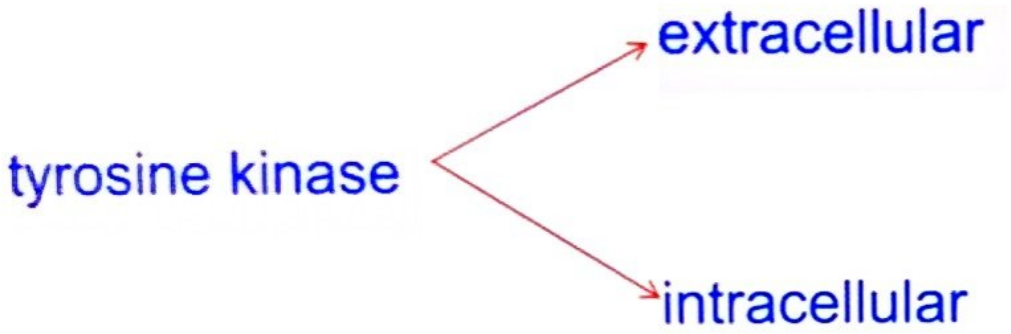
مراجعة سريعة لعملية الـ tyrosine kinase

عشان يصير في action لازم يصير ارتباط على المستقبل ويعمل oxidation بعدين يصير signaling

عشان يعمل تاثير للـ sense



مابتكون مرتبطة باي اشي : inactive form

مجرد ما اجا عنا ligand like Insulin بصير في ارتباط binding of 2 peptide of tyrosine kinase

وهاي العملية تحول المستقبل الى حالته الفعالة active form

وبالاخر بصير في phospholeration

③ Cytokinase : نفس مبدأ الـ tyrosin Kinase

ولكن في الـ tyrosin kinase كان في فسفرة (phospholeration) بحقّ حالو لحالو.

- Cytokinase : extrinsic (not intrinsic activity)

يعني لازم يرتبط مع المستقبل عشان يبلش يصير activation

ملاحظة : لساتنا بنحكي عن trans membrane receptor

- extracellular domain
- intracellular domain

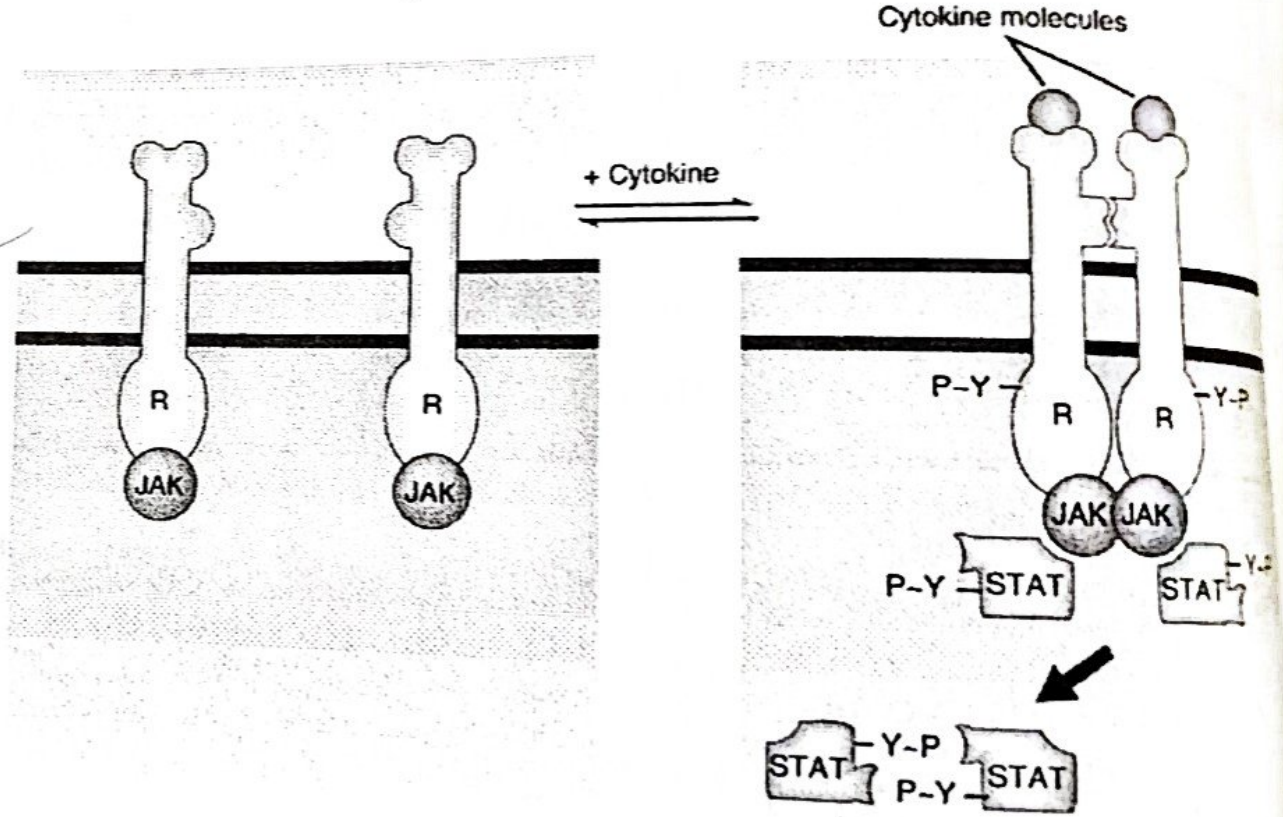
في الـ tyrosin بصير الـ phospholeration بصير active

---

* الـ 2 ligand الي موجودين هنا رح يكونوا مسؤولين عن كل ...eration

3. Cytokines receptors

- Example:
  Growth hormone and erythropoietin.
- Similar to receptor tyrosine kinases except the tyrosine kinase activity is not intrinsic to the receptor molecule.



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

phospholeration

phospholeration لهيك كنا رح يكونوا مسؤولين عن ال ligand 2 اللي موجودين *

JAK kinase بتأثر sytokine receptor اللي موجودة على tyrosine resdue ال

another substrate is التحفيز او بتي phospholeration وبعد ما يصير رح يتم *
→ STAT (signaling transduction activator transcription)
كمان يرتبط مع JAK وهيدين يصيرو فسفرة كمان مرة

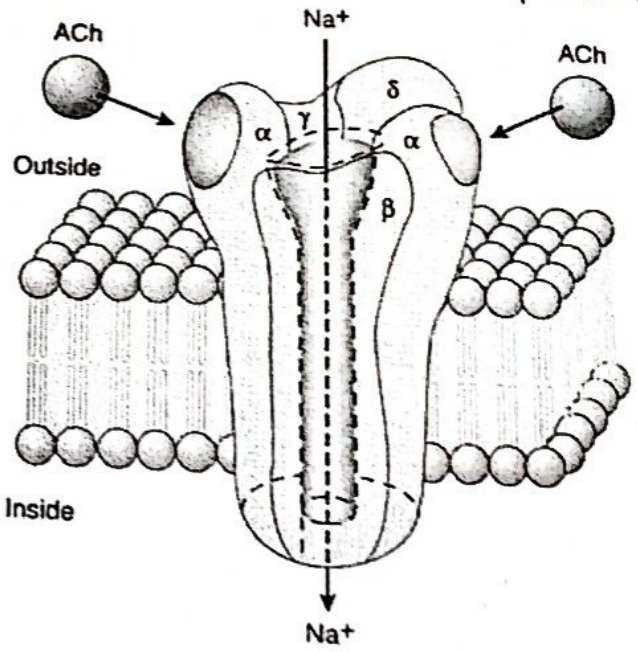
(inactiv → active form) من cytokinase ال recepton رح تنقل ال phospholeration مجرد ما

phosphalerated بعدين ال STAT 2 بروحوا على ال cytoplasm ويرتبطوا مع tyrosine resdue

* ارتباطهم سوا بعطي عملية ال transcription

4. Ligand and Voltage-gated channels

- Example on ligand-gated channels: Nicotinic Acetylcholine (ACh) receptors.
- Voltage-gated ion channels do not bind neurotransmitters directly but are controlled by membrane potential.
- For example, verapamil inhibits voltage-gated calcium channels that are present in the heart and in vascular smooth muscle, producing antiarrhythmic effects and reducing blood pressure without mimicking or antagonizing any known endogenous transmitter.



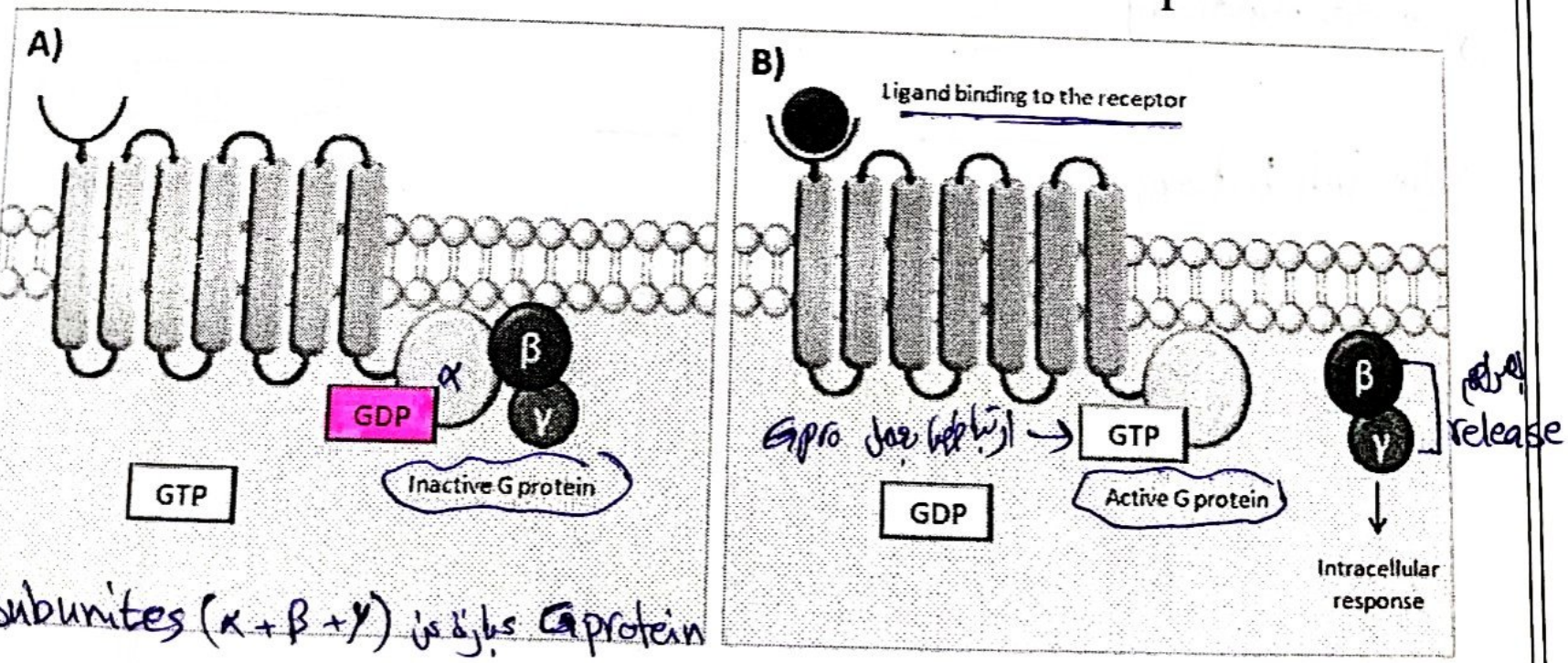
Source: Katzung BG, Masters SB, Trevor AJ: Basic & Clinical Pharmacology, 12th
www.accessmedicine.com

5. G protein-coupled receptors (GPCR)

trans membrane receptor
- extracellular receptor
- intra cellular receptor

* معظم الادوية تعمل من خلال هذه المستقبلات

- G-protein: GTP-binding protein.
- GTP: Guanosine triphosphate .
- Examples: muscaranic Ach receptors, β adrenoceptors.



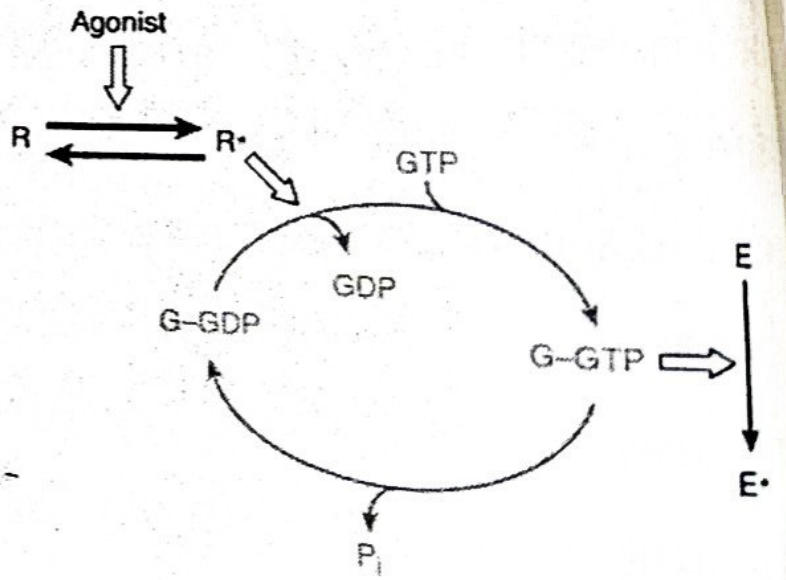
3 subunites (α + β + γ) في أي G protein

Guanosine diphosphate

G protein

- 3 subunits: α, β and γ.
- G proteins modulate different effectors, such as adenylyl cyclase, phospholipase C or ion channels.
- The effectors commonly synthesize or release second messengers such as cAMP, inositol triphosphate (IP_3), diacyl glycerol (DAG) or Ca^{2+}.
- Different subtypes:

Gs, Gi and Gq.



Source: Katzung BG, Masters SB, Trevor AJ: Basic & Clinical Pharmacology, 12th

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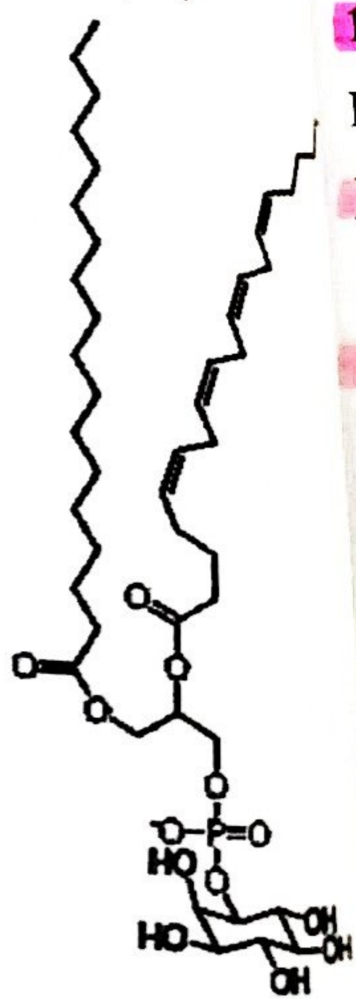
G proteins types

Type	Effector	Effector substrate	Second messenger response
Gs جزء stimulatory	Adenylyl cyclase	ATP	Increase cAMP
Gi جزء inhibitory	Adenylyl cyclase	ATP	Decrease cAMP
Gq جزء stimulatory	Phospholipase C	Membrane phospholipids	Increase IP3 and DAG

2)
(c

3) Phosphoinositides and Calcium

- Phosphotidylinositol (PI) is a phospholipid.
- Phosphoinositides: phosphorylated phosphotidylinositol (PI) to form phosphatidylinositol phosphate (PIP), phosphatidylinositol bisphosphate (PIP_2) and phosphatidylinositol trisphosphate (PIP_3).



tra

Cha

1) Signal

Example

First, a

pro

Second

the c

transcription: نسخ transduction: نقل

Characteristics of signal transduction

1) Signal amplification

Example: GPCRs, two phenomena account for signal amplification (التضخيم):

First, a single ligand–receptor complex can interact with many G proteins, thereby multiplying the original signal manyfold.

Second, the activated G proteins persist for a longer duration than the original ligand–receptor complex.

Characteristics of signal transduction

2) Receptor regulation

Receptors are dynamically regulated in ① number, ② location, and ③ sensitivity.

- **Tachyphylaxis:** Short-term reduction of the drug effect due to repeated exposure to agonists. In this phenomenon, the receptors are still present on the cell surface but are unresponsive to the ligand. يقل تأثير الدوا
- **Downregulation:** Long-term reductions in receptor number in response to continuous exposure to agonists.
- **Upregulation:** Long-term increase in receptor number when receptor activation is blocked for prolonged periods (usually several days) by pharmacologic antagonists. nicotine ← ليك هيك

Characteristics of signal transduction

2) Receptor regulation

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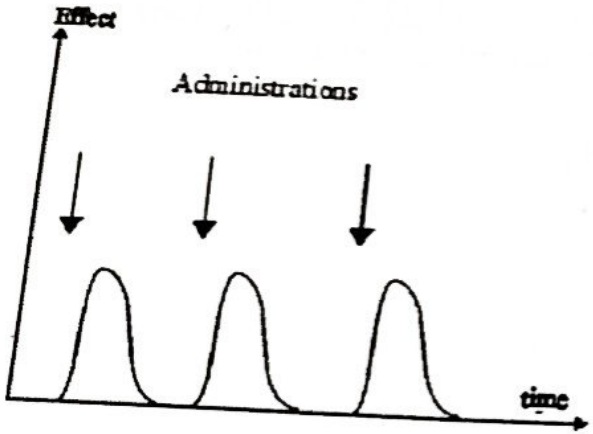
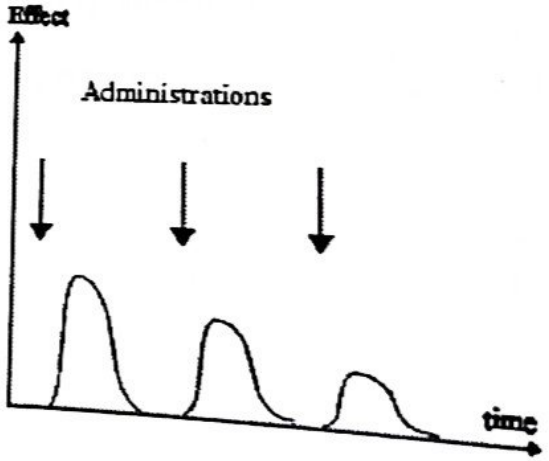
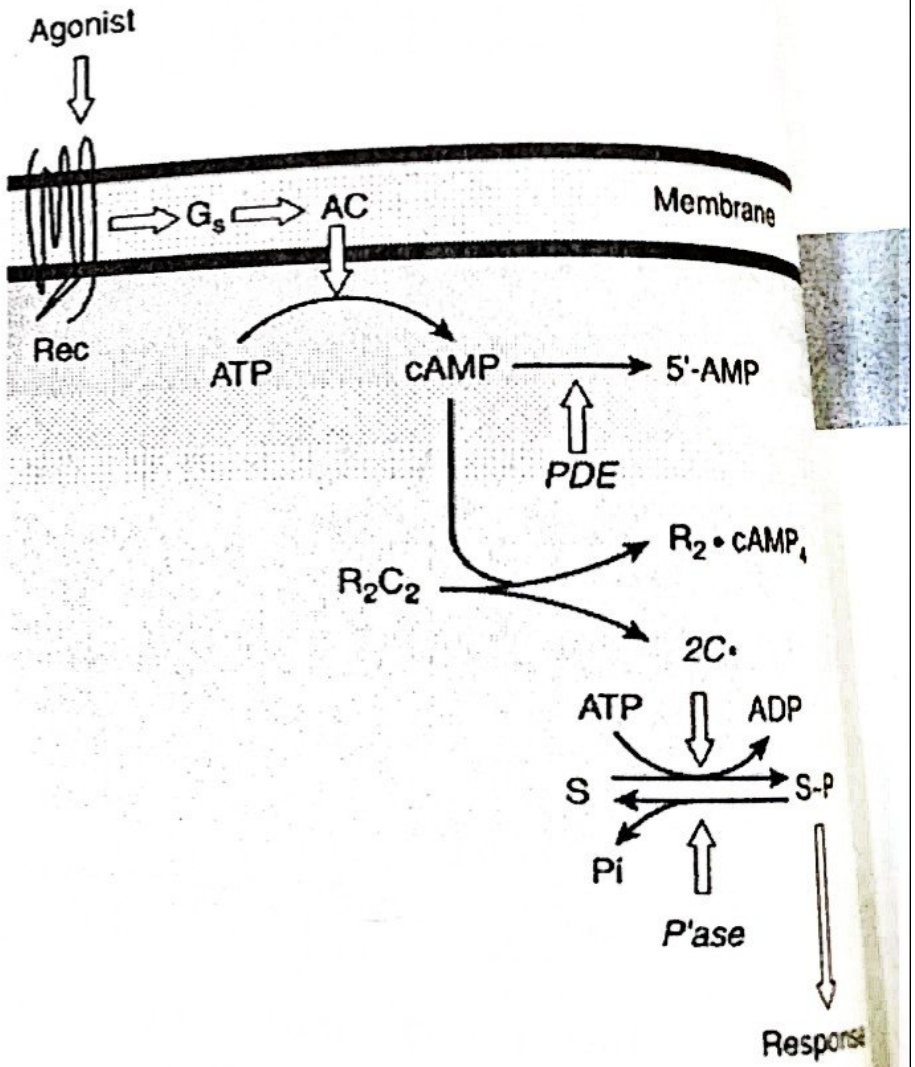




Receptor classes and Drug develpement

- New drug development is not confined to agents that act on receptors for extracellular chemical signals.
- Increasingly, pharmaceutical chemists are determining whether elements of signaling pathways distal to the receptors may also serve as targets of selective and useful drugs.



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*
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Pharmacokinetics

تأثير الجسم على الدوا

- The aim of drug therapy is to ① cure, ② prevent or ③ control various diseases.
- To achieve that, adequate drug doses must be delivered to the target tissues so that therapeutic yet nontoxic levels are obtained.
- Pharmacokinetics examines the movement of a drug over time through the body.
- The ① speed of onset of drug action, ② the intensity of the drug's effect, ③ the duration of drug action are controlled by four fundamental pathways of drug movement and modification in the body.

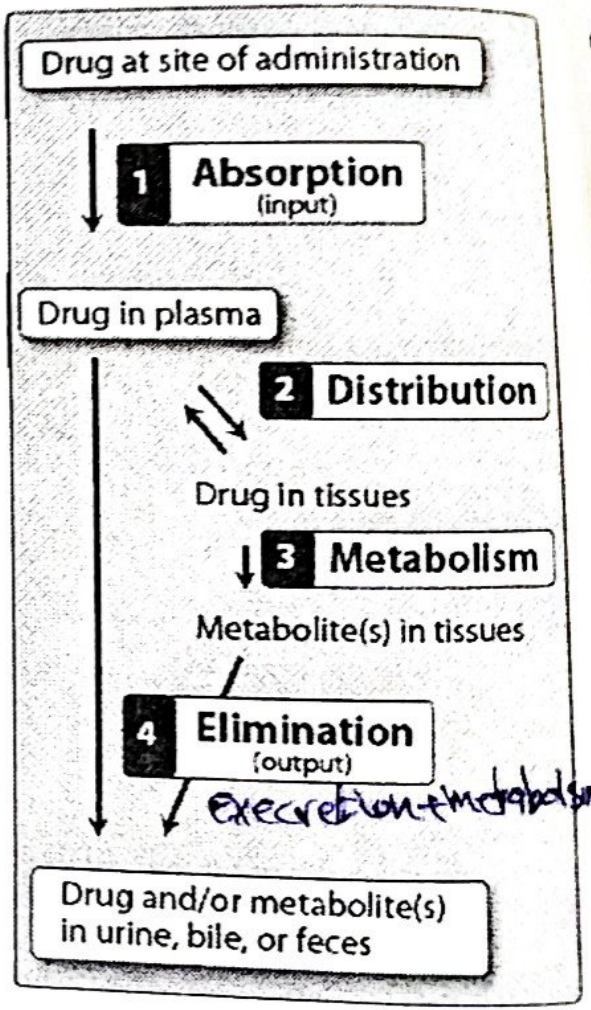
يتحدد اكل pharmakokinetic parameters:
- speed of onset: الوقت اللي يظهر فيه تأثير الدوا
- intensity of drug: شدة التأثير للدوا
- duration of drug: مدة بقاء الدوا في الجسم وبستمر فيها تأثير الدوا

absorption, distribution, metabolism, elimination

Pharmacokinetics

Pharmacokinetics

- Drug movement and modification in the body are presented in the following **pharmacokinetics principles**:
  1. **Absorption**
  2. **Distribution**
  3. **Biotransformation**
  4. **Elimination.**



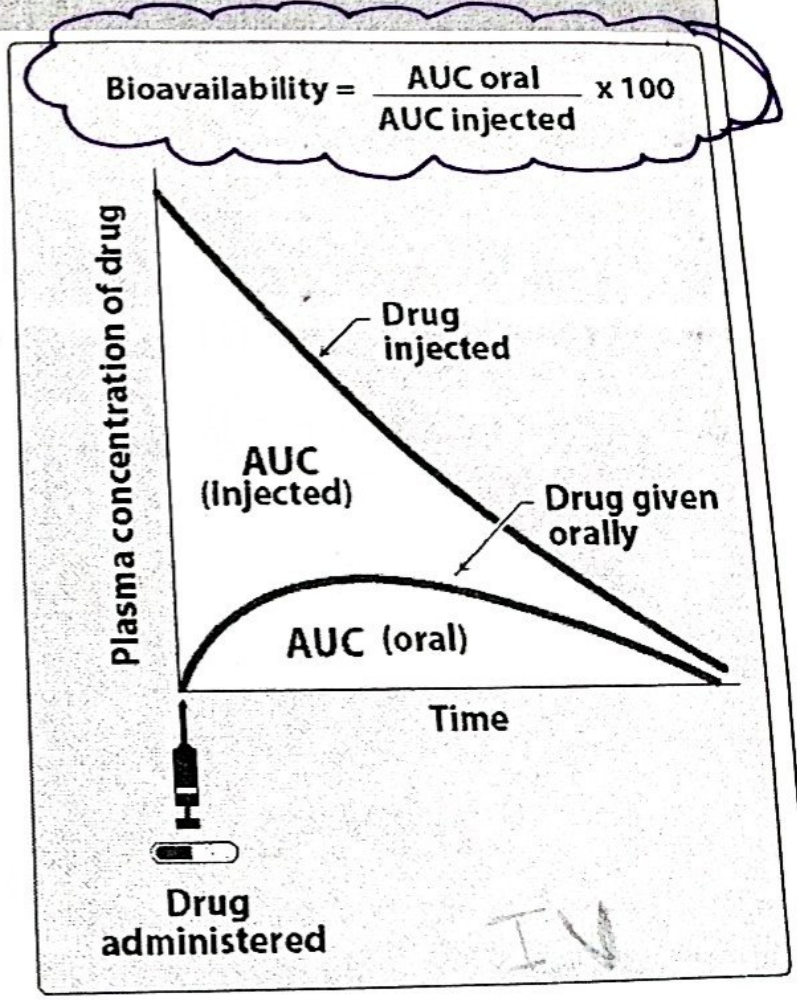
1. Absorption

عشان نحكي انو الدواء وصل للدورة الدموية blood circulation لازم يكون امتص

- Absorption is the transfer of a drug from its site of administration to the bloodstream.
- The rate and efficiency of absorption depend on the route of administration.
- For IV delivery, absorption is complete; that is the total dose of drug reaches the systemic circulation (Bioavailability of intravenous injection is 100%).

Bioavailability

- **Bioavailability** is the fraction of administered drug that reaches the systemic circulation.
- The area under the time-plasma concentration curve (AUC) is used to calculate the bioavailability of a drug.
- Bioavailability is determined by comparing plasma levels of a drug after a particular route of administration with plasma drug levels achieved by IV injection.



100% ปริมาณยา → absolute bioavailability

ยา 1 ชนิด 100 % ปริมาณยา → relative bioavailability

Factors affecting the bioavailability

1. Extent of absorption
2. First-pass elimination in the liver

non-ionized form

$A + B^- \rightleftharpoons \boxed{HA}$ acid

$BH^+ \rightleftharpoons H^+ + \boxed{B}$ Base

pKa ↓
acidic ↓

is (weak acid, weak Bases)

Factors affecting absorption

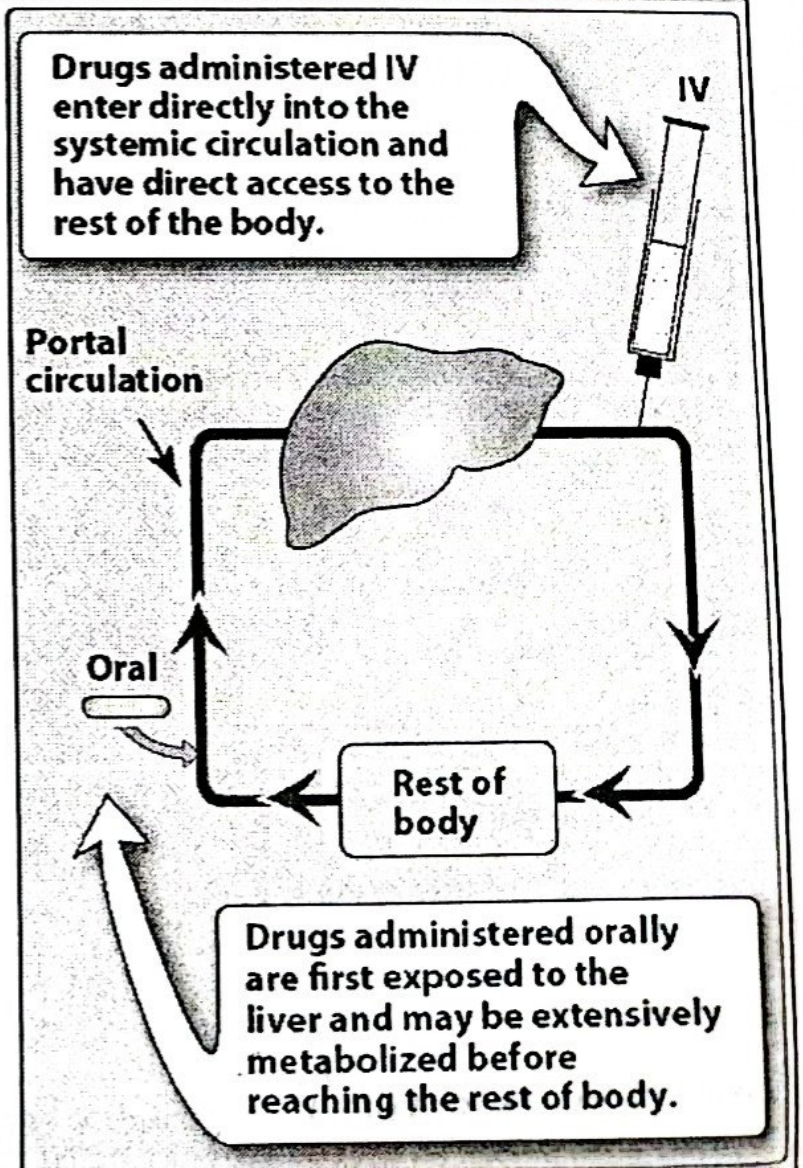
Factors affecting absorption

1. Effect of pH in drug absorption.
2. Blood flow to the absorption site.
3. Total surface area available for absorption.
4. Contact time at the absorption surface.
5. Expression of P-glycoproteins.

First-pass effect

Bio availability على أثر هذا

- First-pass effect is drug metabolism before reaching the systemic circulation. (in the liver)
- Drug metabolism could occur in the gut wall, in the portal blood or most commonly in the liver.

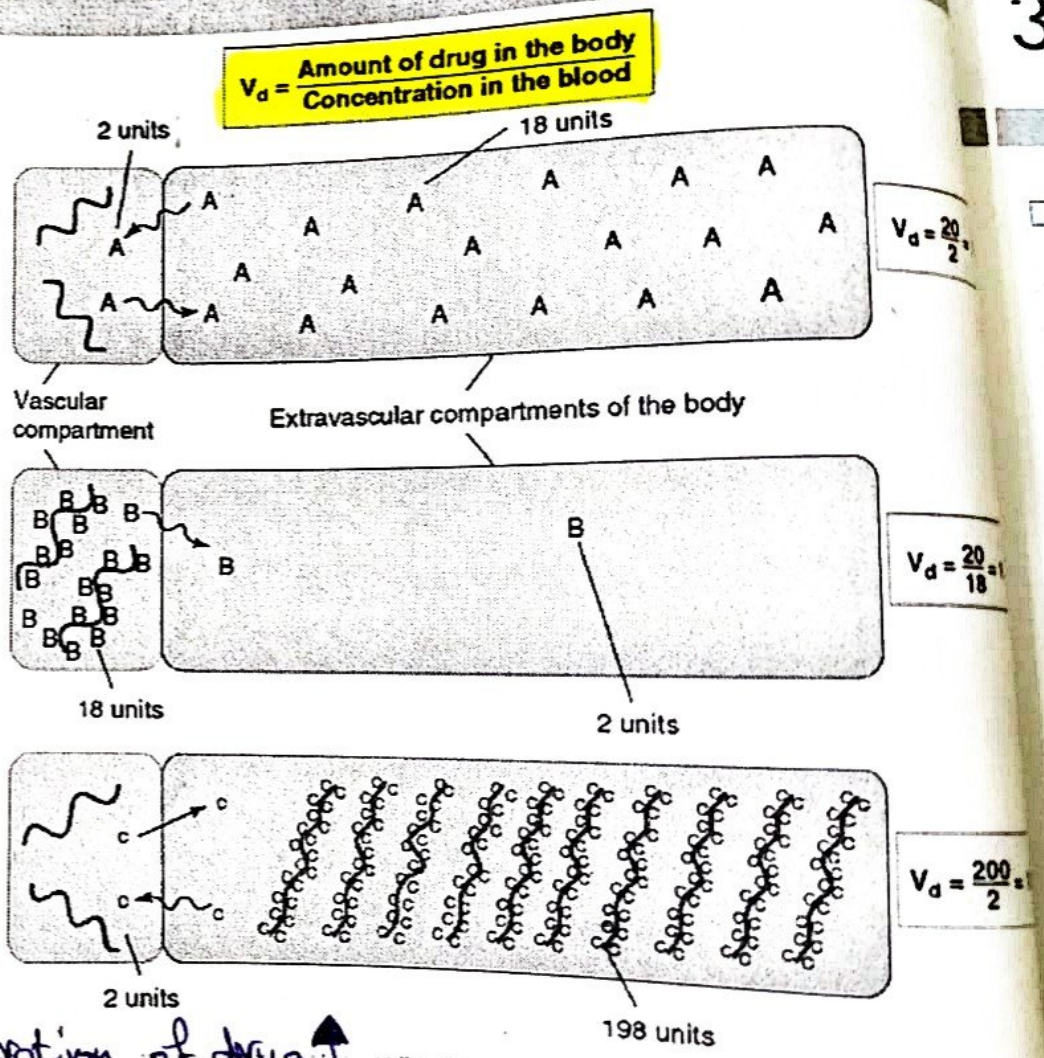


2. Distribution

- Drug distribution is the process by which a drug reversibly leaves the bloodstream and enters the interstitium (extracellular fluid) and/or the cells of the tissues.

Volume of distribution

- The apparent volume of distribution (V_d) relates the amount of drug in the body to the plasma concentration.
- Drugs with very high volumes of distribution have much higher concentrations in extravascular tissue than in the vascular compartment.



volume of distribution ↑ concentration of drug ↑

2. Distribution

2. Distribution

- Factors affecting drug distribution:
  - Binding to plasma proteins (like Albumin) / ↓ Volume of distribution
  - Binding to tissue proteins ↑ Volume of distribution
  - Hydrophobicity

    more soluble in lipid

    more distribution

3. Elimination

- Elimination of drug from the body may involve processes occurring in the kidney, the lung, the liver, and other organs.

Clearance

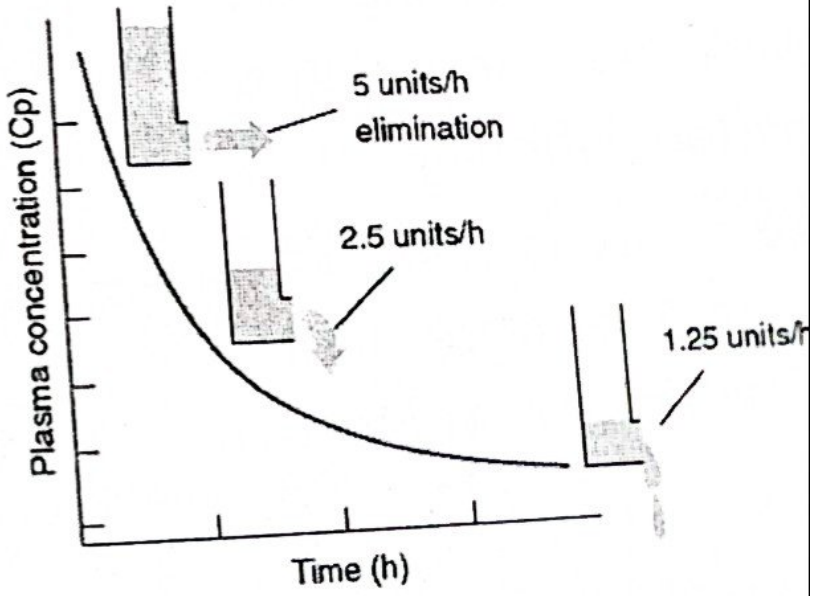
excretion تخلص الجسم من الدوا

- Clearance (CL) relates the rate of elimination to the plasma concentration.
- For a drug eliminated with first-order kinetics, clearance is a constant. ثابتة
- H.W
  - 1st order vs. zero order kinetics?? clearance متغيرة
  - Examples of drugs with zero order kinetics?? aspirin, ethanol, fonetol ← enzymes capacity

$$\text{Clearance (CL)} = \frac{\text{Rate of elimination}}{\text{Plasma concentration (Cp)}}$$

CL ثابت — Rate of elimination متغير

Rate of elimination = CL x Cp



Source: Trevor AJ, Katzung BG, Kruidering-Hall M, Masters SB: Katzung & Tre
Pharmacology: Examination & Board Review, 10th Edition: www.accesspharm

Artery Academy

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