تفريغ فارما ١

اسم الموضوع: Metabolism of drugs

إعداد الصيدلاني/ـة: Bayan Al-Harahshah

"اللهم إنّي أسألك زيادةً في العلم والدين، وسهولةً في الفهم والحفظ، وبركةً في العمر والرزق"🙌🏻

Soul Academy

لجان الدُفعات

METABOLISM OF DRUGS

- 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)

اهم مكان بصير فيه الmetabolismفي الجسم

بنسميها الminor reactions

الGeneral conceptلوظيفة metabolism

بالجسم انه يحول الlipophilic drugs

لHydrophilic drug يعني بكون more polar&watersoluble وبرضو بحول الactive products الى inactive product والجسم بعمل

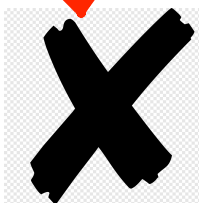
هذا الكلام مشان يصير الelimination اسرع

شو المقصود بهذا الحكي ؟

هذا الدواء شو مواصفاته؟

Active

Lipophilic



1. المقصود انه انا عندي دواء X هذا الدواء دخل على جسم الانسان واعطى الeffect هسا الجسم بده يحاول تخلص منه

2. هسا بمر عنا هذا الدواء بphase 1reactions ممكن يكون عندي 3عمليات oxidation.1 Reduction 3. Hydrolysis.2حسب تركيبة الدواء نفسه

فرضا صرله oxidation صار عندي الدواء oxidiesX

ميزته انه more polar ويكون hyedrophilicوممكن يكون inactive

Phase 1

Oxidies X

Phase2

OxidiesX+gluco urinic acid

ال metabolite الي طلع اذا كان polar وhydrophilic بشكل كافي انه يطلع برا الجسم خلص بنوقف هون

Kidney

Elimination with urine

لكن اذا كانت هاي العملية غير كافيه انه الدواء يطلع من الجسم نمر بالمرحلة الثانية وهي phase 2او 3. الcongocation وهي عملية ربط الmetabolite بpolar groups وهاي المجموعه ممكن تكون glouco urinic acid

Amino acid

Glutathione

وميزه هاي الجروبات انه حجمها كبير وpolarوwatrsolubile

هسا رح يصير عندي oxidies X+gluco urinic acid وبكون الدواء او metabolite حجمه صغير مربوط مع جروب اكبر

4. زي الحجرالي مربوط ببالون فبصير التأثير كله للgluco urinic acid فبصير يمشي مع الدم وساحب الدواء معه وبوصل للkidney وبطلع مع الurine فهاي العملية هيا الconjugation

ال liver فيه مجموعة من
ال enzymes هيا المسؤولة
عن عمليات ال metabolism
اسمهم ال cytochrome
P450

Phase I

- Catalyzed by the cytochrome P450 system

هي عبارة عن Family of enzymes

- 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

هاي ال 3minor reactions

- Oxidation/Reduction/Hydrolysis

أمثلة على
cytochromال
eP450

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

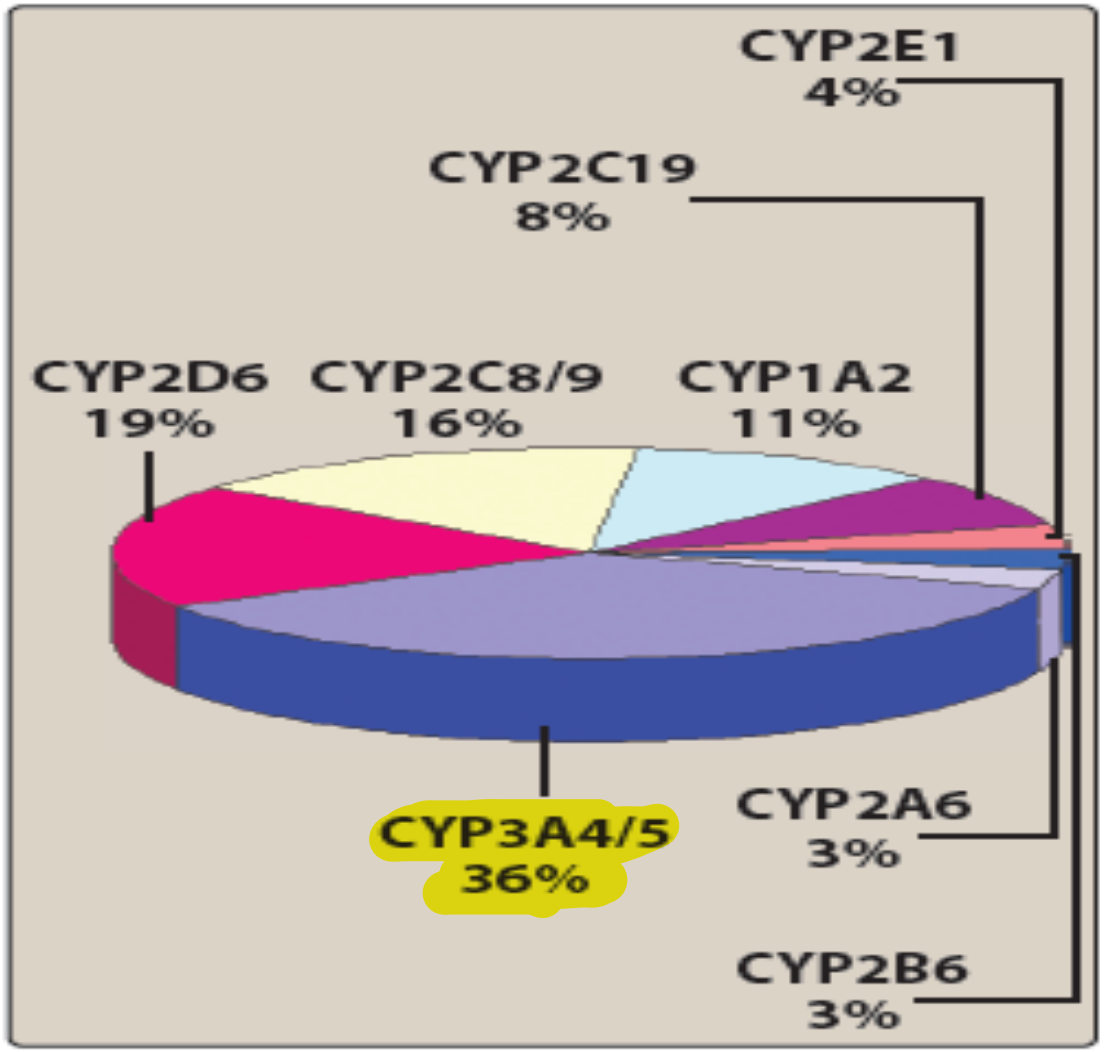


Figure 1.18
Relative contribution of cytochrome P450 (CYP) isoforms to drug bio-transformatin.

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, هذا الدواء بصيرله metabolisem عن طريق انزيم الCYPD6

also lack of CYP2D6 and lack of codeine effect!!

اذا في شخص مثلاًّ من الولادة عنده Genetic variation يعني اختلاف جيني او عندة Genetic mutation طفرة جينية بكون ما عنده او عنده نقص في الانزيم الي بعمل metabolisem للدواء معناته لما يوخذ الدواء هذا الجسم ما رح يقدر يتخلص من الدواء

****هسا النقطة الثانية انه برضو في اشخاص ممكن بكون عندهم زيادة في انزيم معين يعني الدواء بصيرلة metabolisem بسرعة فبصير الelemenation اله اسرع فما بنوخذ الeffect المطلوب منه

CYP450 Inducers بتزيد الMetabolisem

- 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 لازم نغير بالجرعة حتى تصير مناسبة وتعطي تأثير

هسا الي بأثر على الMetabolisem للDrug إما:

انه اختلافات بالجين فكميات الإنزيمGenetic variation

الي الجسم بنتجها ممكن تكون اكثر او اقل من لطبيعي

اوممكن يكون عنا Drug drug interaction

او Drug Food interaction

Examples of Inducers

هسا الدكتور حكى مثال:
انه لنفرض مريض بوخذ الwarfarin بشكل يومي وبنفس الوقت استخدم الRifampin او phenobarbital يعني صار يستخدمهم مع بعض الphenobarbital احنا بنسميه Inducer يعني بزيد الmetabolisem لل warfarin يعني رح يقل تأثير الwarfarin فبصير المريض ما بستفيد منه.

Isozyme: CYP2C9/10

هذا انزيم مسؤول عن الmetabolisem ل

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

هو عبارة عن immuno sub reagent يعني فرضًا لما بدنا نعمل عملية زراعة كلى الجسم بصير يقاومها لانه بفرضها جسم غريب فممكن يقتلها فبنعطيهم هذا الدواء مشان يقلل من مهاجمة الجسم الها وبحافظ عليها وبهاي الحالة المريض ما بصير يوخذ اي دواء من الInducer لانه رح يلغي فعالية الCyclosporine

CYP450 Inhibitors بتقلل الMetabolisem

تثبيط

- Inhibition occurs mainly through competition such as Omeprazole and Ketoconazole, Erythromycin, Ritonavir

واحد من ادوية المعدة

هذا رح يقلل الmetabolisem للOmeprazoleيعني رح يزيد الeffect للomeprazole

- 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

الgrapefruit
juiceهو inhibetor
للأدوية فبالتالي رح
يزيد من فعالية الدواء
بشكل كبير وممكن انه
يصير toxicity

- Serious Interaction with low therapeutic index medications such as : warfarin

هو انه الدواء بعطينا
effect وما بعطينا
toxic

هو دواء اله narrow therapeutic index وهو دواءالpharmacokinetic اله
صعب اصلًا ولازم اكون كثير دقيقة بإعطاءه

Minor Rxns

- **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)*.

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 i**nactive** and are excreted rapidly in the urine and feces.

هسا الMetabolismليش بصير ؟

1.حتى احول الدواء الinactive ل active

2.واحوله من lipophilic لHydrophilic

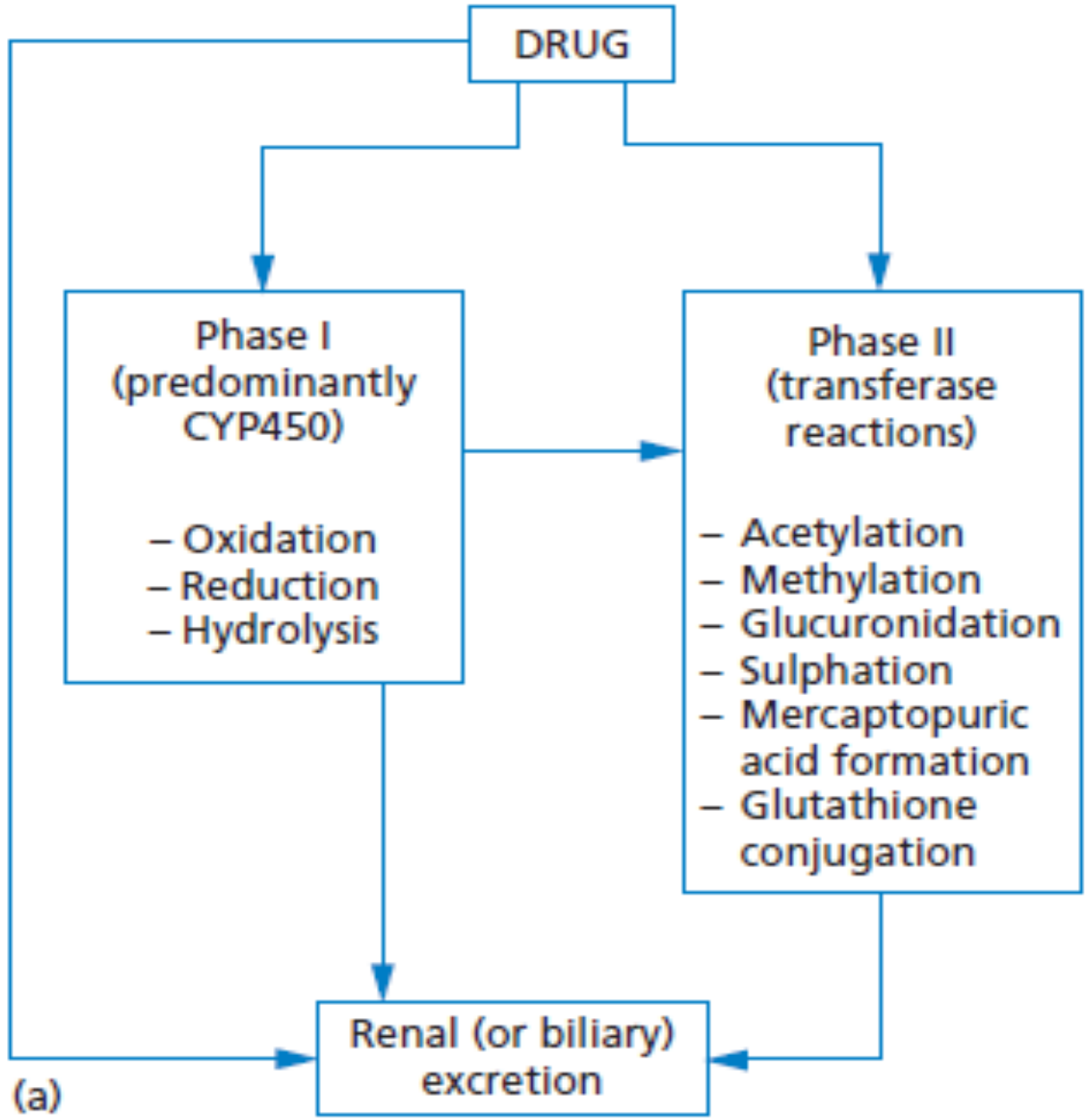
مشان جسمي يقدر يتخلص منه

هسا في عنا exceptionsوهاي الاستثناءات ممكن تكون اشي كويس او الهاdisadvantages

الي الها سلبيات انه مرات الجسم بحولي بعض الادوية بعدالmetabolisem من more لactive يعني زي الmorphineبعد الmetabolisem بتحول لمادة اسمها morphine 6loco urinine حتى بعد الconjocation وهاي المادة هيا more active than morphine يعني تأثيرة بالجسم بكون زاد وبيستمر لفترة طويلة------فهاي الشغلة بكون حلها انه بدل ما اعطي 10mlمن الmorphine بعطي 5ml والباقي بتعوض بالmetabolisem

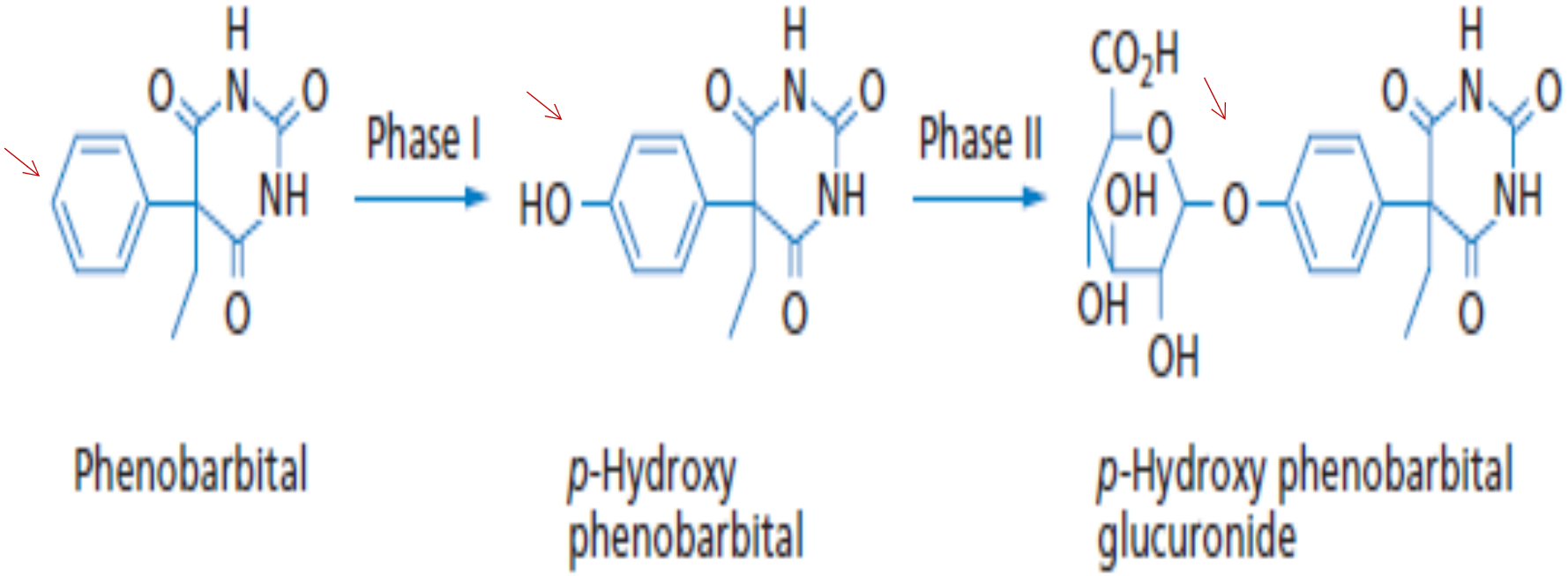
الشغلة الثانية انه من فترة طويلة شركات الادوية بستخدموا طريقة تصنيع لبعض الادوية على شكل Prodrug

هوا بالعادة بكون inactive بس لما يدخل عالجسم بروح عالfirst pass effectبالكبد فبصيرله metabolisimnفبتحول منinactive الى active فعال وهاي الحركة مشان ازيدمرور


DRUG
Phase I
(predominantly
CYP450)
– Oxidation
– Reduction
– Hydrolysis
Phase II
(transferase
reactions)
– Acetylation
– Methylation
– Glucuronidation
– Sulphation
– Mercaptopuric
acid formation
– Glutathione
conjugation
Renal (or biliary)
excretion

(a)

Example


Phase I
Phase II
Phenobarbital
p-Hydroxy phenobarbital
p-Hydroxy phenobarbital glucuronide

Excretion of Drugs

- Generally, drugs are excreted either:

➢ Unchanged (hydrophilic drugs) ما بتغير وما بصيرله metaboliseme لانه اصلا بذوب بالماء بشكل كبير

➢ Changed (metabolites) Lipophilic drugs هي الي بصيرلها metaboliesm

مثال زي ال(vitamin C)

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

Excretatory Organs:

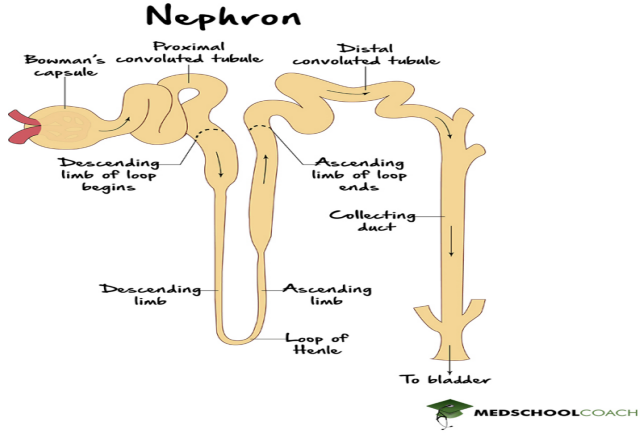
- Kidney
- Intestine
- Lungs (mucus)
- Breast Milk

وممكن يخرج عن طريق الsalivaوsweat

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

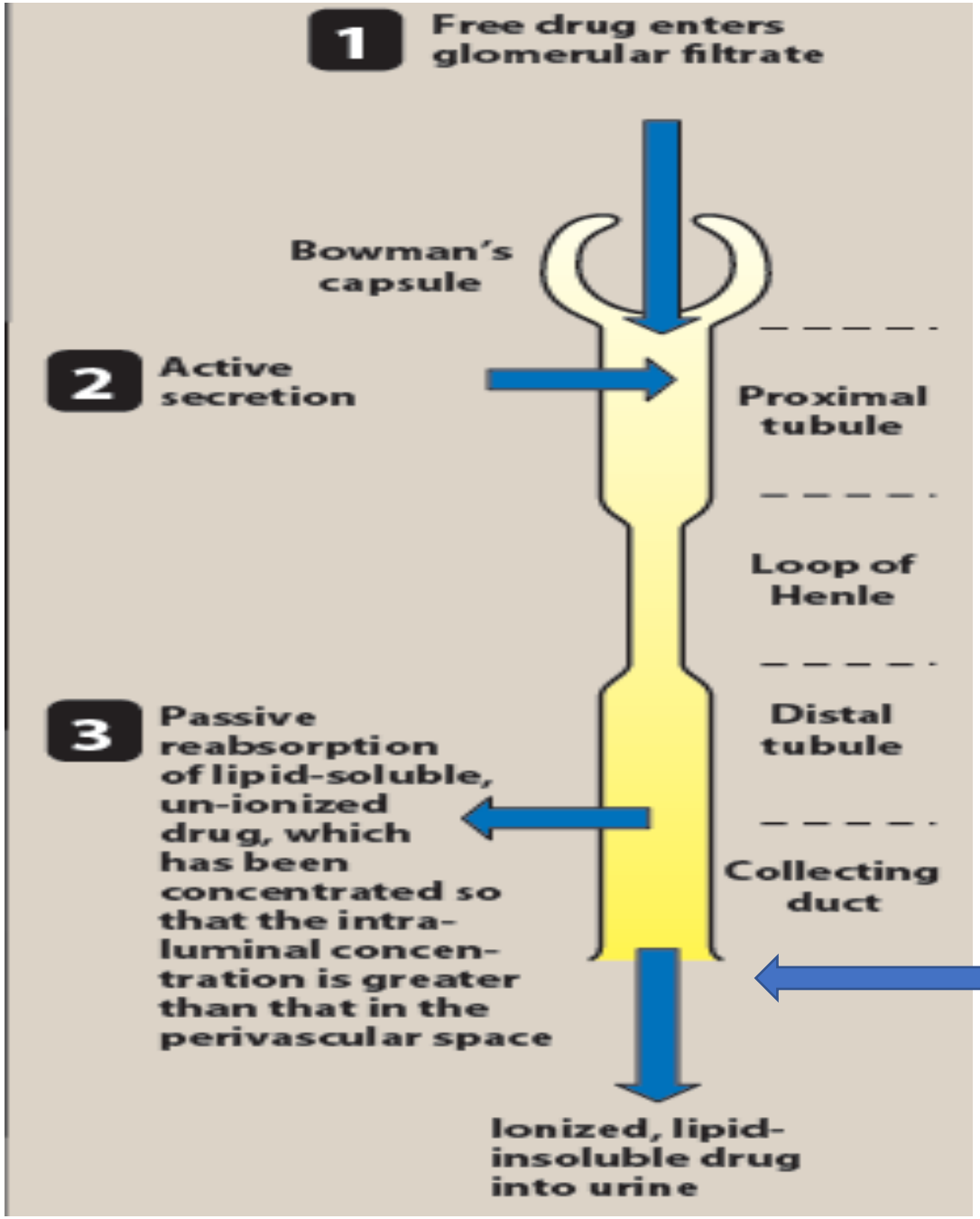
- Unfiltered drugs will pass through the efferent arteriole
- Drugs undergo selective secretion via carriers

- 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.”



بهمني انه لما الدواء يصل لعملية الfiltration اه يكون الدواء Ionized حتى يصيرله exicretion اما اذا كان unionixed فرح تزيد فرصة انه يصيرله reabsorption ومارح اقدر اتخلص منه.

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

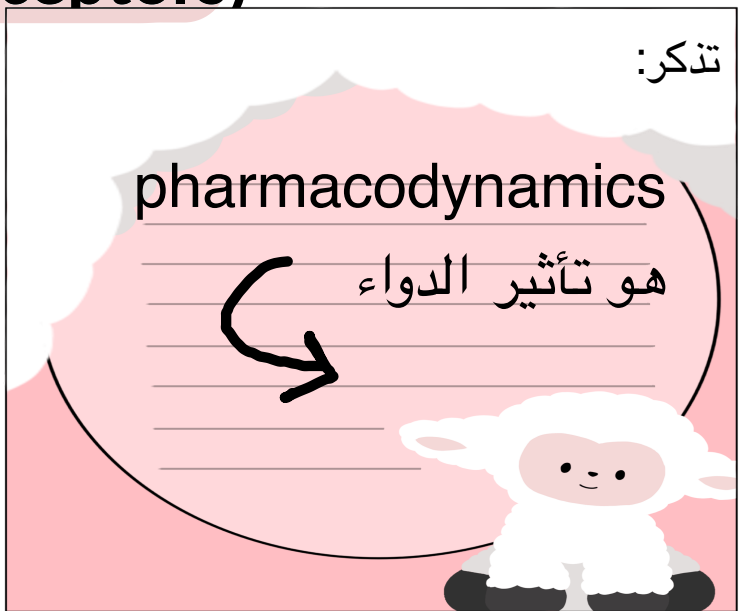
- Sweat
- Saliva
- Tears

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

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

هو ممكن يكون بروتين عالأغلب وبيستقبل اشي ممكن يكون endogenous انزيم او هرمون .

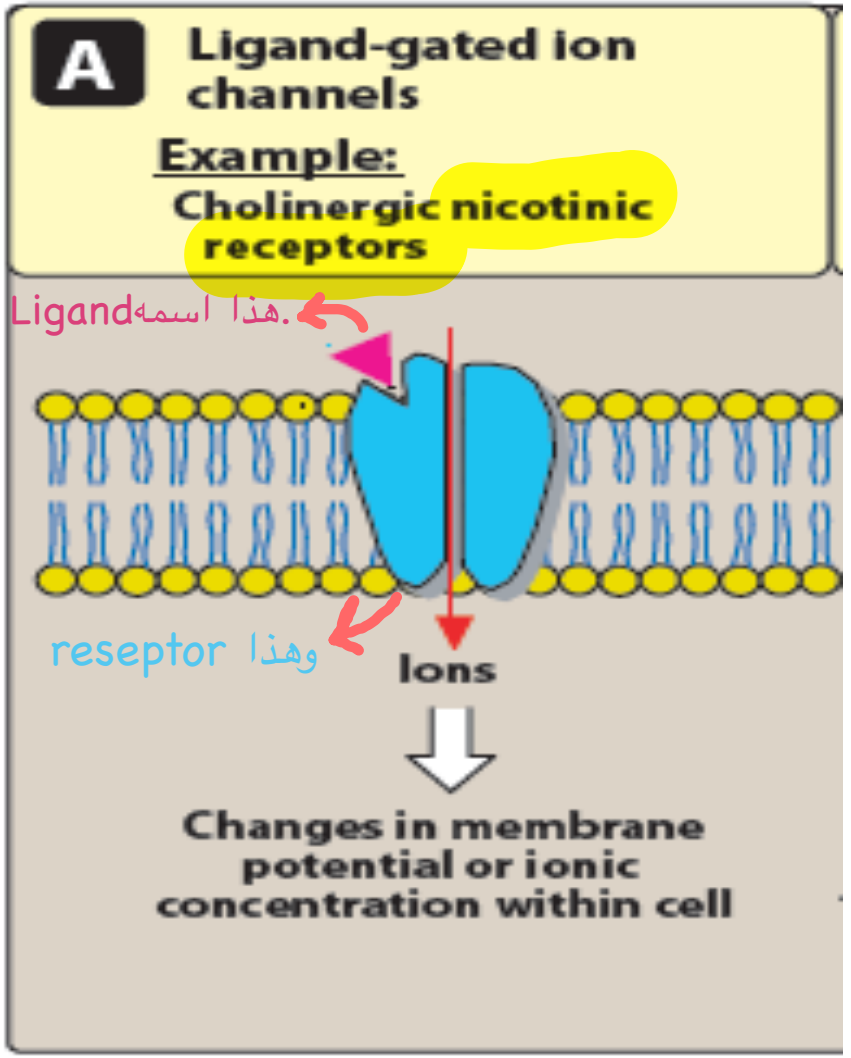
- The term *receptor* denotes the component of the organism with which the chemical agent is presumed to interact.
- Receptors are mainly protein, such as :
  - Receptors for endogenous ligands: hormones,
  - Enzymes
  - Pumps
- Also Nucleic acids also serve as receptors

Receptor Families

1. **Transmembrane ligand-gated ion channels** زي البوتاسيم & صوديوم channels
2. **Transmembrane G protein–coupled receptors**
3. **Enzyme-linked receptors**
4. **Intracellular receptors**

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



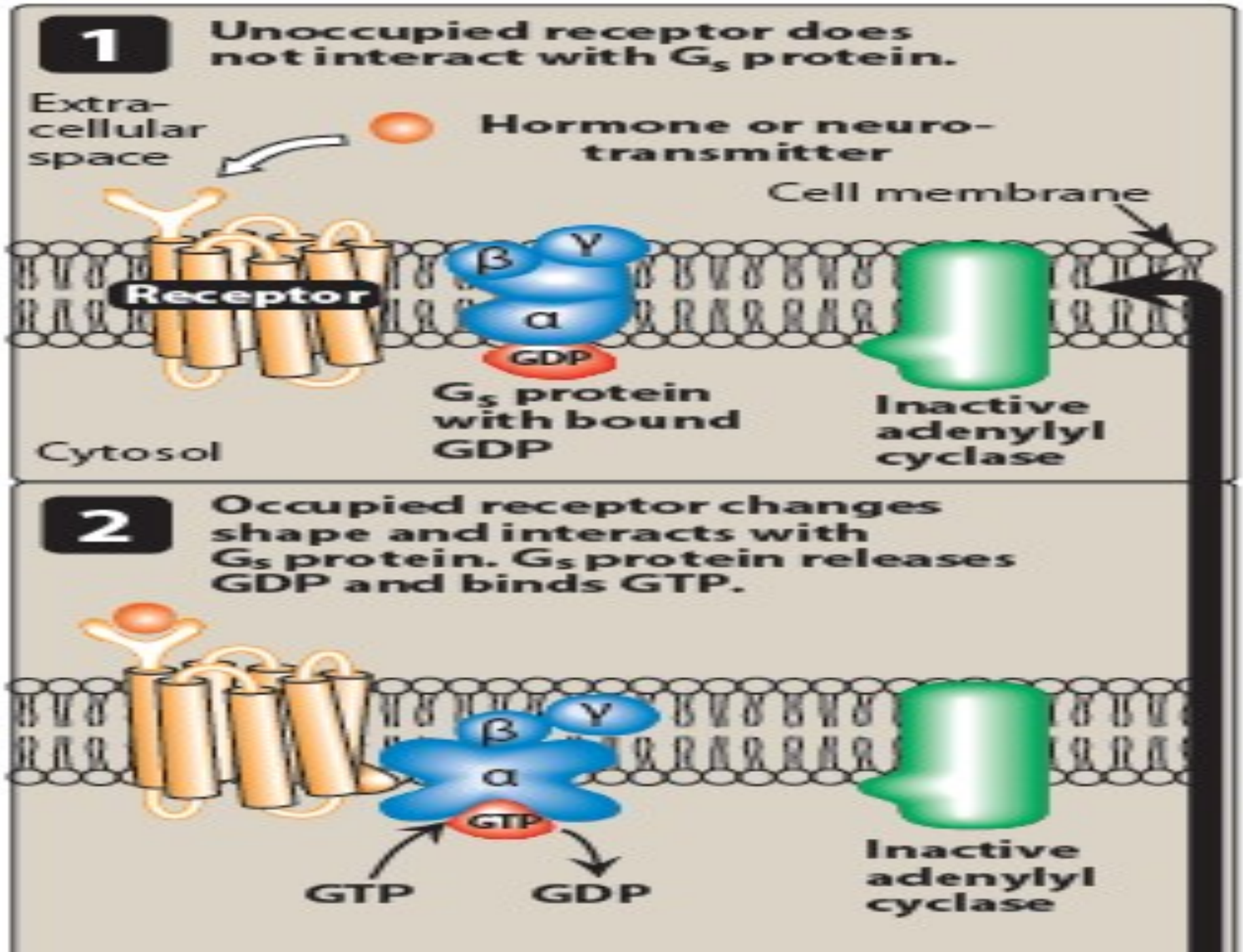
2. Transmembrane G protein–coupled receptors

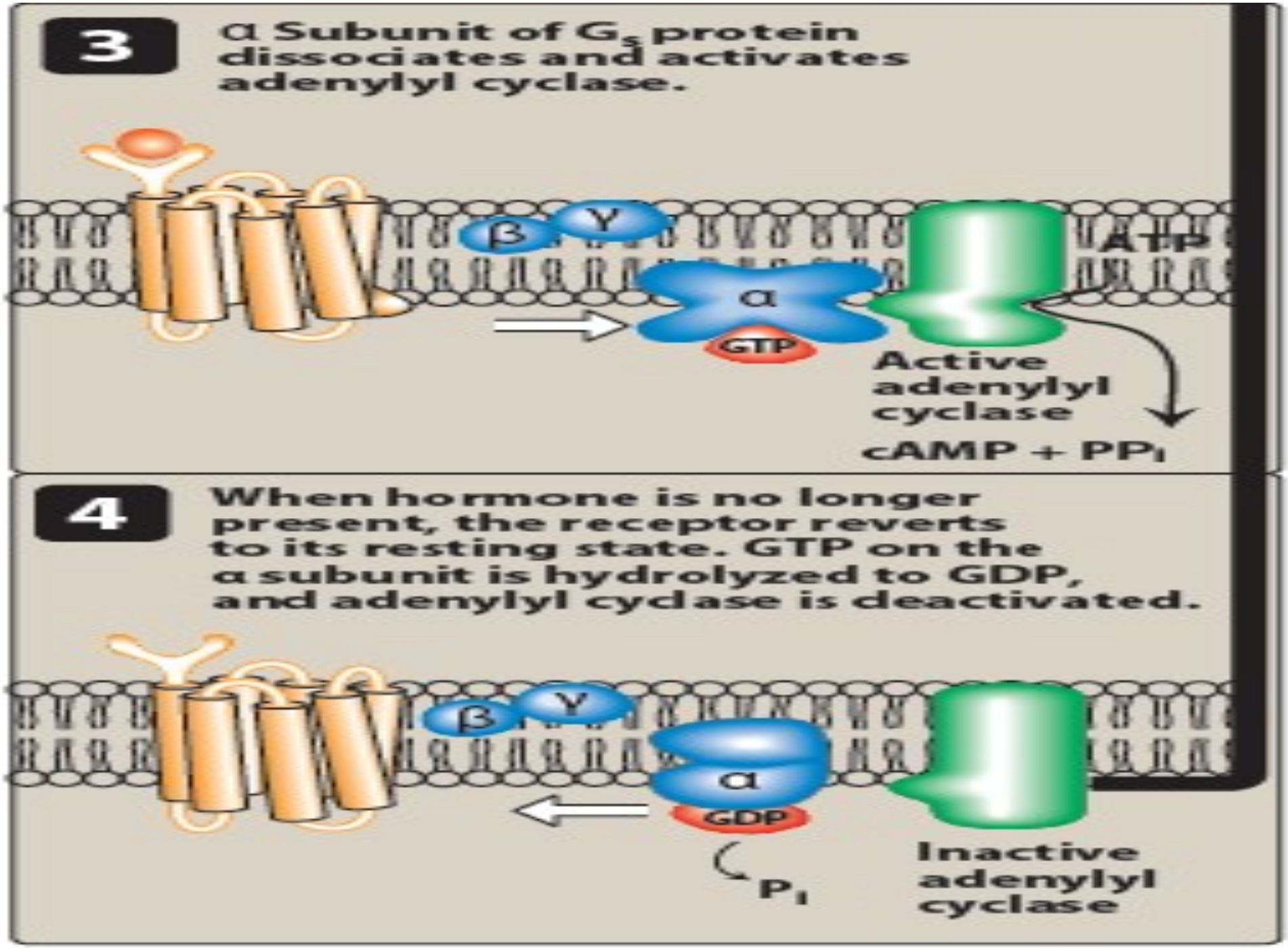
- The extracellular domain of this receptor usually contains the ligand-binding area
- Intracellularly, these receptors are linked to a G protein which consist of Alpha,Beta & Gamma subunits
- Upon activation, G-protein disscociates to activate Secondary messenger
- Responses occurs within seconds to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

- **Second messengers:**

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

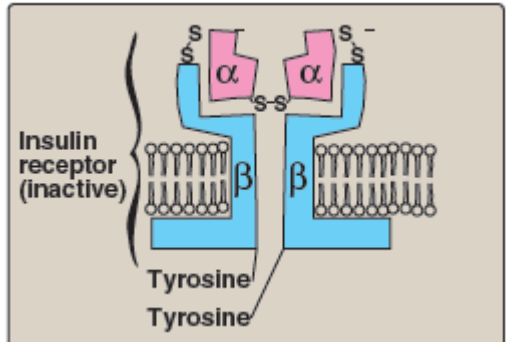
Example : cAMP, leads to protein phosphorylation, and downstream gene induction

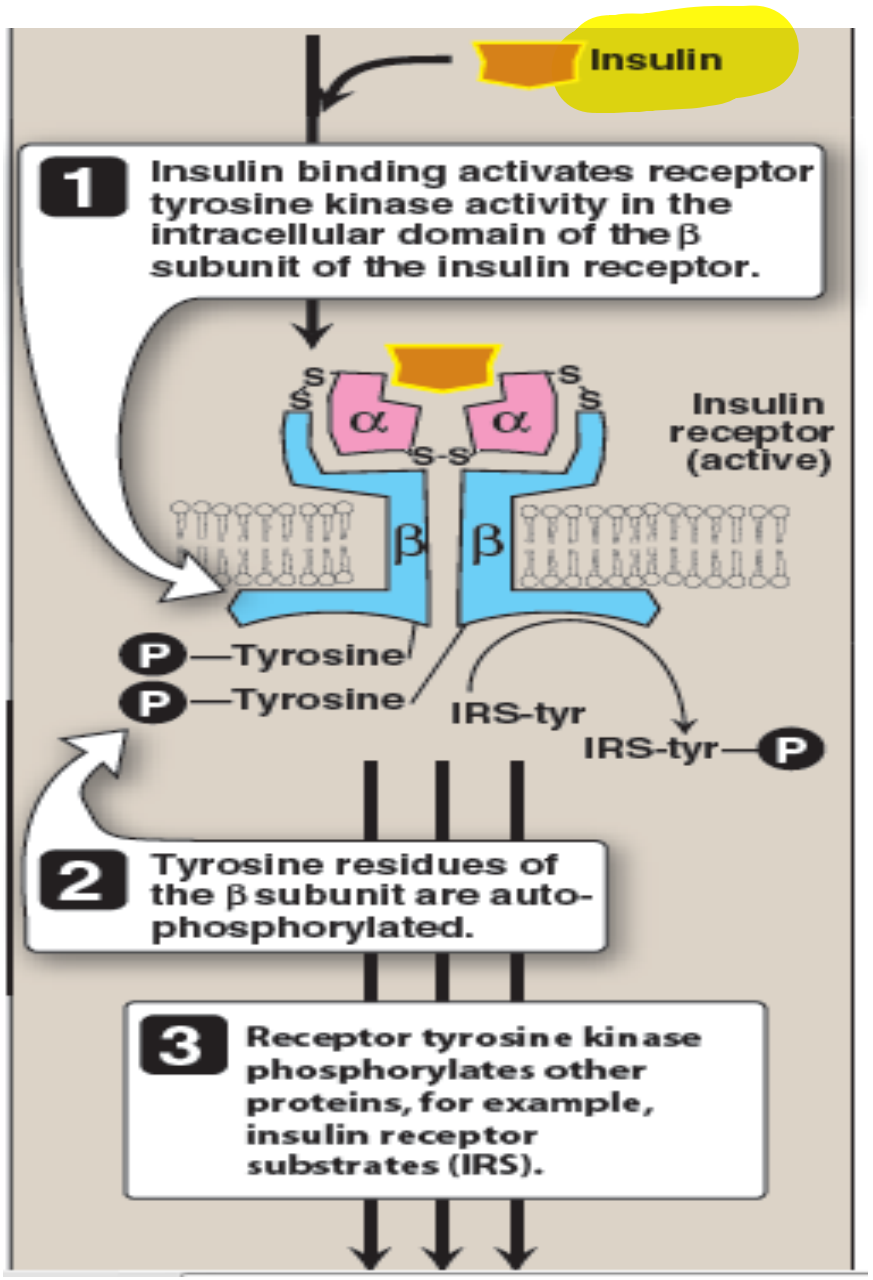

1
Unoccupied receptor does not interact with G_s protein.
Extra-cellular space
Hormone or neuro-transmitter
Cell membrane
Receptor
β
γ
α
GDP
G_s protein with bound GDP
Inactive adenylyl cyclase
Cytosol
2
Occupied receptor changes shape and interacts with G_s protein. G_s protein releases GDP and binds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

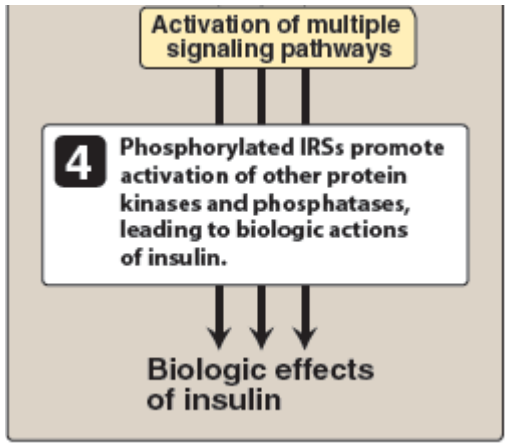

3
α Subunit of G_s protein dissociates and activates adenylyl cyclase.
β
γ
α
GTP
ATP
Active adenylyl cyclase
cAMP + PP_i
4
When hormone is no longer present, the receptor reverts to its resting state. GTP on the α subunit is hydrolyzed to GDP, and adenylyl cyclase is deactivated.
β
γ
α
GDP
P_i
Inactive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

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