تفريغ فارما ١

اسم الموضوع: Lec . 3

إعداد الصيدلاني/ـة: ياسمين خليل

Soul Academy

لجان الدفعات

بعدما مكنا عن إمتصاص الدواء ووصوله للدم، وتوزيعه حسب حاجة الماء سواء في البلازما

أو خارجها (Vd)، وأخذنا بعقول الطلاب، هاد وقت نتخلص من الدواء عن الجهاز الخاص

يعتبر مادة سامة لازم الجسم يتخلص منها، ونتخلص عن طريق عملية اسمها metabolism، من أهم الشروط إلي لازم تتوفر في الدواء للتخلص

منه هي: [inactive + polar] وعن طريق metabolism بزا الدواء بـ phase I بس في أدوية هاي بترجع بعدها بتتحول لشي ضعيف

بتروح إلى phase II، رح نعرف الفرق بينهم إن شاء الله:

كثفوا الدعاء للمسلمين المستضعفين وحسبنا الله ونعم الوكيل.

METABOLISM OF DRUGS

liver is the major site of metabolism

- Lipophilic drugs can not be excreted from the body
- Therefore, they have to be metabolized into more hydrophilic molecules
- Liver metabolism of drugs consists of 2 phases:
  1. Phase I (convert drug into more polar cpds)
  2. Phase II (conjugation rxn)

يوجد عائلات إنزيمات في الكبد كثير بتعمل في metabolism في phase 1 وأهمها وأشهرها عائلة اسمها Cyp450

تذكروا إنها عائلة و ليست إنزيم واحد

Phase I

- Catalyzed by the cytochrome P450 system
- Cytochrome P450, designated as CYP, is a superfamily of hemecontaining isozymes that are located in most cells but are primarily found in the liver and GI tract.

- The P450 system is important for the metabolism of many endogenous and exogenous compounds

يتم تحويل المركبات من hydrophobic إلى hydrophobic عن طريق عدة تفاعلات:

- Oxidation/Reduction/Hydrolysis → Phase 1

أهم واحد ← Mihor rxns

أفراد عائلة
Cyt P 450

CYP3A4/5,(also in intestinal mucosa)
CYP2D6,
CYP2C8/9,
CYP1A2

Conjugation: phase 2

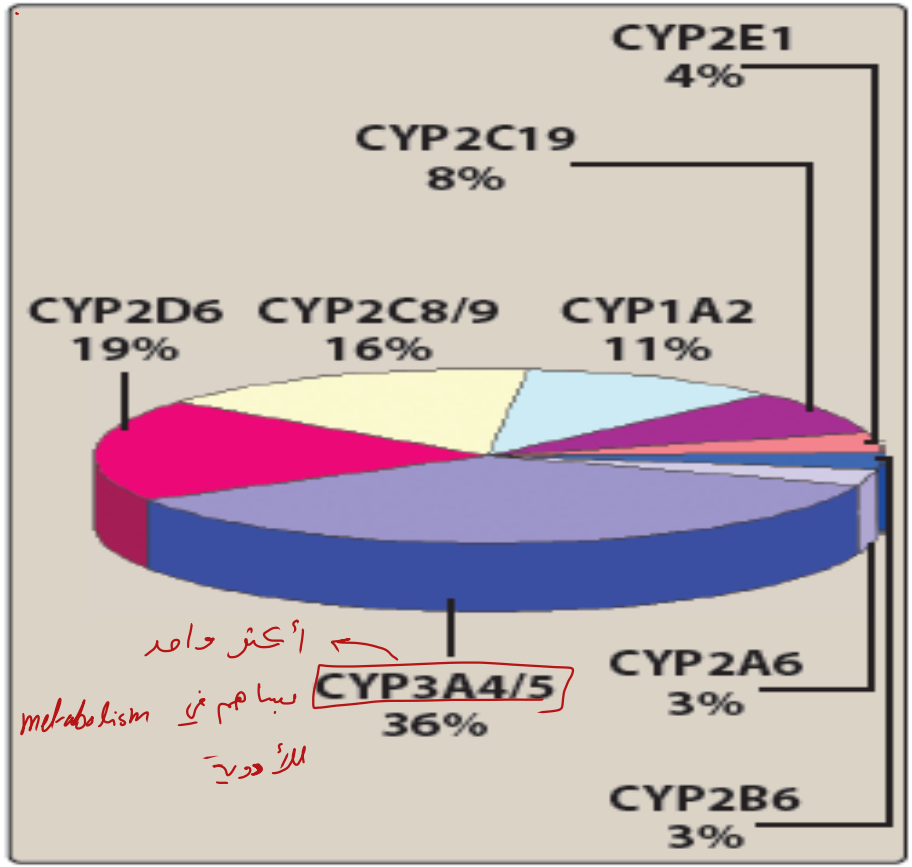


Figure 1.18
Relative contribution of cytochrome P450 (CYP) isoforms to drug bio-transformatin.

Genetic variability in CYP450 enzymes

- Difference in genetic make up may lead to different enzymatic activities!!
- Poor metabolizer (enhanced drug response!)
- Rapid metabolizer (lower drug response)
- Ultra rapid metabolizer (very low response)

✓ Examples are : clopidogrel,

also lack of CYP2D6 and lack of codeine effect!!

CYP450 Inducers

drug – drug interaction

as: warfarin + aspirin

- Xenobiotics that induce CYP gene expression

- Results in more drug biotransformation , lower plasma levels , and lower pharmacological response of substrates

➢ Dose alteration is needed to maintain efficacy

Examples of Inducers

Isozyme: CYP2C9/10

COMMON SUBSTRATES	INDUCERS
Warfarin	Phenobarbital
Phenytoin	Rifampin
Ibuprofen	
Tolbutamide	

Isozyme: CYP3A4/5

COMMON SUBSTRATES	INDUCERS
Carbamazepine	Carbamazepine
Cyclosporine	Dexamethasone
Erythromycin	Phenobarbital
Nifedipine	Phenytoin
Verapamil	Rifampin

CYP450 Inhibitors

- Inhibition occurs mainly through competition such as Omeprazole and Ketoconazole, Erythromycin, Ritonavir
- Results in less drug biotransformation, higher plasma levels and more pharmacological effect.
- For instance, because grapefruit and its juice inhibits CYP3A4, drugs such as *nifedipine, clarithromycin, and simvastatin* will be less metabolized
- Serious Interaction with low therapeutic index medications such as : warfarin

Minor Rxns

- amine oxidation
- alcohol dehydration
- esterases
- hydrolysis

- **Phase I reactions not involving the P450 system: These include:**

amine oxidation (for example, oxidation of catecholamines or histamine), alcohol dehydrogenation (for example, ethanol oxidation), esterases (for example, metabolism of *pravastatin in* liver), and hydrolysis (for example, of *procaine).*

⬇️ لو كان عندي دواء حابب صعوبة ايش صار قبل ، او إنه كيف liphophil حيروح يكون مصيره ؟

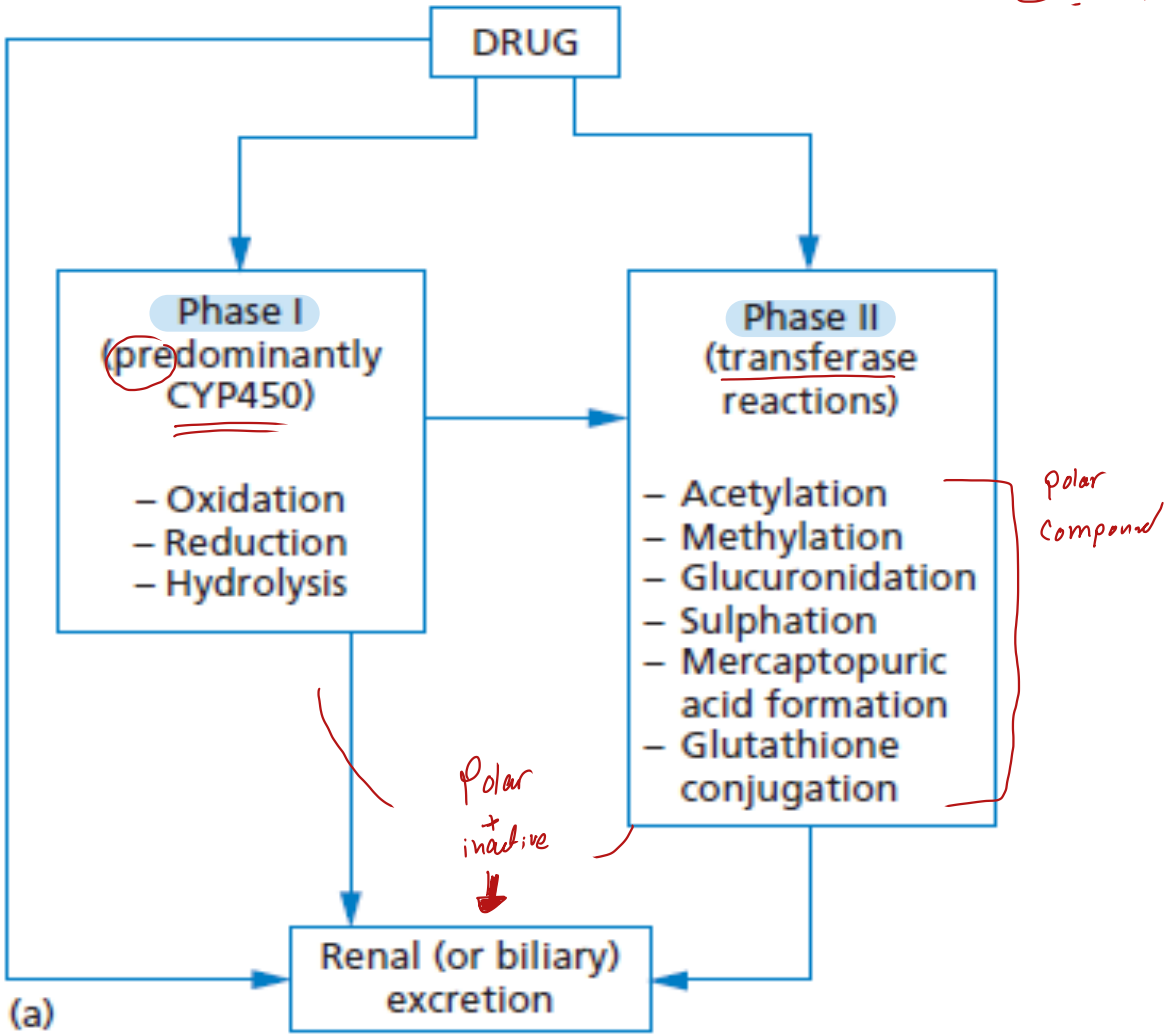
Phase II (conjugation):

- Many phase I metabolites are still lipophilic, so, subsequent conjugation occurs with endogenous substrates such as:

  - Glucuronic acid
  - Sulfate
  - Glutathione
  - Amino acids
  - Acetate

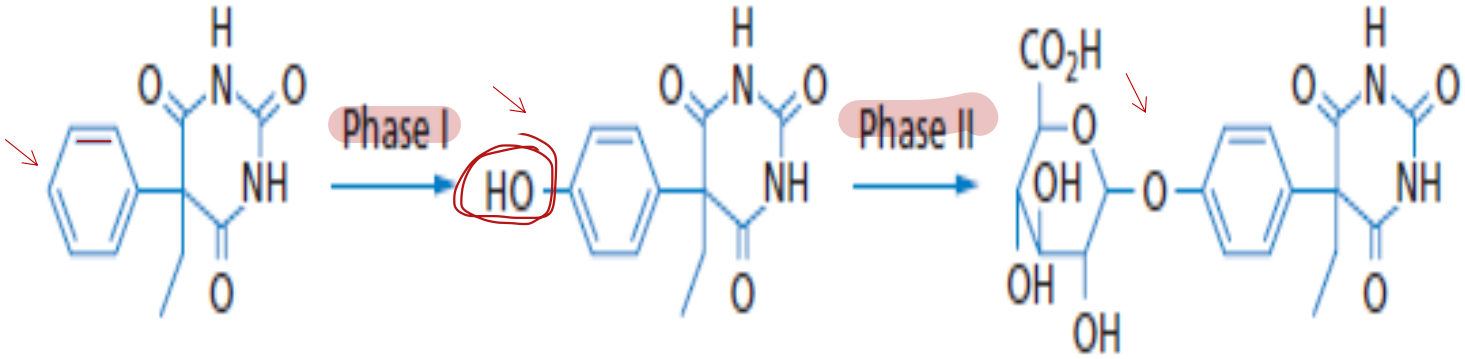
These highly **polar** water soluble conjugates generally are **inactive** and are excreted rapidly in the urine and feces.

ملخص السلايدات :



ربِّ إني لما أنزلت إليَّ من خيرٍ فقير .

Example


Phase I
Phase II
HO
CO2H
OH
OH
OH
O
NH
H
N
O
Phenobarbital
p-Hydroxy phenobarbital
p-Hydroxy phenobarbital glucuronide

آخر عملية هي الإخراج والطرد، بأي شكل، سواء دموع، بول، عرق، لعاب، ...

Excretion of Drugs

- Generally, drugs are excreted either:
  - ➢ Unchanged (hydrophilic drugs)
  - ➢ Changed (metabolites)

❑ *Lipid-soluble drugs thus are not readily eliminated until they are metabolized to more polar compounds*.

لازم يصير polar + inactive

Excretatory Organs:

أعضاء الإخراج

- Kidney
- Intestine
- Lungs (mucus)
- Breast Milk

Kidney

Renal Excretion

Excretion of drugs and metabolites in the urine involves three distinct processes :

1) Glomerular filtration
2) Active tubular secretion
3) Passive tubular reabsorption

"In the treatment of drug poisoning, the excretion of some drugs can be hastened by appropriate alkalinization or acidification of the urine"

Glomerular filtration

- Free drugs enters Bowman's capsule
- The normal glomerular filtration rate (125 mL/min)
- Filtration is not altered by pH or lipophilicty
- Filtration rate and drug protein bindings are main factors

Proximal tubular secretion

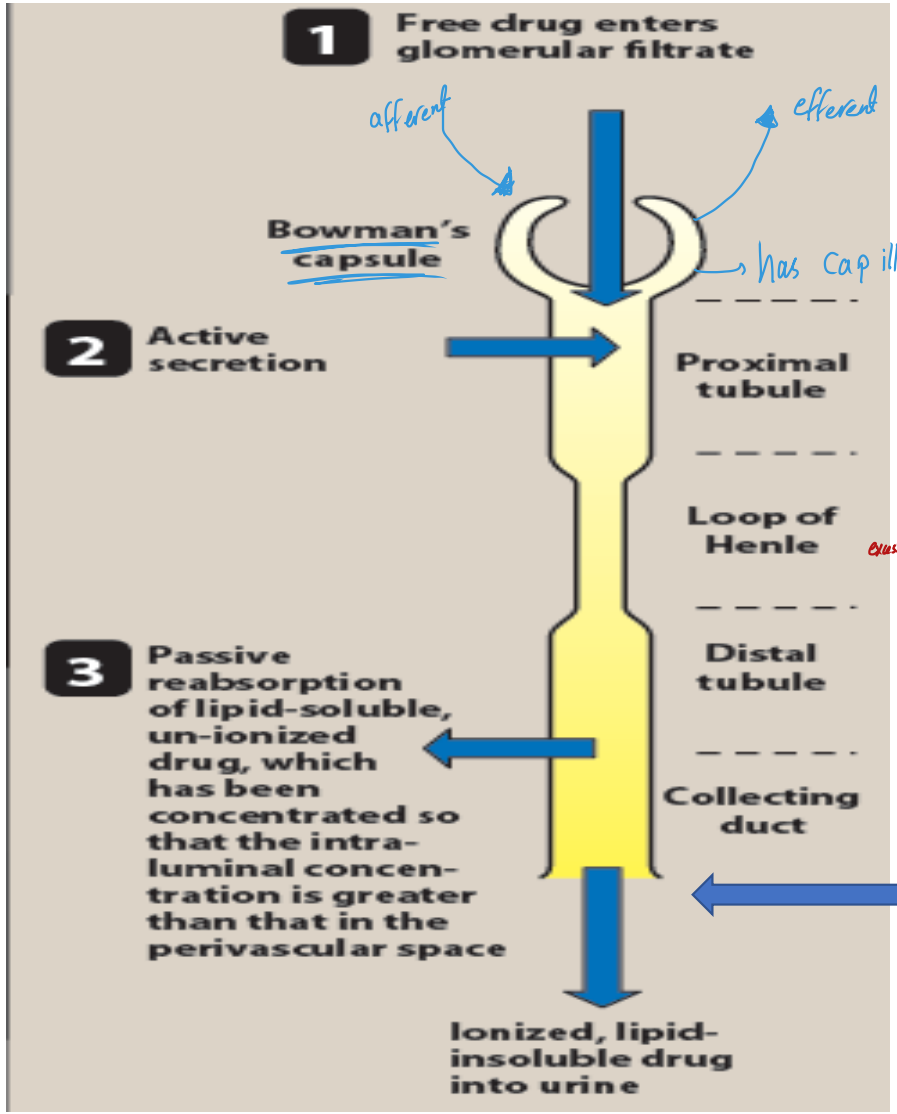
- Unfiltered drugs will pass through the efferent arteriole
- Drugs undergo selective secretion via carriers

- Carriers are not specific, so transporter can carries different compounds. Drug competition should be considered.

Distal tubular reabsorption

- Uncharged drugs diffuse out from lumen to circulation

- As a general rule, weak acids can be eliminated by alkalinization of the urine,whereas elimination of weak bases may be increased by acidification of the urine “Ion trapping.”


1
Free drug enters glomerular filtrate
afferent
efferent
Bowman's capsule
has capillaries with high permeability
2
Active secretion
Proximal tubule
Loop of Henle
Distal tubule
Collecting duct
3
Passive reabsorption of lipid-soluble, un-ionized drug, which has been concentrated so that the intra-luminal concen-tration is greater than that in the perivascular space
Ionized, lipid-insoluble drug into urine
Filtrat (fluids) فيها أدوية وتركيبات صغيرة أيضا وميتش (ions) محتاجينها even glucose
125 ml/min = filtration حجم للشخص الطبيعي
بس الأكبر ميتش كله بطلع برا الجسم عشان فيه ممكن أيونات صعب الجسم reabsorption يعيدها ف صغير
وعشان الدواء يخترق الجدار لازم يكون not linked with protein + uncharged
واذا كان مرتبط لازم ينفصل عشان يقدر يطلع برا الجسم
Phase I and II by products

Biliary and Fecal Excretion

- Drugs are mainly conjugated with glucouronic acid or glutathion, or sulfate conjugates, then they are excreted via the biliary duct to the intestine.
- this conjugate maybe hydrolyzed through intestinal enzymes and is reabsorbed (thus prolonging drug effect or poison effect) this phenomenon is termed as Enterohepatic- recycling

Excretion by Other Routes

- Sweat عرق
- Saliva لعاب
- Tears دموع

❖ $CL_{total} = \mathbf{CL_{hepatic}} + \mathbf{CL_{renal}} + CL_{pulmonary} + CL_{other}$

the act of drug on the body

PHARMACODYNAMICS

- Pharmacodynamics deals with the study of the biochemical and physiological effects of drugs and their mechanisms of action.

- The effects of most drugs result from their interaction with macromolecular components of the organism .. **(Receptors)**

Drug Receptors

المستقبلات هم بروتينات

- The term *receptor* denotes the component of the organism with which the chemical agent is presumed to interact.
- Receptors are mainly protein, such as :
  - Receptors for endogenous ligands: hormones,
  - Enzymes
  - Pumps
- Also Nucleic acids also serve as receptors

Transmembrane : يعني المستقبل يمتد من أول الغشاء إلى آخره، طول cell membrane

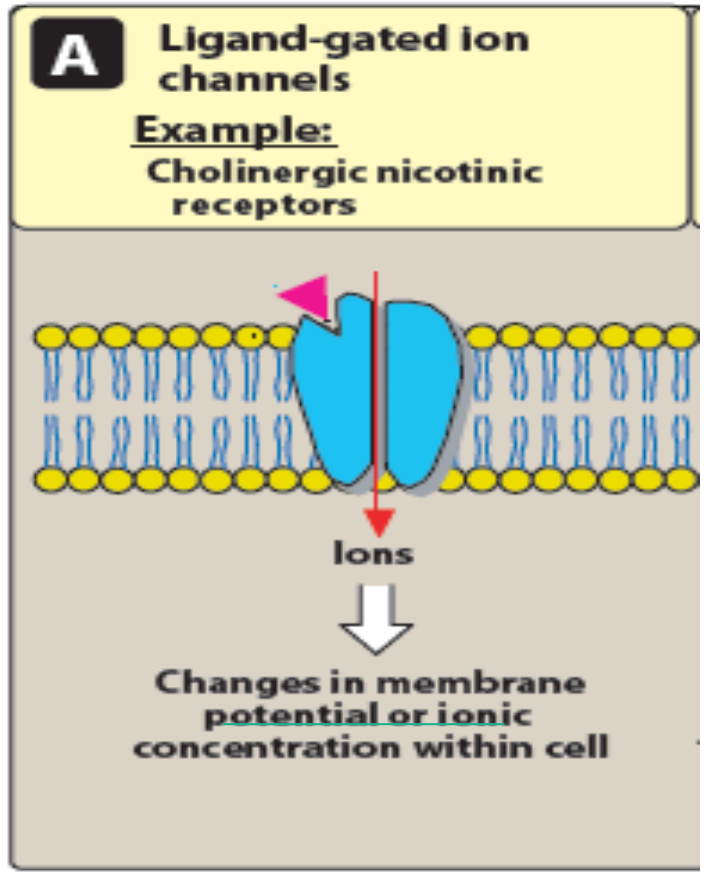
Receptor Families

Cell membrane

1. **Transmembrane ligand-gated ion channels** — chemical that produced by the body — تحكم الأيونات إلى خارج الخلية أو تدخلها داخلها
2. **Transmembrane G protein–coupled receptors**
3. **Enzyme-linked receptors**
4. **Intracellular receptors** = داخل الخلية

1. Transmembrane ligand-gated ion channels

- Regulation of the flow of ions across cell membranes
- Ultra rapid response *(m.seconds)*
- Neurotransmission
- Cardiac conduction
- Muscle contraction



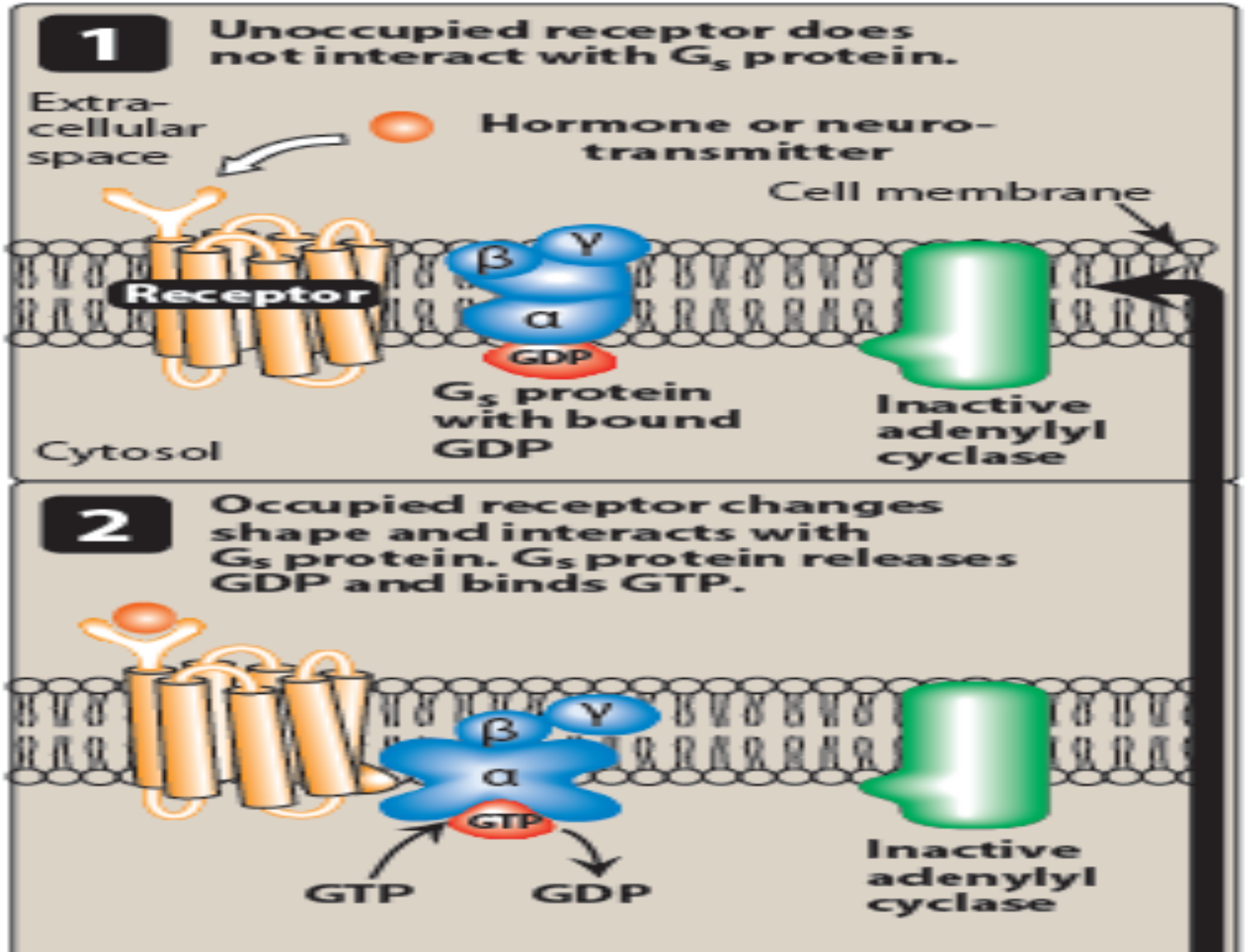
2. Transmembrane G protein–coupled receptors

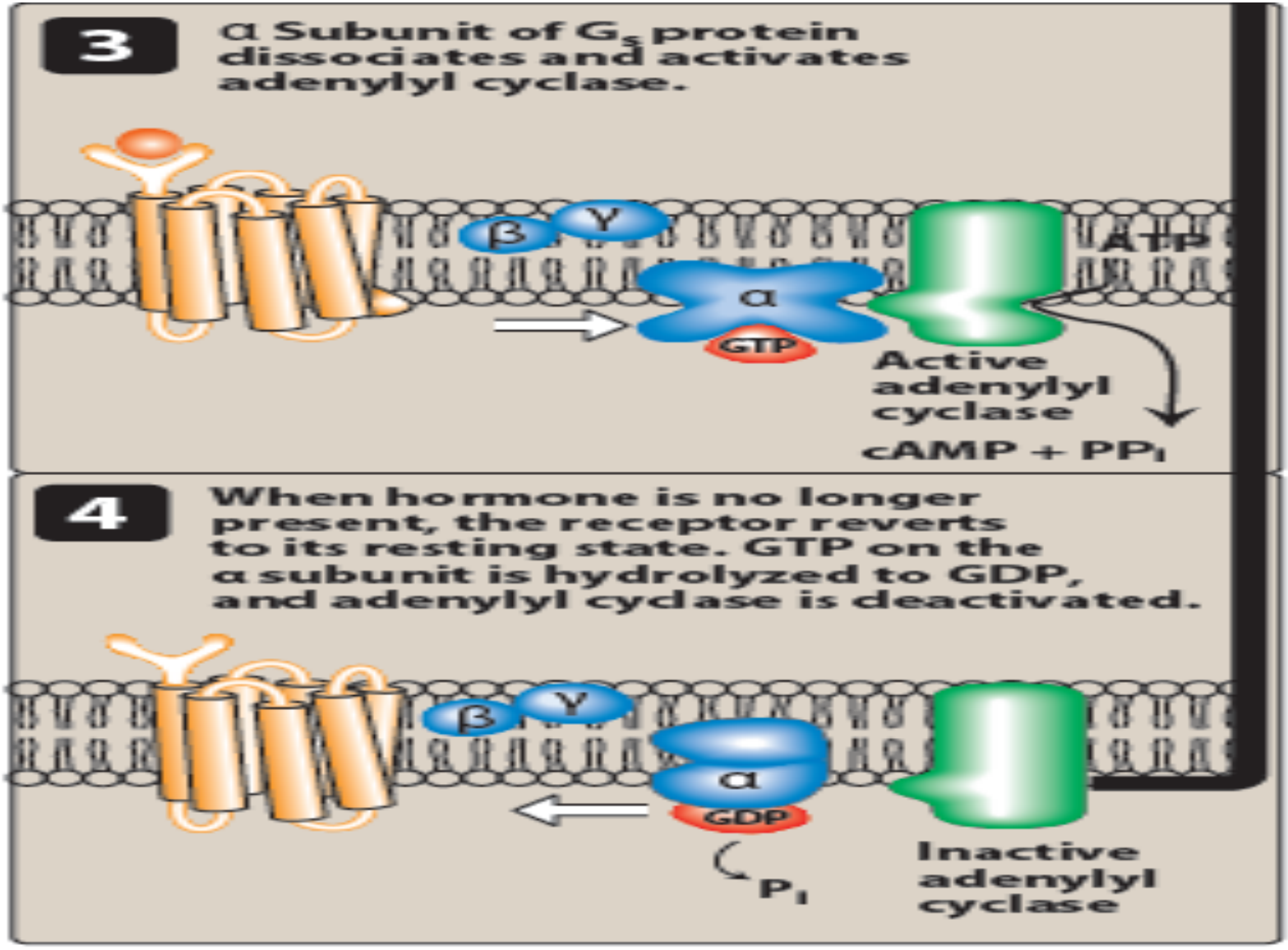
- The extracellular domain of this receptor usually contains the ligand-binding area
- Intracellularly, these receptors are linked to a G protein which consist of Alpha,Beta & Gamma subunits
- Upon activation, G-protein disscociates to activate Secondary messenger
- Responses occurs within seconds to minutes

- **Second messengers:**

  These are essential in conducting and amplifying signals coming from G protein–coupled receptors.

Example : cAMP, leads to protein phosphorylation, and downstream gene induction

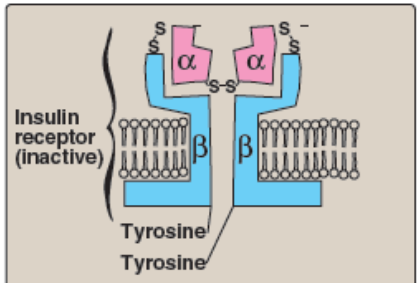

1
Unoccupied receptor does not interact with G_s protein.
Extra-cellular space
Hormone or neuro-transmitter
Cell membrane
Receptor
β
γ
α
GDP
G_s protein with bound GDP
Inactive adenylyl cyclase
Cytosol
2
Occupied receptor changes shape and interacts with G_s protein. G_s protein releases GDP and binds GTP.
β
γ
α
GTP
GTP
GDP
Inactive adenylyl cyclase

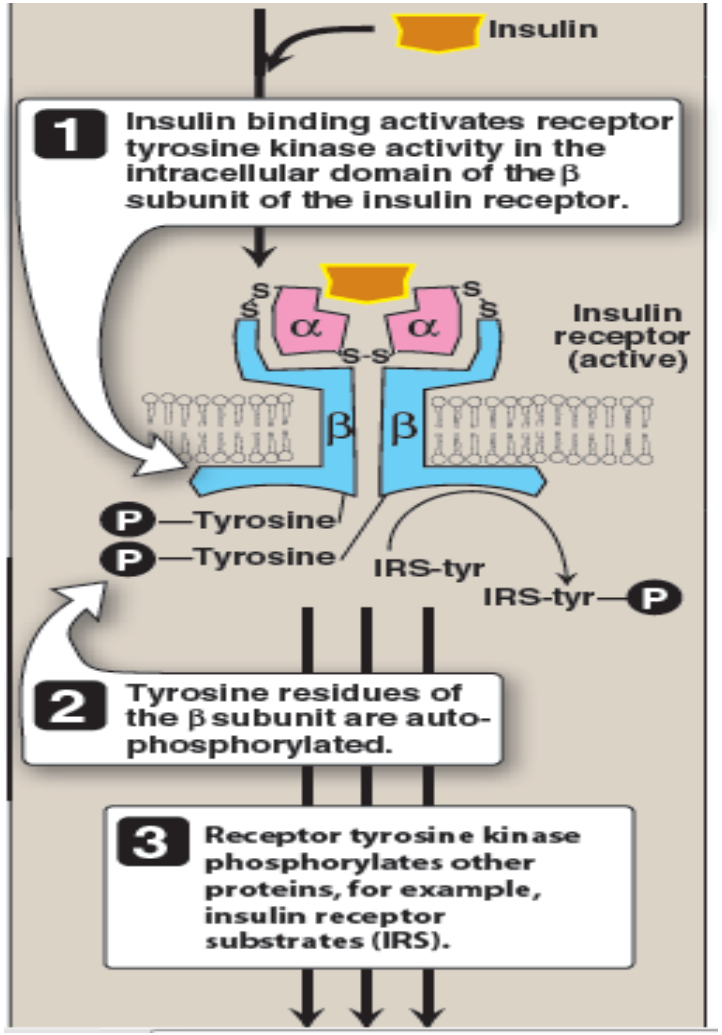

3
α Subunit of G_s protein dissociates and activates adenylyl cyclase.
β
γ
α
GTP
ATP
Active adenylyl cyclase
cAMP + PP_i
4
When hormone is no longer present, the receptor reverts to its resting state. GTP on the α subunit is hydrolyzed to GDP, and adenylyl cyclase is deactivated.
β
γ
α
GDP
P_i
Inactive adenylyl cyclase

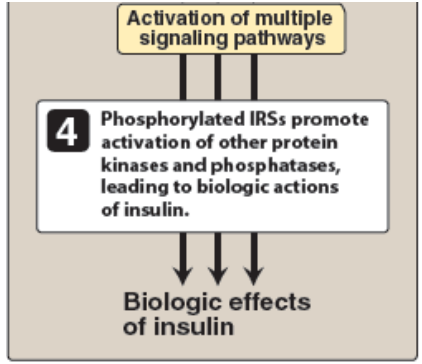
minutes to hours

3. Enzyme-linked receptors

- Multisubunit complexes linked to intracellular cytosolic enzymes
  (tyrosine kinase activity as part of their structure)
- Response occurs in minutes to hours
- Metabolism
- Growth
- Differentiation


Insulin receptor (inactive)
α
α
β
β
Tyrosine
Tyrosine


Insulin
1
Insulin binding activates receptor tyrosine kinase activity in the intracellular domain of the β subunit of the insulin receptor.
Insulin receptor (active)
α
α
β
β
P—Tyrosine
P—Tyrosine
IRS-tyr
IRS-tyr—P
2
Tyrosine residues of the β subunit are auto-phosphorylated.
3
Receptor tyrosine kinase phosphorylates other proteins, for example, insulin receptor substrates (IRS).


Activation of multiple signaling pathways
4
Phosphorylated IRSs promote activation of other protein kinases and phosphatases, leading to biologic actions of insulin.
Biologic effects of insulin

- اللهم اغفر لي ولوالدتي وللمسلمين والمسلمات الأحياء والأموات
- اللهم إنّا نسألك الجنة ونعوذ بك من النار وما قرب إليها من قول أو عمل
- اللهم انصر الإسلام والمسلمين، وزلزل الأرض تحت أعداء الإسلام وأعوانهم وأخوانهم وأعوانهم
- اللهم اجمعنا وأهلنا والمسلمين عند حوض رسولك الكريم صلى الله عليه وسلم
- اللهم ارحم أبي واغفر له وأدخله الجنة بغير حساب ولا عذاب واجمعه وأهله في الفردوس الأعلى آمين
- ربِّ إني لما أنزلت إليّ من خيرٍ فقير
- اللهم أدخلنا مدخل صدق، وأخرجنا مخرج صدق، واجعل من لدنك سلطانًا نصيرًا
- سبحان الله، والحمد لله، لا إله إلا الله، الله أكبر، اللهم ارزقني وارحمني واغفر لي واهدني بنور الدنيا والآخرة

آمين ♡