Pharmacology

(تغيير الدواء) * التغييرات التي يحدث فيها الجسم على الدواء

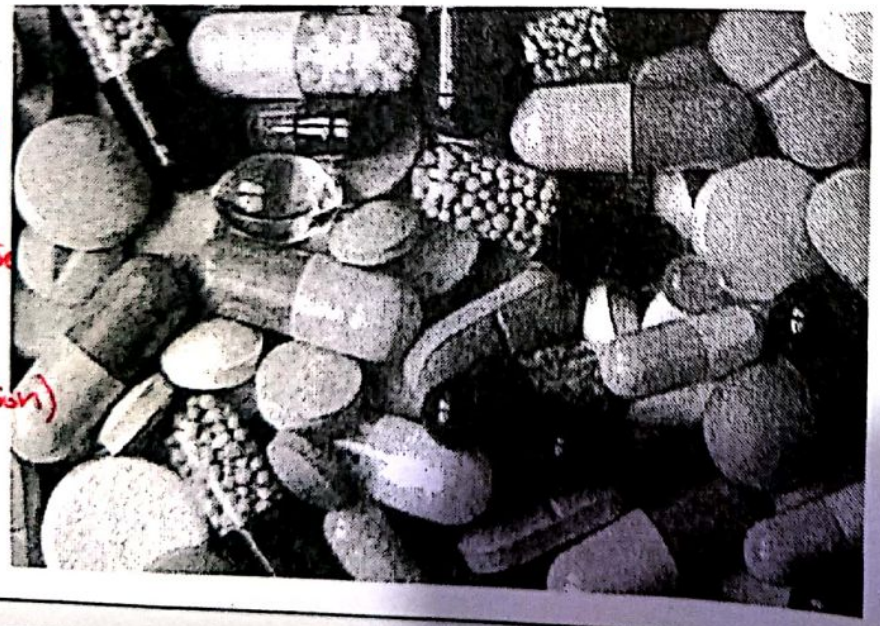
- pharmacokinetic : Science that study fate of the drug.
- pharmacodynamic : Science that study the (طريقة استجابة الجسم للدواء) Response of our body to drug.

- The word pharmacology is derived from the Greek words pharmakon (drug) and logia (the study of).

- **Pharmacology** can be defined as the study of substances that interact with living systems through chemical processes, especially by binding to regulatory molecules and activating or inhibiting normal body processes.

* عشان أحكي عن أي دواء في drug في شرطين ع

1. binding with regulatory molcules (receptor)
2. make a response on the body. (activation or inhibition)



* لازم drug يحدث تأثير في الجسم .

What is a drug?

- A drug : any substance that brings about a change in biologic function through its chemical actions.
  1. To achieve a beneficial therapeutic effect on some process within the patient
  2. Or for their toxic effects on regulatory processes in parasites infecting the patient.
     → to kill microorganism that cause infection in body.

- Drugs may be synthesized within the body (eg, hormones) or may be chemicals *not* synthesized in the body (ie, xenobiotics, from the Greek *xenos*, meaning "stranger")

غريبة

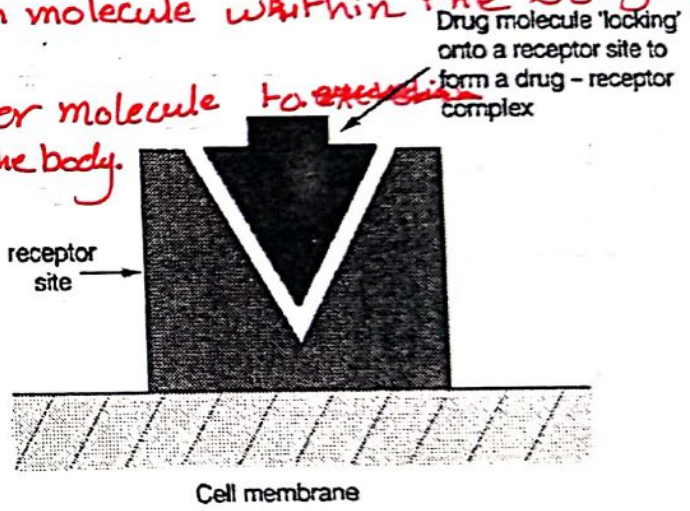
لها مواد غريبة عن الجسم

* analogues مادة وكافئة لمواد مصنعة داخل أجسامنا (hormones)

* حتى يعطينا الدواء Response الذي يرتبط مع موقع محدد في الخلية (Receptor)

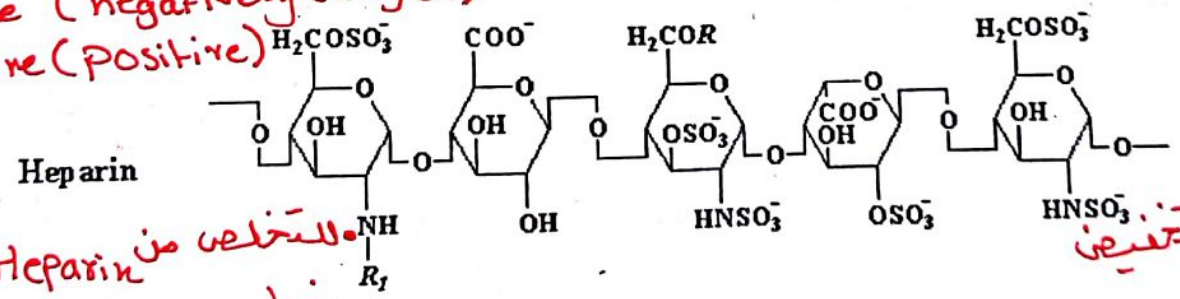
Drug- receptor interaction

- Drug action is exerted mostly by interaction with receptors.
  not all
- Exceptions: ← استثناءات (لا يرتبط مع receptor)
  1. Chemical antagonists : interact with molecule within the body.
  2. Osmotic agents : interact with water molecule to excretion out of the body.



* Response of drug ex
- inhibition of enzyme or process
- activation of enzyme or process

- Heparine (negatively charged)
- protamine (positive) Sulfate



* يرتبط الدواء مع جزيء المادة لإخراجه من الجسم وفتح إعادة امتصاصه لتخفيض ضغط الدم (BP).

• Heparin في الجسم، للتخلص من antidot يعطى المريض protamine sulfate. فيرتبط معه ويخرجه خارج الجسم

What is a receptor?

allmost it is protine in nature.

- The component of a cell or organism that interacts with a drug and initiates the chain of events leading to the drug's observed effects.
- Receptors must be: (Properties to achive function)
  1. **Selective** in choosing ligands (لكل Receptor له مادة محددة يرتبط فيها) — انتقائي
  2. **Modifiable**, so as to bring a change in function upon ligand binding.
     - ability to exert the pharmalogical effect.

* هاي الخصائص لازم تتوفر في receptor :-

١. لإحداث تأثير على الجسم .

٢. لعمل continous pharmalogical effect على الخلية .

Macromolecular Nature of Drug Receptors

- Most receptors are **proteins**.

- A few are macromolecule other than protein, such as DNA.

http://www.atdbio.com/content/16/Nucleic-acid-drug-interactions

* معظم الـ drugs تترتبط مع regular receptor وبعضها ترتبط مع irrigular protines مثل

ترتبط مع الأدوية الـ main binding protines في الدم (البلازما) ، وهي (albumin)

. Highly protine ⇐ لها binding.

* molcules interact with DNA :-

1. group binders → tow starands في الخلايا ترتبط على (on miner groups)

2. inter calated bidnder → between tow strands.

3. alkylaters → alkyl substitution on DNA.

4. Cleaver agents → cutting of dauple strands.

Macromolecular Nature of Drug Receptors

- Drug receptors could be:
  - **Regulatory proteins.** eg, G-protein-coupled receptors (GPCR), the receptors for many neurotransmitters.
  - **Enzymes.** eg, dihydrofolate reductase, the receptor for the antineoplastic drug methotrexate.
  - **Transport proteins.** eg, Na^+/K^+-ATPase, the membrane receptor for cardioactive digitalis glycosides.
  - **Structural proteins.** eg, tubulin, the receptor for colchicine, an anti-inflammatory agent.

step of DNA formation.

(digoxin)

in muscles

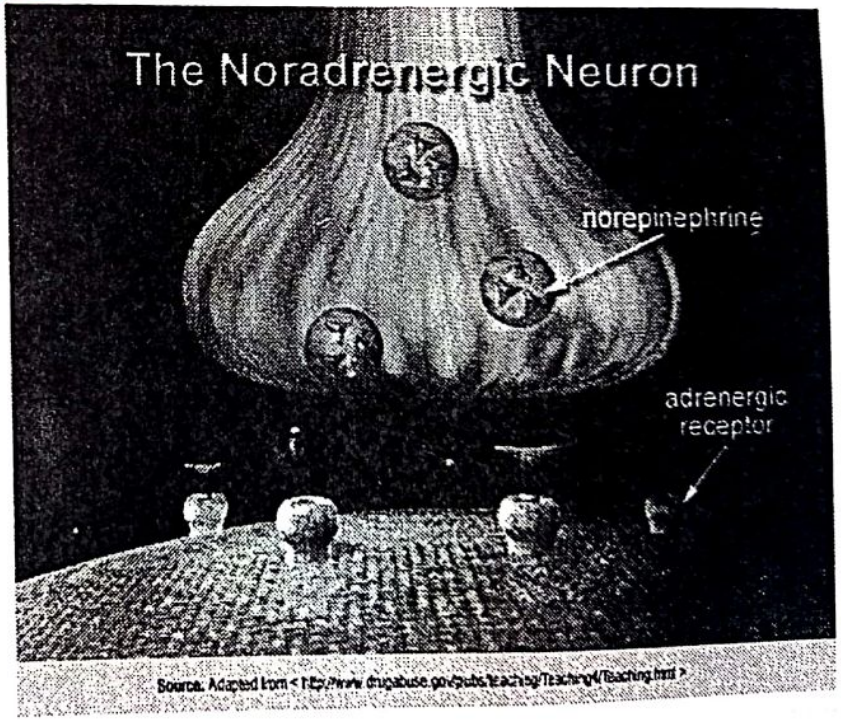
to treating gout (علاج النقرس)

(ibuprofen).

Macromolecular Nature of Drug Receptors

- Drug receptors could be:
  - **Regulatory proteins.** eg, G-protein-coupled receptors (GPCR), the receptors for many neurotransmitters.
    النواقل العصبية

* an synabs between preganglionic and postganglionic neurons.



Macromolecular Nature of Drug Receptors

- Drug receptors could be:
  -
  - **Enzymes.** eg, dihydrofolate reductase, the receptor for the antineoplastic drug methotrexate.

* ~~methotrexate~~ convert dihydrofolate to tetrahydrofolate by dihydrofolate reductase.
* methotrexate inhibit dihydrofolate reductase enzyme and prevent DNA formation

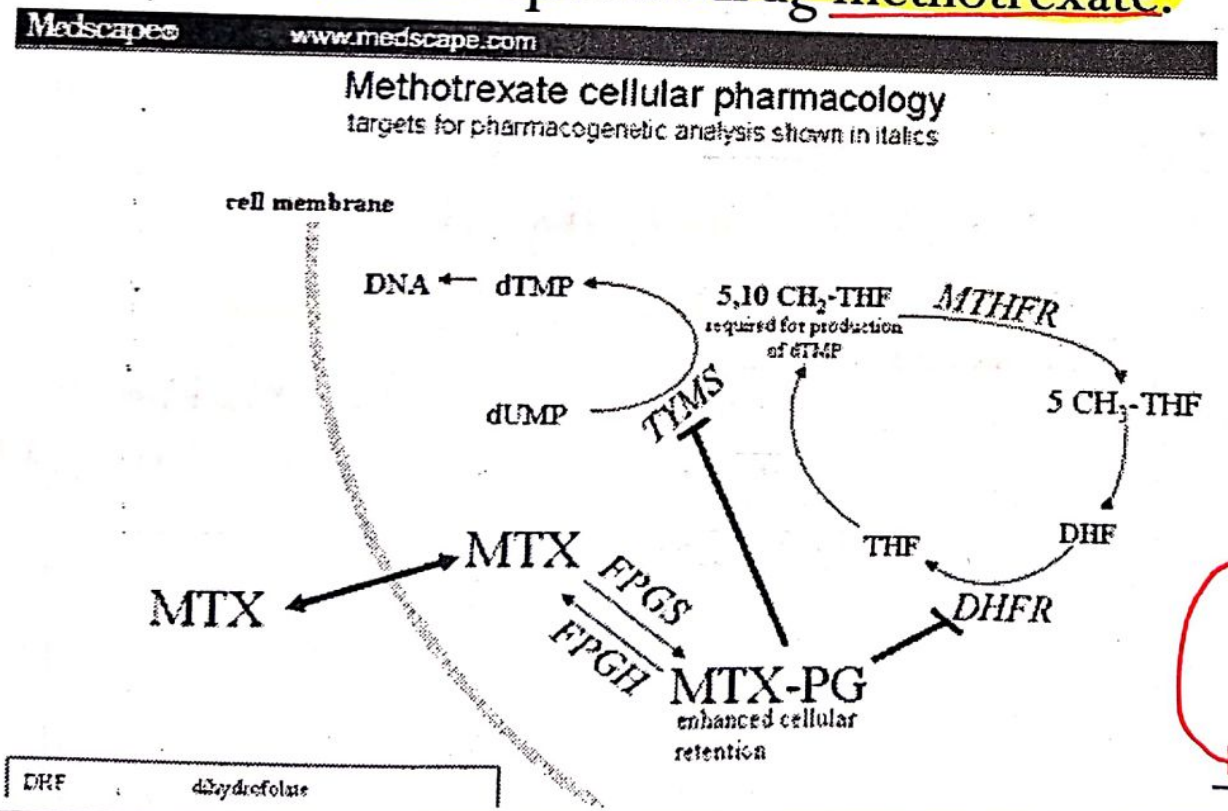


Image shows open bottle of methotrexate drug - one of the first chemotherapeutic drugs used in the early 1950s

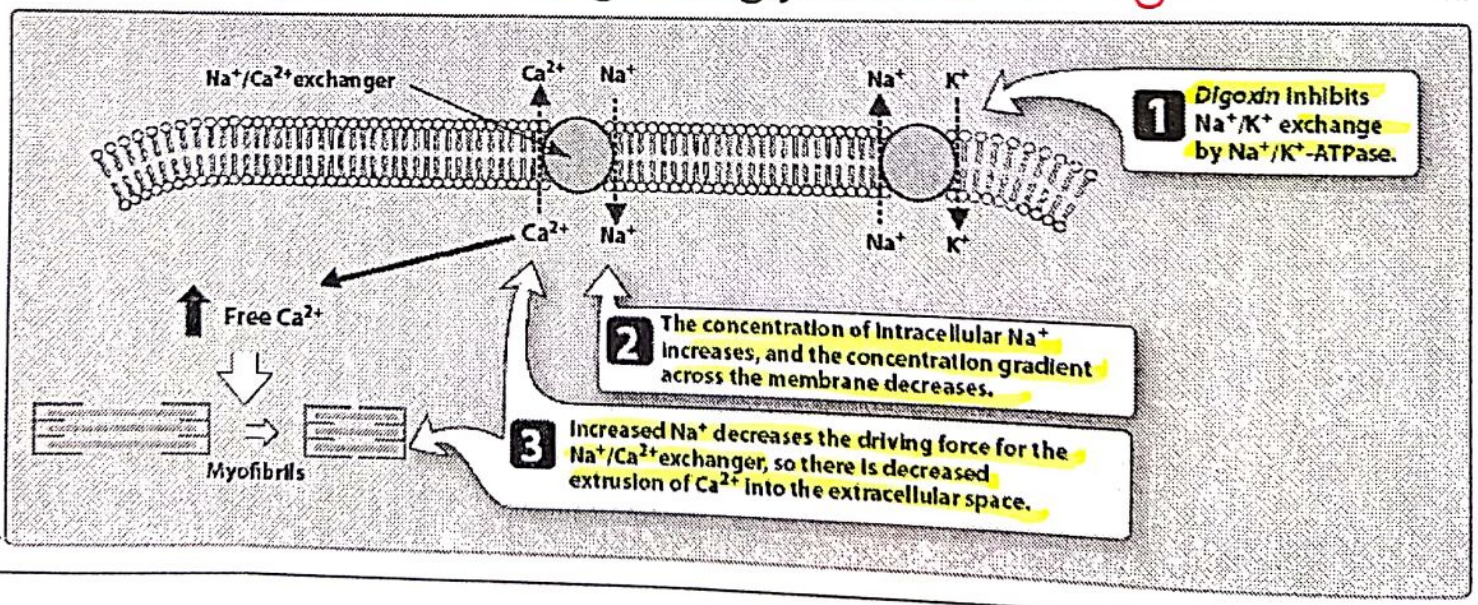
anti cancer drugs.

Macromolecular Nature of Drug Receptors

Na^+ → extracellular
K^+ → intracellular.

- Drug receptors could be:
  -

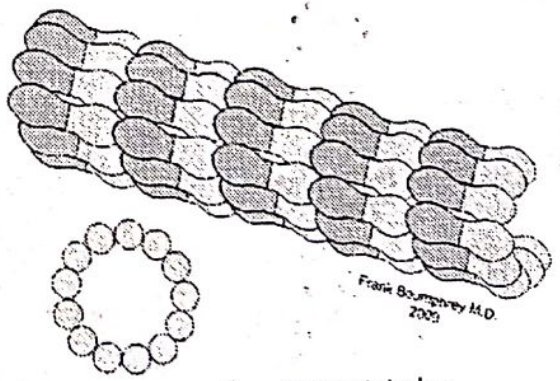
- digoxin ⇒ inhibition of Na^+/K^+ ATPase.
  * فيزداد تركيز Na^+ داخل الخلية ويؤثر على Ca^+ فيزداد تركيزه خارج الخلية
  • atrial fibrillation: علاج هذا وهذا للعضلة خاصة في القلب وتقل contractility.
- **Transport proteins.** eg, Na^+/K^+-ATPase, the membrane receptor for cardioactive digitalis glycosides. → digoxin



Macromolecular Nature of Drug Receptors

- Drug receptors could be:
  -
  -
  -
  - **Structural proteins.** eg, tubulin, the receptor for colchicine, an anti-inflammatory agent.

- Colchicine
(gout) مرض النقرص * يستخدم لعلاج



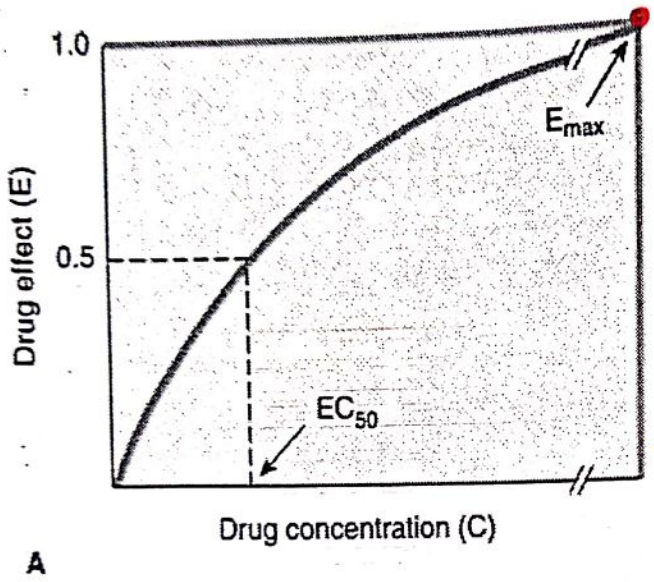
Construction of Microtubules from α & β Tubulins

Relation between Drug Concentration & Response

1. **Graded dose-response curve** (concentration-effect curve) : a graph of increasing response to increasing drug concentration or dose.

- Dose : related to drug conc.

Graded dose-response curve



A

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmac*
www.accessmedicine.com

Presented graphically by a hyperbolic curve

The relation between drug concentration and effect is described mathematically by the following equation:

$$E = \frac{E_{max} \times C}{C + EC_{50}}$$

C: drug concentration.

E: the effect observed at concentration C.

E_{max}: the maximal response that can be produced by the drug.

EC_{50}: the concentration of drug that produces 50% of maximal effect.

responses to low doses of a drug usually increase in direct proportion to dose. As doses increase, however, the response increment diminishes; finally, doses may be reached at which no further increase in response can be achieved.

Constant effect

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* يستمر التأثير بالازدياد مع ازدياد التركيز حتى نصل لنقطة معينة من التركيز ثم يصبح ثابتاً مهما ازداد التأثير وتسمى هذه النقطة E_{max}.

* عند ازدياد conc. أكثر من التركيز عند E_{max} ، الزيادة في الدواء تبدأ بإحداث التأثيرات الجانبية أو السلبية للدواء.

If the percentage of receptors that bind the drug is blotted against drug concentration, a similar curve will be obtained (because drug effect is due to binding to a receptor).

It is described mathematically by analogous equation:

$$B = \frac{B_{max} \times C}{C + K_d}$$

C: drug concentration.

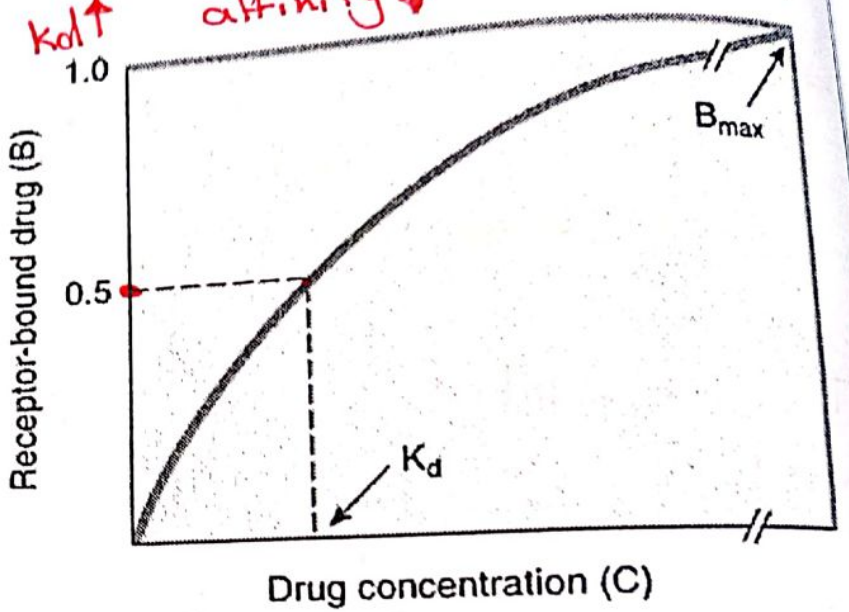
B: percentage of bound receptors at concentration C.

B_{max}: the total concentration of receptor sites (ie, sites bound to the drug at infinitely high concentrations of free drug).

K_d (the equilibrium dissociation constant): the concentration of free drug at which half-maximal binding is observed.

Kd ↓ affinity ↑ dissociation ↓

Kd ↑ affinity ↓ dissociation ↑



B

ogy, 12th edition:

When the Kd is low, binding affinity is high, and vice versa.

* يتم حساب Kd عندما نصل إلى 50٪ من Receptors. مرتبطة مع جزيئات drug

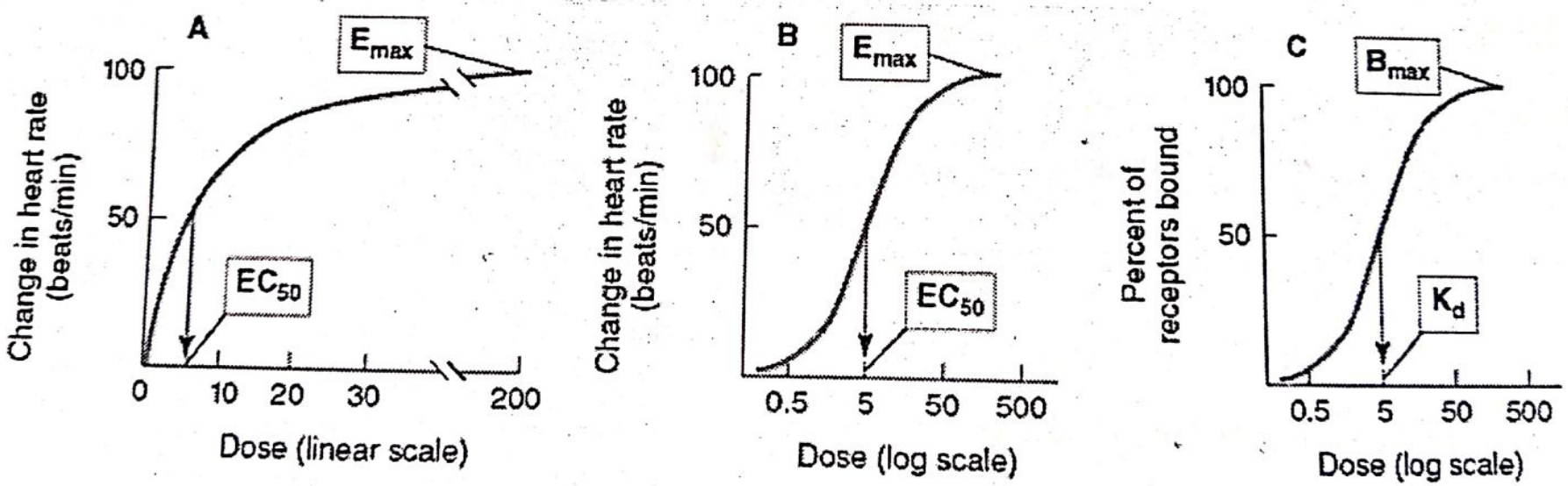
* Kd هي نقطة تعادلية بين عدد Receptors المرتبطة بالدواء وجزيئات الدواء التي بدأت تفي مرحلة اختراجها منا كسم والتخلص منها.

Free drug = Receptor-bound drug.

* نحول من Hyperbolic curve الى Sigmoidal عن طريق أخذ Log(conc.).

- Plotting the drug effect against the *logarithm* of the concentration transforms the hyperbolic curve into a sigmoid curve.
- This expands the scale of the concentration axis at low concentrations (where the effect is changing rapidly) and compresses it at high concentrations (where the effect is changing slowly), which simplifies the mathematical manipulation of the dose-response curve but has no special biologic or pharmacologic significance.

لهذا لا يوجد له معنى في التأثير على الجسم.



* يبين أنه عند التركيز القليل من drug يزداد التأثير أسرع منه عند التركيز العالي حتى يشبع عند E_{max}.

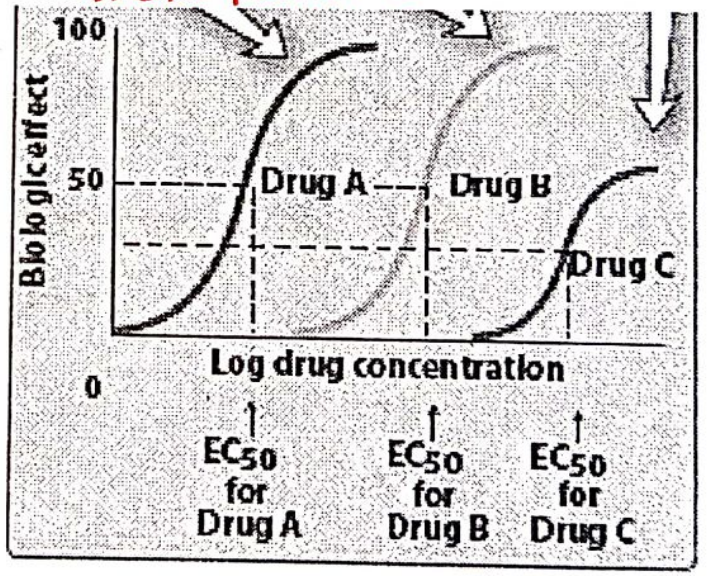
Potency

* الكمية التي نحتاجها ليحدث تأثير من drug.

- a measure of the amount of drug necessary to produce an effect of a given magnitude.
- Potency is determined by EC50. → Conc. needed to occure half-maximal effect.
- Drug with lower EC50 is more potent.

* كل ما كان التركيز الذي يحتاجه الجسم من الدواء ليحدث نفس التأثير الأعلى أقل، كلما كان الدواء أقوى (more potent).

* If drug more potent, the dose must be lowered.



- Drug A more Potent than B, C.
- Drugs A, B more effective than C.

- narrow therapeutic index (digoxin), the therapeutic dose very close of toxic dose.
- wide therapeutic index (amoxicillin), the therpetic dose very far of toxic dose.

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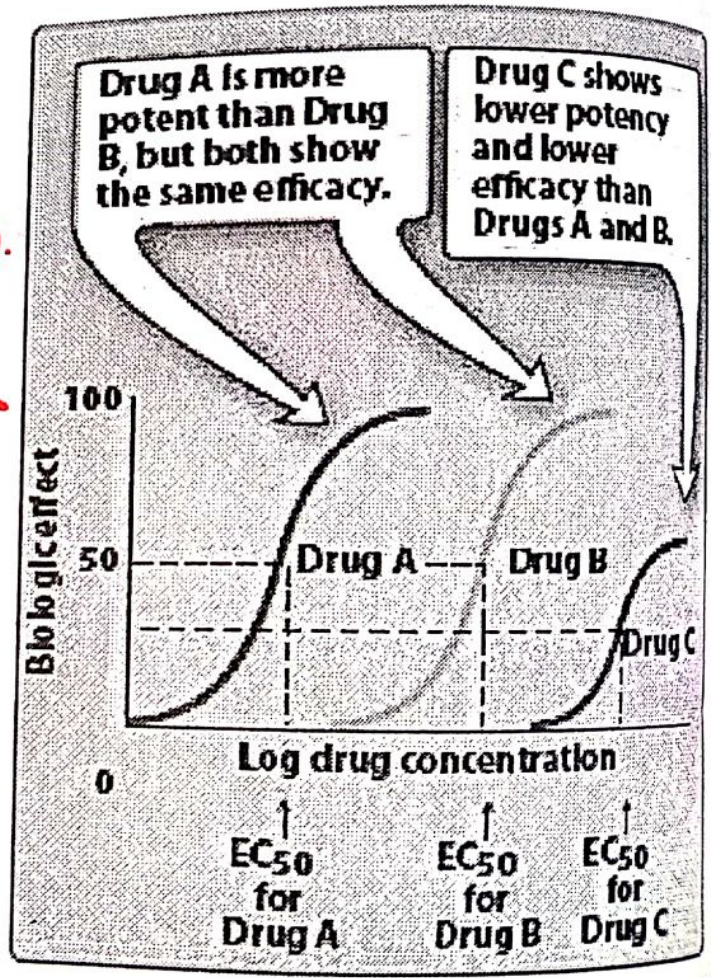
* wider therapeutic index, more safe drug, and vice versa.

* أعلى نسبة تأثير يحققها الدواء بغض النظر عن التركيز الذي حقق هذا التأثير.

Efficacy

- is the ability of a drug to elicit (يحقق أعظم) a response when it interacts with a receptor.
- Maximal efficacy is determined by Emax.
- Efficacy is dependent on: (Factors)
  - the number of drug–receptor complexes formed (saturation of receptor by drug molecules).
  - the efficiency of the coupling of receptor activation to cellular responses (receptor-effector coupling). (مدى تأثير ارتباط drug-Receptor على الخلية.)
- Efficacy is more important than drug potency. A drug with greater efficacy is more therapeutically beneficial than one that is more potent.

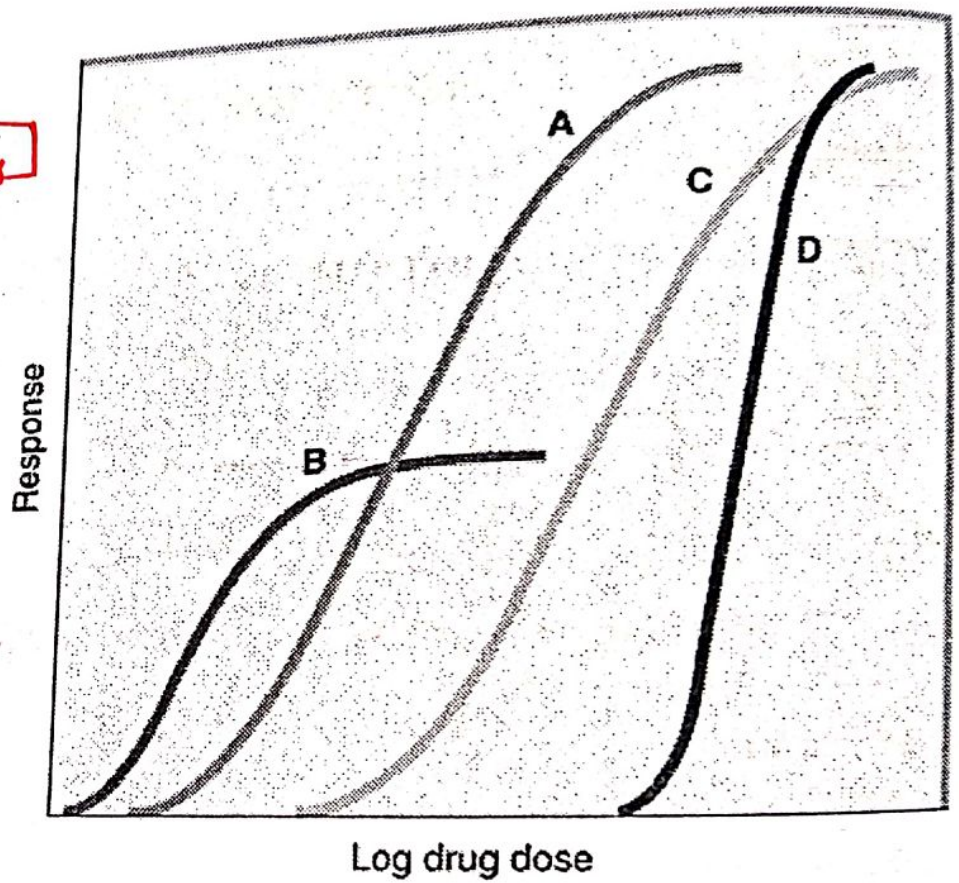


A and B = Same efficacy.

* الدواء الأكثر فعالية (more efficacy) هو أكثر فائدة علاجية من الدواء (more potent drug).

Which drug is....

- the most potent → Drug B
  . effect نحتاج كمية أقل لحدوث نفس
- the most efficacy → A, C, D
  Conc. بغض النظر عن ذي E_{max} لها نفس
- the least potent → D.
- the least efficacy → B.



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 12th edition*: www.accessmedicine.com

Artery Academy

Done by Aya Rabbaa