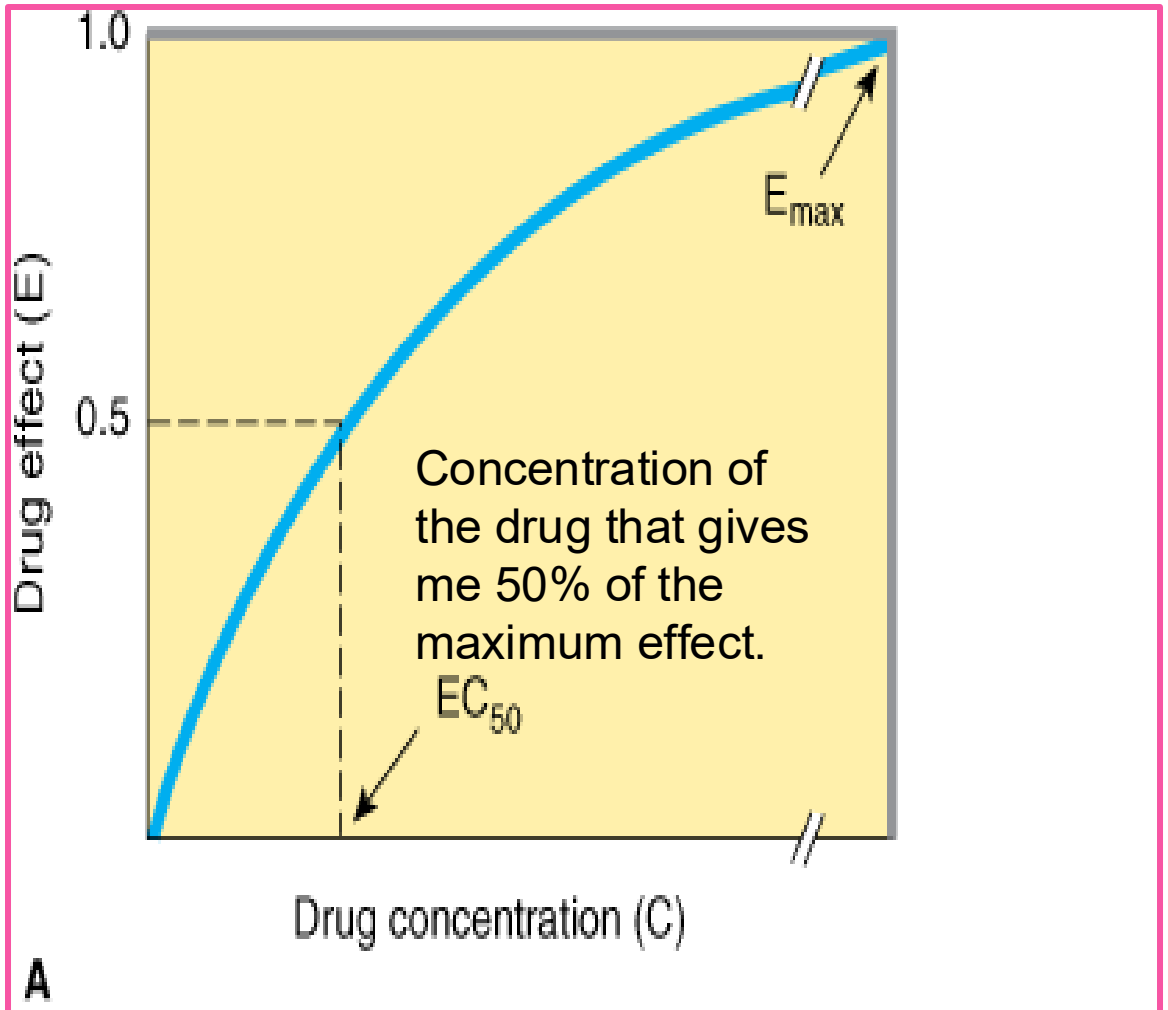
As the dose administrated to single subject or isolated tissue is increased , the pharmacologic effect will also increase.

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

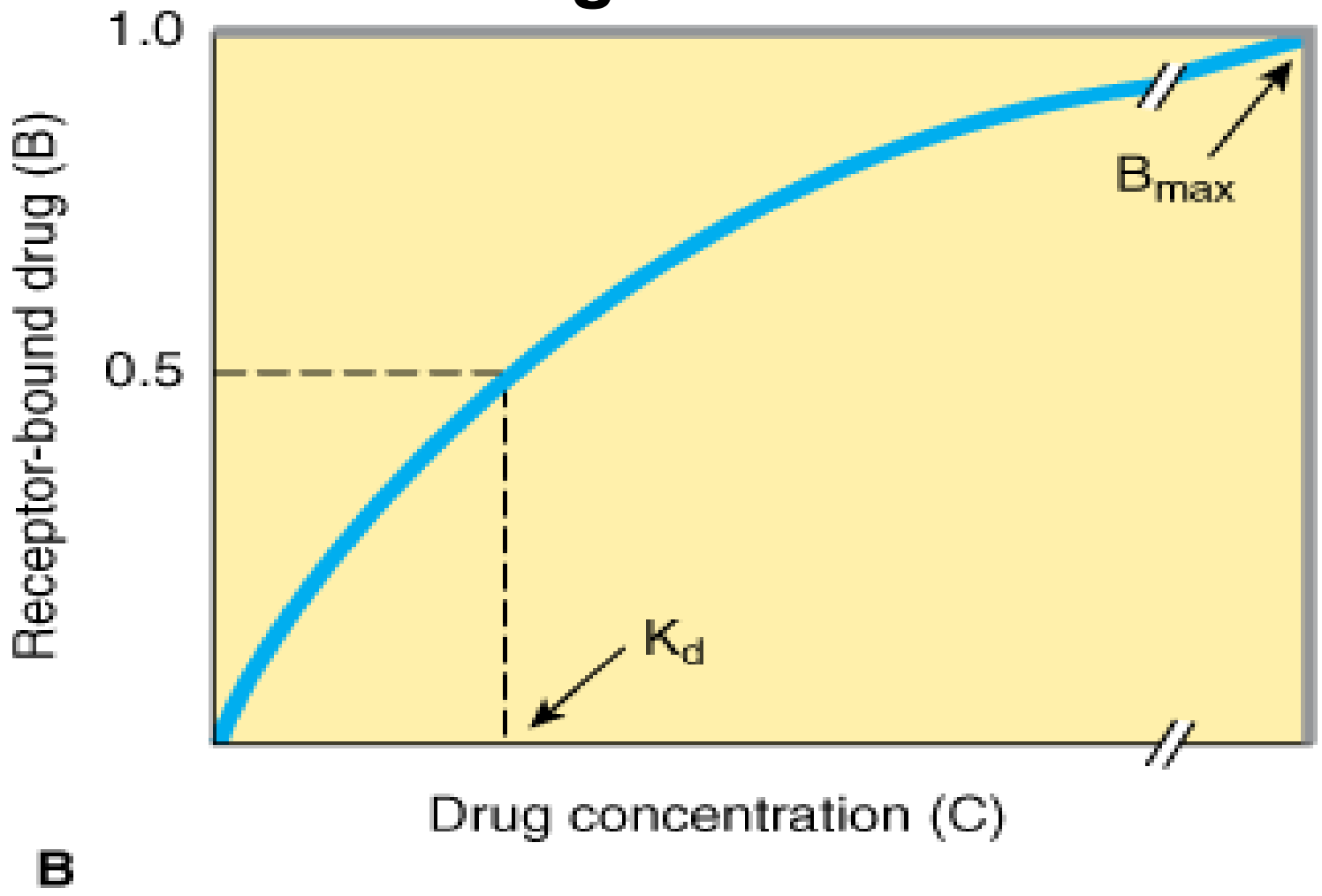
For example, consider nicotinic receptors in skeletal muscles. I take a small portion of that muscle and place it in a water bath for my study. I start by adding 1 mg of acetylcholine and measure the muscle contraction. Then, I gradually increase the concentration and observe the effect, until I reach a point where further increases in concentration no longer change the response.

We call this point the maximum effect (Emax). Emax represents the maximum response that can be achieved with a drug, and it is determined by the maximum number of drug-receptor complexes formed, which is ultimately controlled by the number of receptors present in that tissue.



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

Relations between drug concentration and receptor-bound drug



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

Potency

A potent drug is a drug that produces a large effect at a small concentration.

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

The difference between ED50 and EC50 is that D stands for dose and C stands for concentration.
Dose (ED50) is the amount of drug you take.
Example: 500 mg of paracetamol.
Concentration (EC50) is the amount of drug actually present in the blood.
Not 100% of the drug you take reaches your bloodstream. This depends on absorption, which will be discussed in detail in pharmacokinetics

Write your notes here ?

Why are Kd and EC50 different?

1)The effect of a drug depends on affinity and intrinsic activity.

I can have two drugs with the same affinity and concentration but different effects, depending on the ability of the drug to activate the signaling pathway(intrinsic activity)

2)not all receptors need to be occupied to reach the maximum effect.

Explained more in the next slides

The difference: Kd measures binding, while EC50 measures the actual effect, which depends on binding, intrinsic activity, and the number of functional receptors

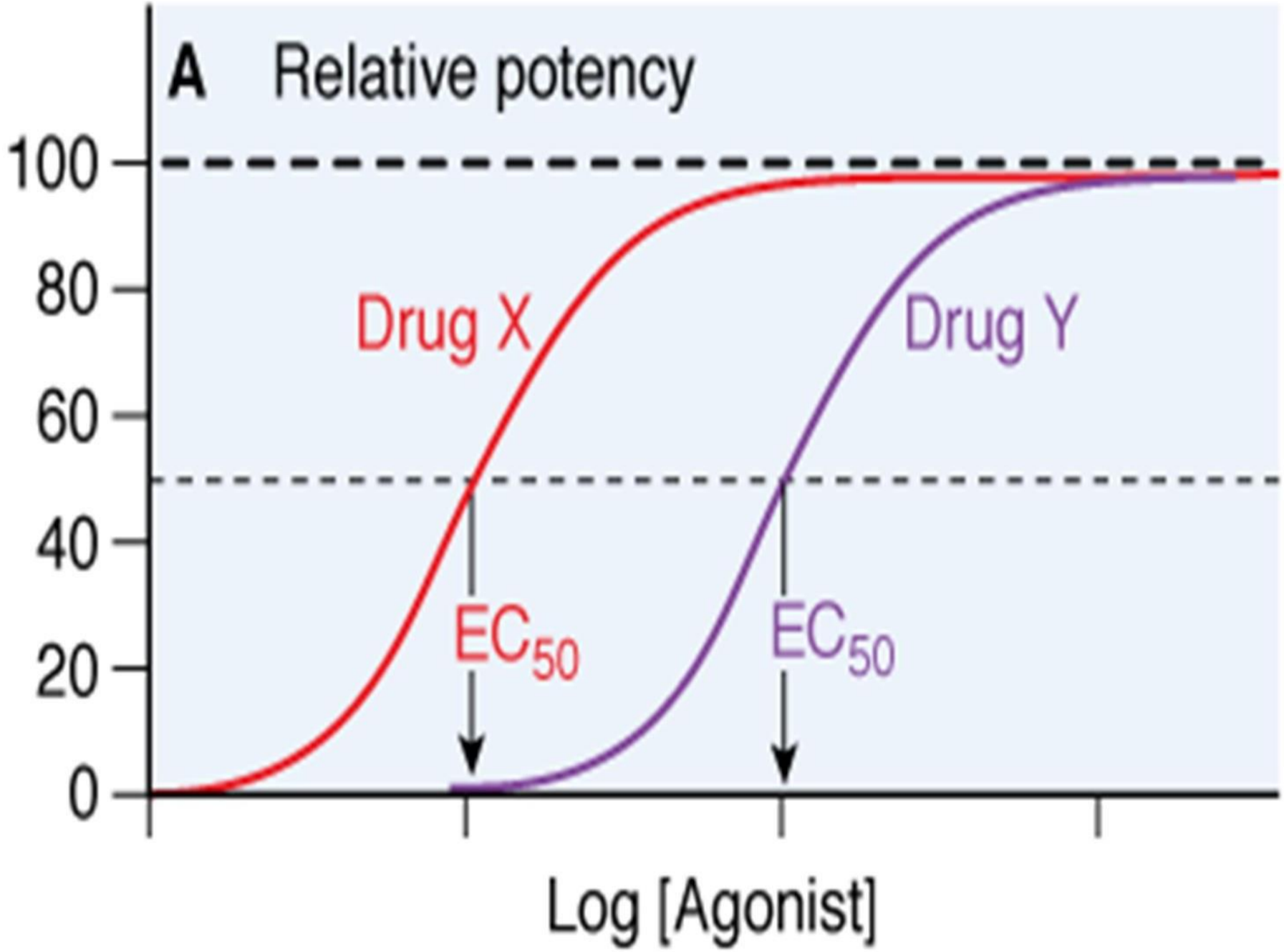
Potency:

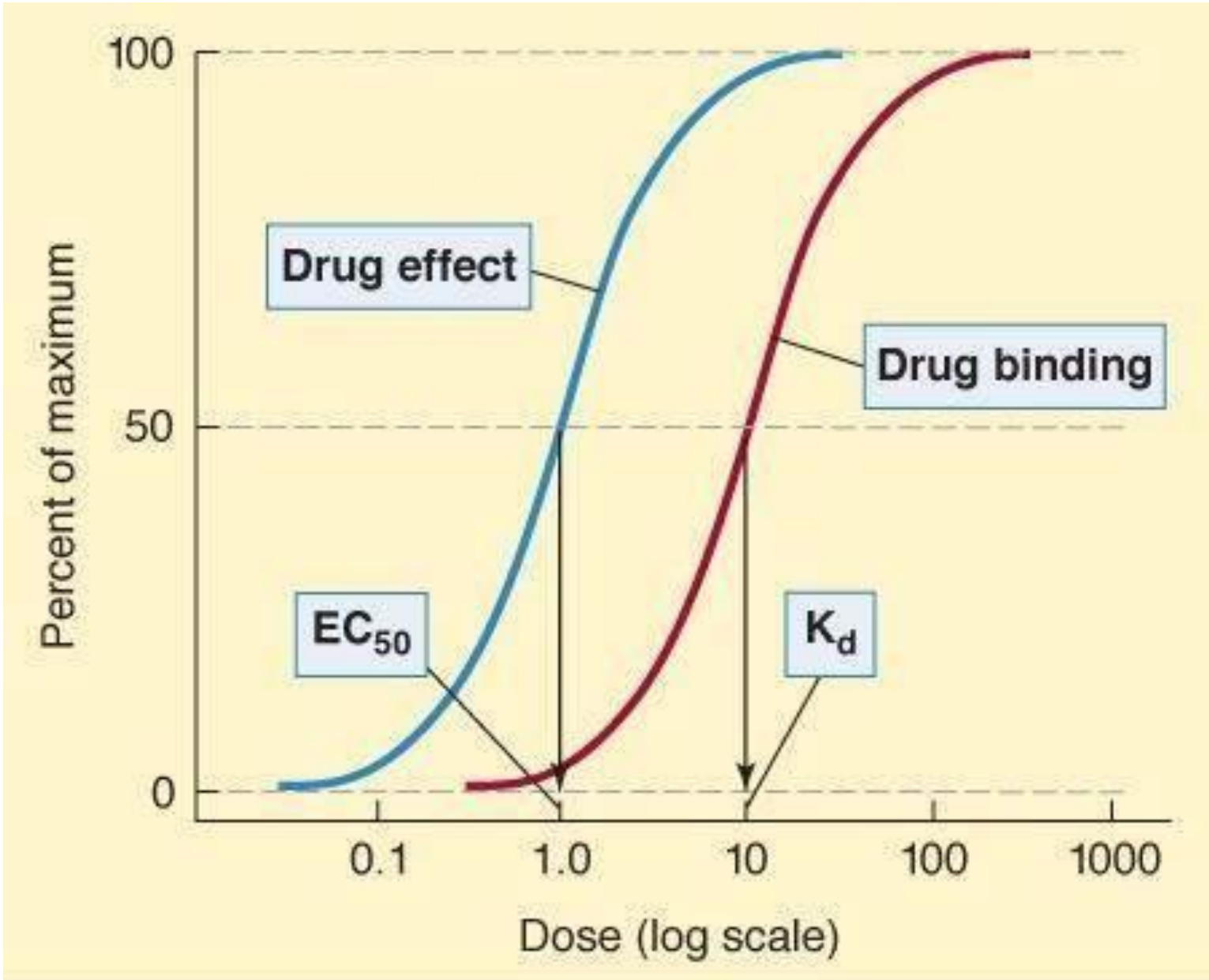
A term used whenever we compare the activity of two drugs producing the same effect

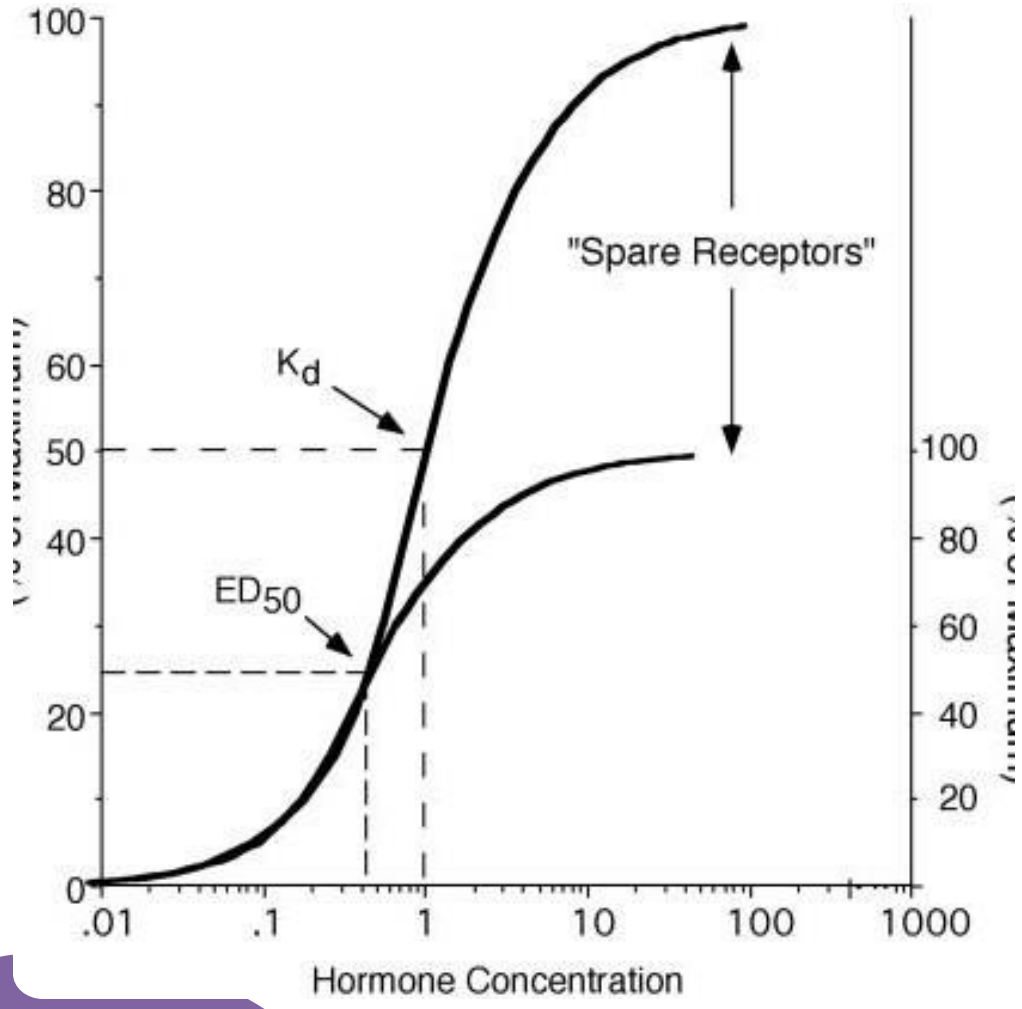
Defined as the dose of one drug necessary to produce a specific response as compared to a second drug producing the same effect

- Affinity:

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


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


100
50
0
Percent of maximum
Drug effect
Drug binding
EC50
Kd
0.1
1.0
10
100
1000
Dose (log scale)



- Here in this graph, Kd is different from EC50. EC50 here is lower. I have a maximum binding of about 100, but the maximum response is reached at a lower level, approximately 50.
-

- As an example, consider insulin. We only use 1% of insulin receptors, keeping the remaining 99% as spare receptors.
-

- In brief, only 1% of these receptors are utilized to achieve the maximum response.

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.

- 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

Why do we have all these 99% spare receptors when our endogenous insulin only uses 1%?
This is for tight control over blood glucose regulation. We have this reserve to handle discrepancies in glucose levels and prevent disregulation, which is important in conditions like diabetes.

However, this is not the case for all receptors .
In receptors with small reserves, EC50 and Kd are close, meaning the maximum response is reached only when most receptors are occupied.

For example, in beta receptors, having only a small number of spare receptors can be problematic, as in heart failure, because the system lacks the reserve to compensate.

Chat gpt explanation

🧠مستقبلات الإنسولين (مع احتياطية كبيرة):
تخيل لديك 100 مفتاح لفتح قفل، ولكنك تحتاج فقط مفتاح واحد لفتح القفل، والباقي احتياطي للطوارئ.

🧠مستقبلات بيتا في القلب (مع احتياطية قليلة):
تخيل لديك 10 مفاتيح فقط لفتح قفل كبير و مفتاح فقط للطوارئ، إذا توقف مفتاحين عن العمل، القفل لن يفتح بالكامل ولن يكون هناك نسخ احتياطية كافية

Additional Resources:

رسالة من الفريق العلمي:

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			