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)

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

- Oxidation/Reduction/Hydrolysis

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

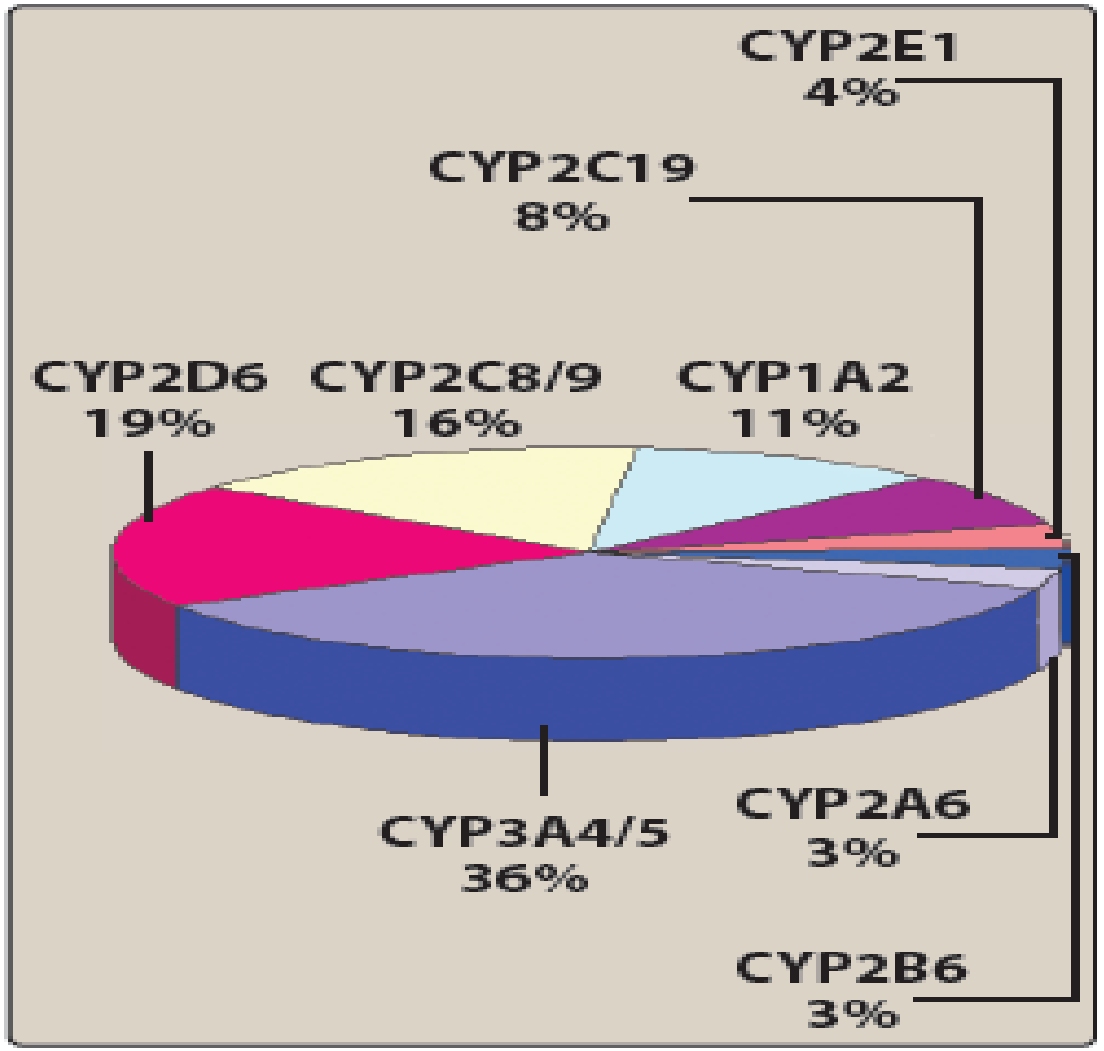


Figure 1.18
Relative contribution of cytochrome P450 (CYP) isoforms to drug bio-transformatin.

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,

also lack of CYP2D6 and lack of codeine effect!!

CYP450 Inducers

- 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

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

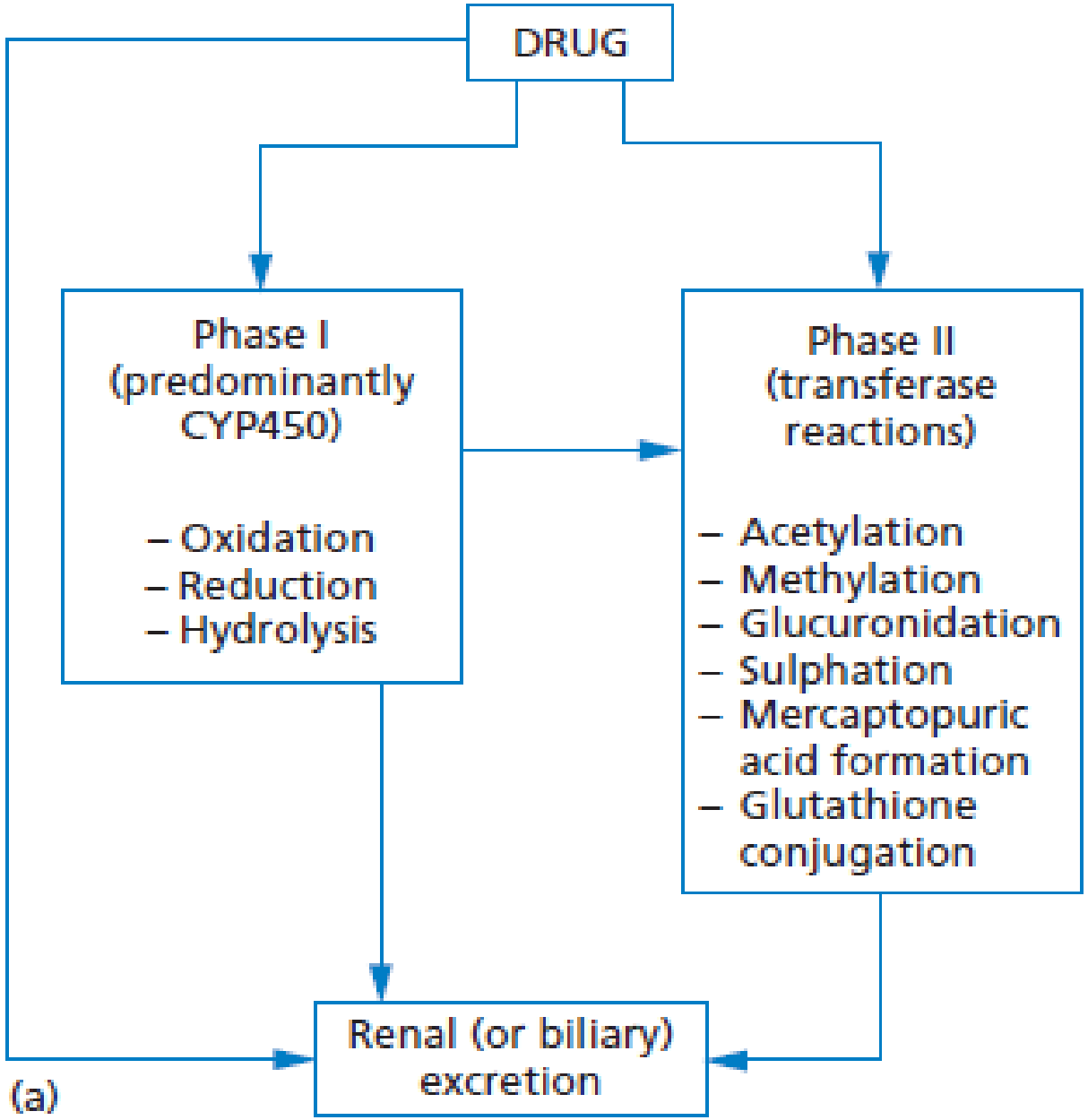
  amine oxidation (for example, oxidation of catecholamines or histamine), alcohol dehydrogenation (for example, ethanol oxidation), esterases (for example, metabolism of *pravastatin in* liver), and hydrolysis (for example, of *procaine).*

Phase II (conjugation):

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

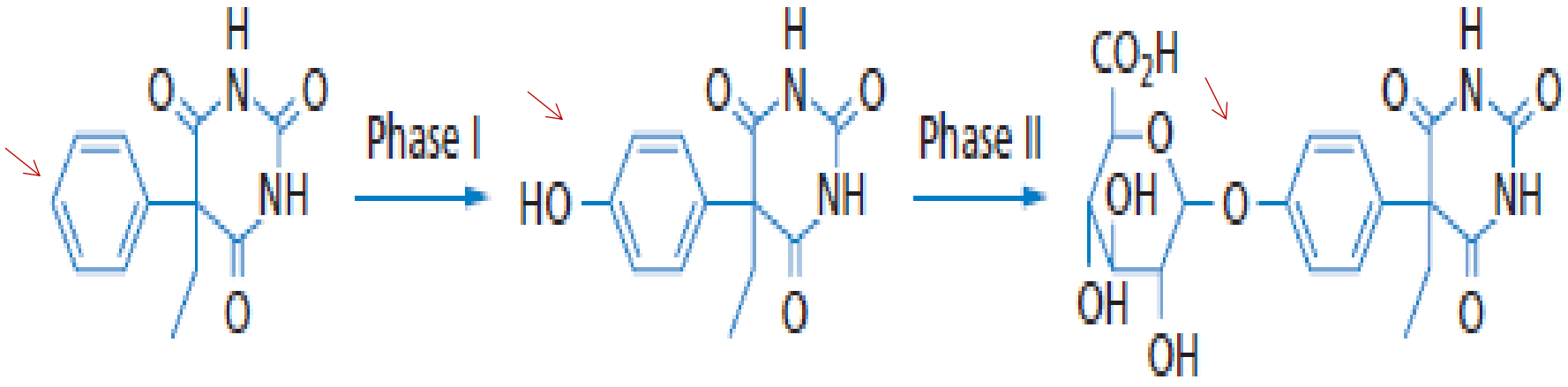
  - Glucuronic acid
  - Sulfate
  - Glutathione
  - Amino acids
  - Acetate

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


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)

➢ Changed (metabolites)

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

Excretatory Organs:

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

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

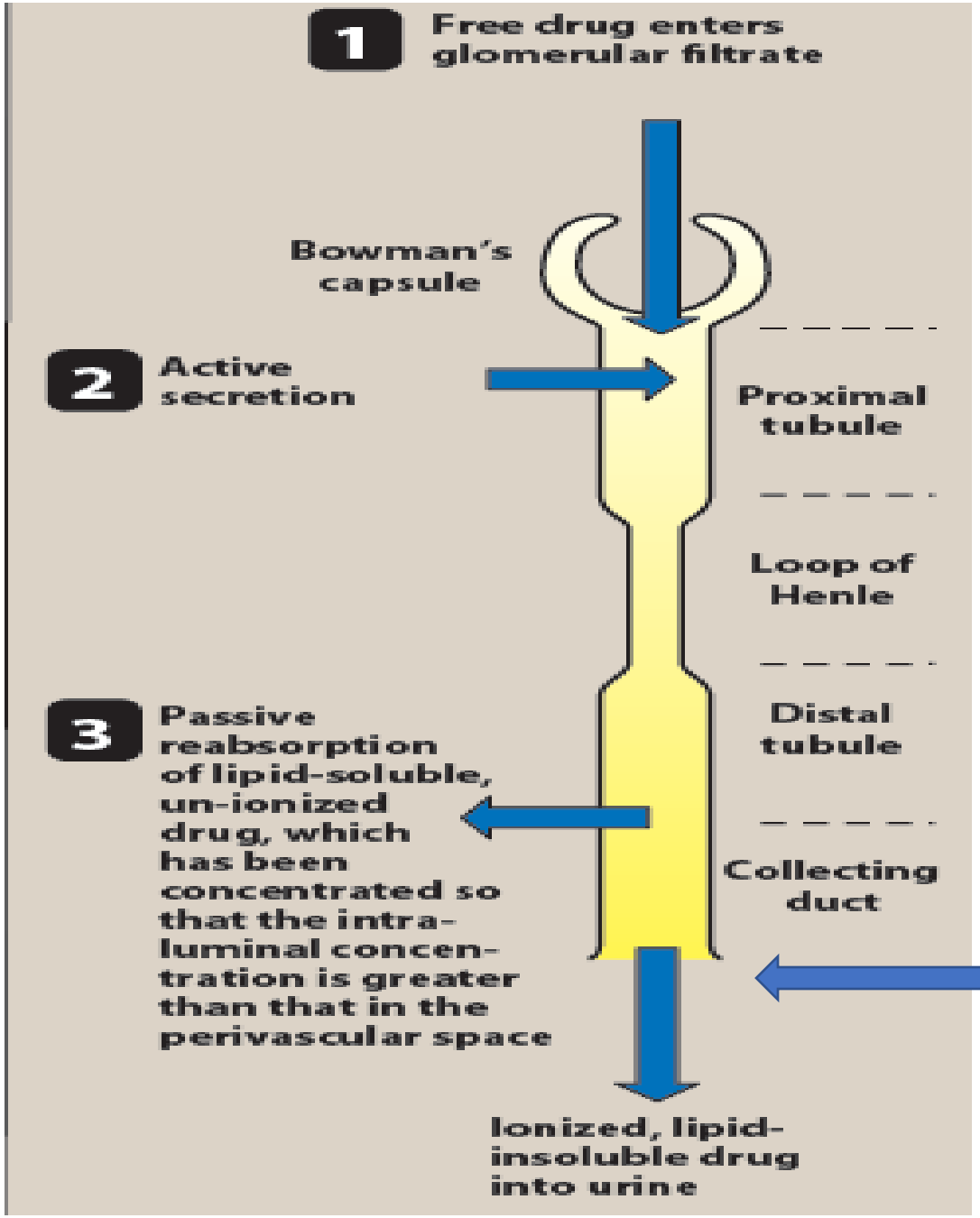
- Unfiltered drugs will pass through the efferent arteriole
- Drugs undergo selective secretion via carriers

- 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.”



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

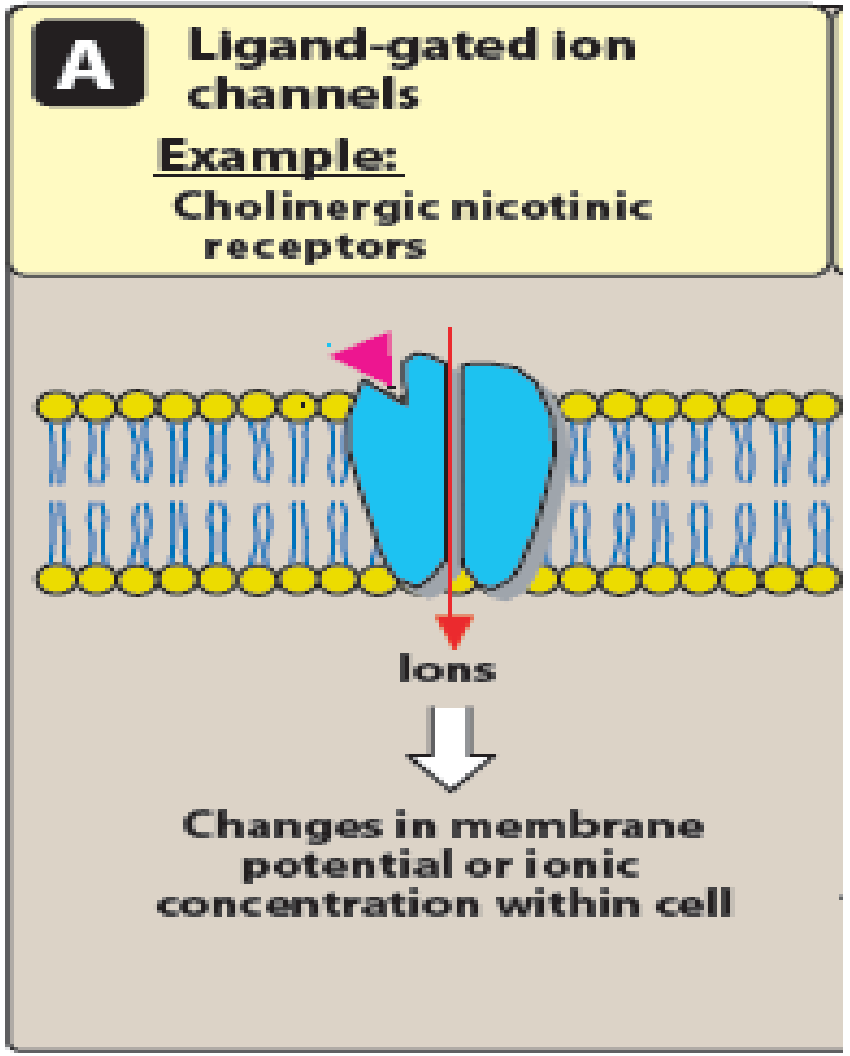
- The term *receptor* denotes the component of the organism with which the chemical agent is presumed to interact.
- Receptors are mainly protein, such as :
  - Receptors for endogenous ligands: hormones,
  - Enzymes
  - Pumps
- ❖ Also Nucleic acids also serve as receptors

Receptor Families

1. **Transmembrane ligand-gated ion channels**
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



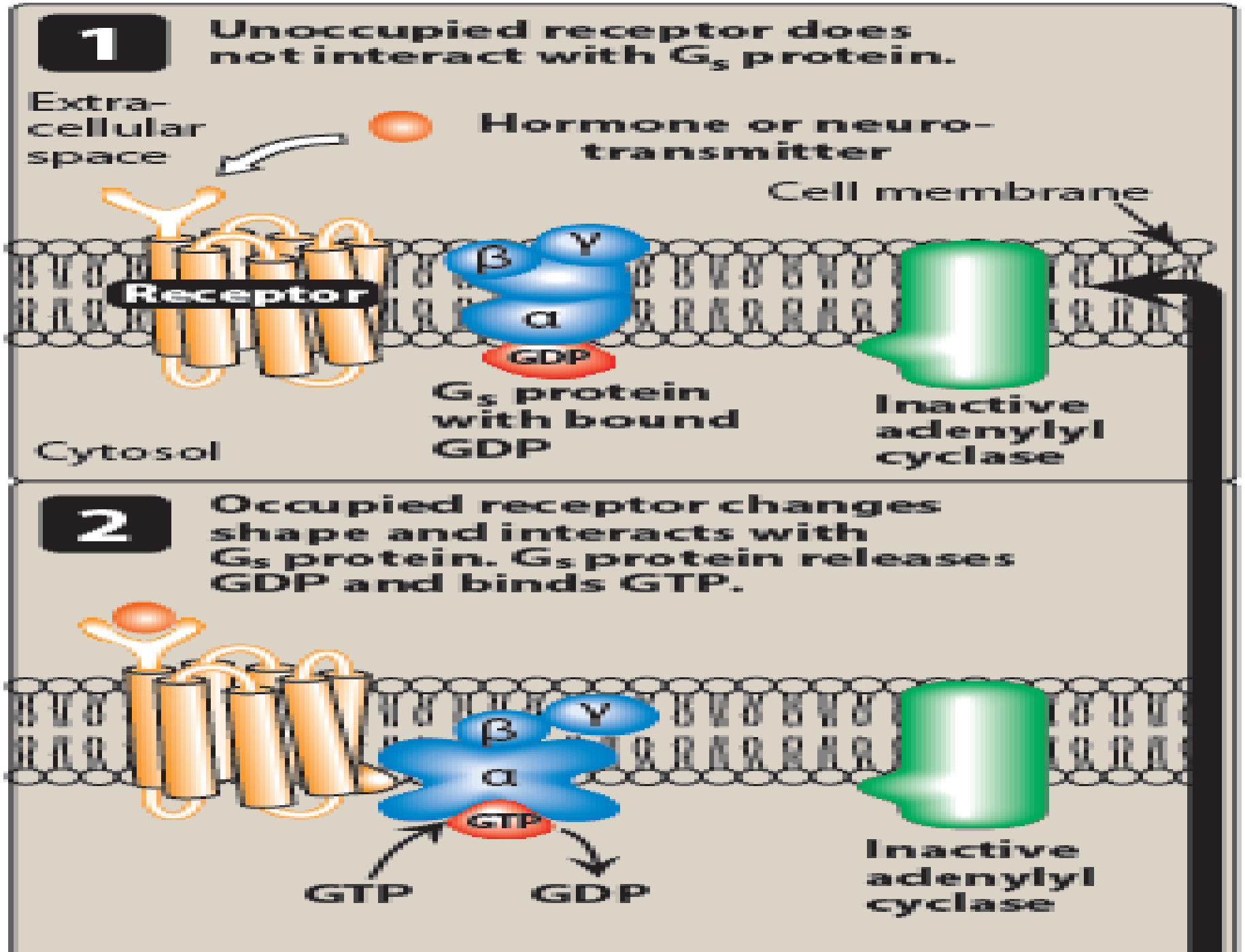
2. Transmembrane G protein–coupled receptors

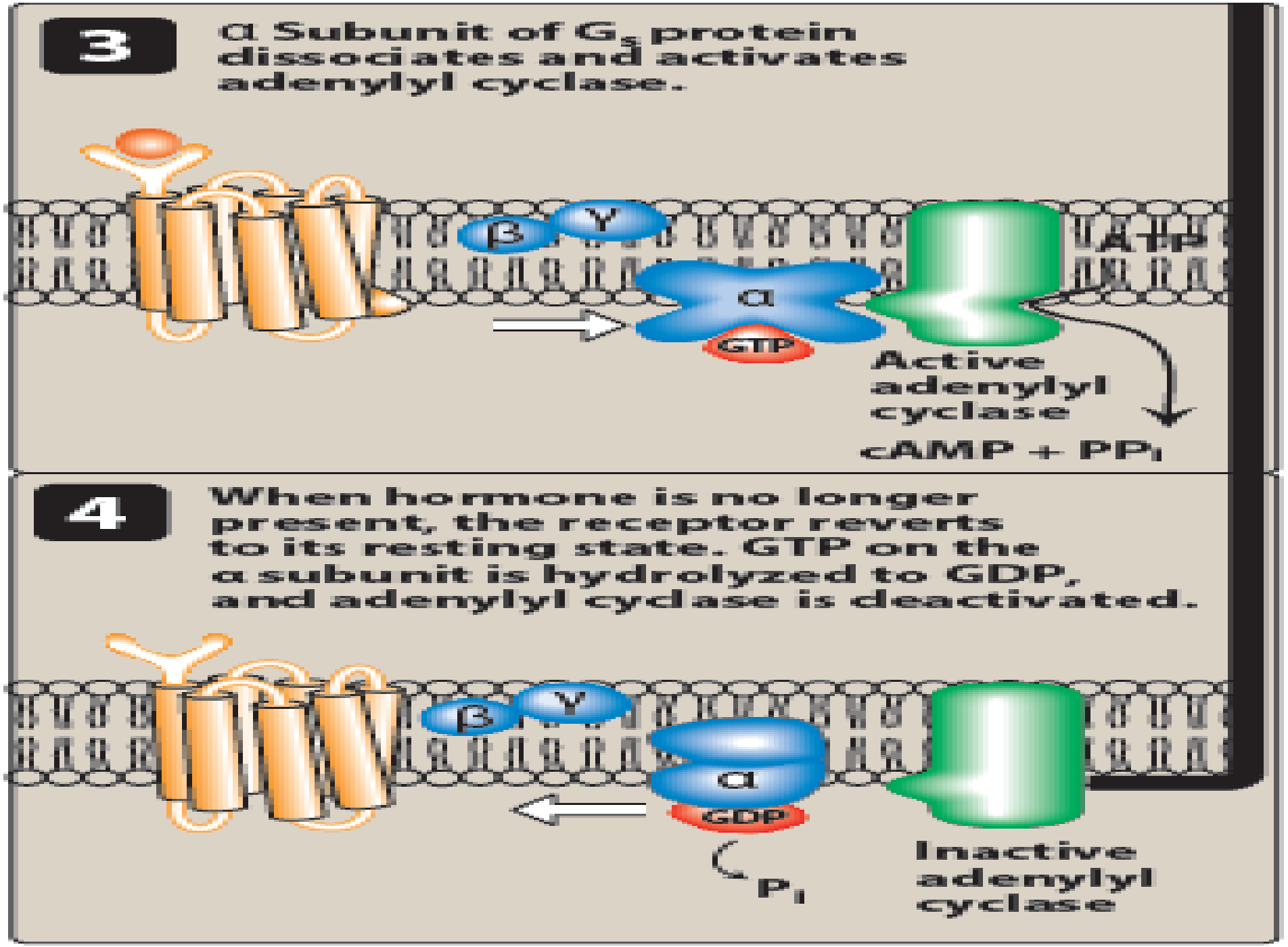
- The extracellular domain of this receptor usually contains the ligand-binding area
- Intracellularly, these receptors are linked to a G protein which consist of Alpha,Beta & Gamma subunits
- Upon activation, G-protein disscociates to activate Secondary messenger
- Responses occurs within seconds to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

- **Second messengers:**

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

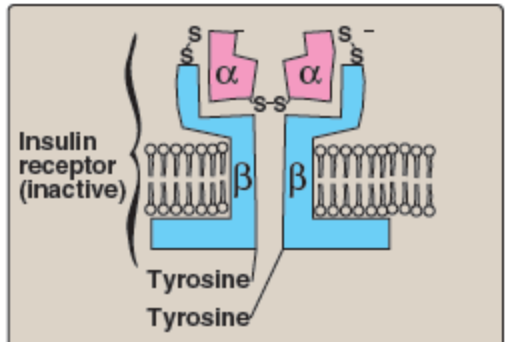
  Example : cAMP, leads to protein phosphorylation, and downstream gene induction

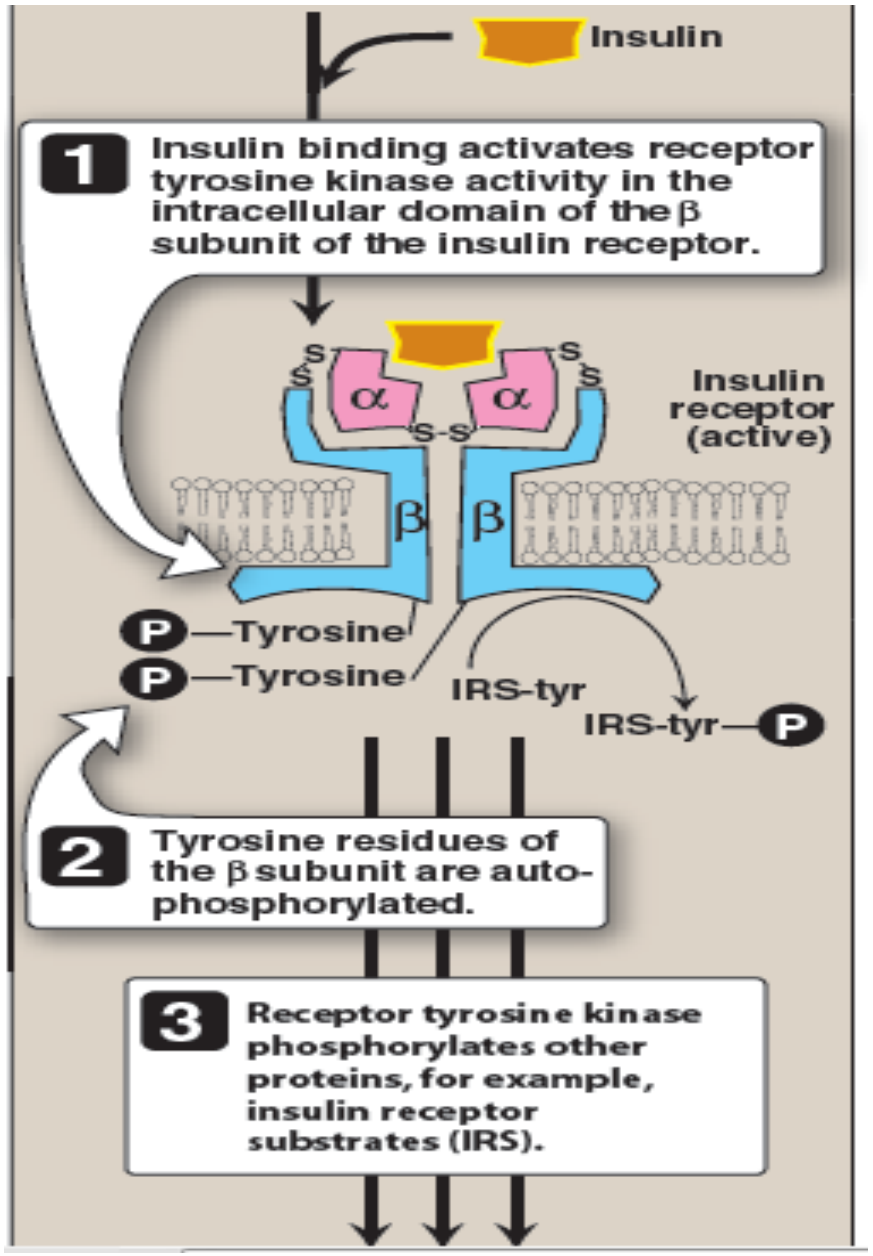

1
Unoccupied receptor does not interact with G_s protein.
Extra-cellular space
Hormone or neuro-transmitter
Cell membrane
Receptor
β
γ
α
GDP
G_s protein with bound GDP
Inactive adenylyl cyclase
Cytosol
2
Occupied receptor changes shape and interacts with G_s protein. G_s protein releases GDP and binds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

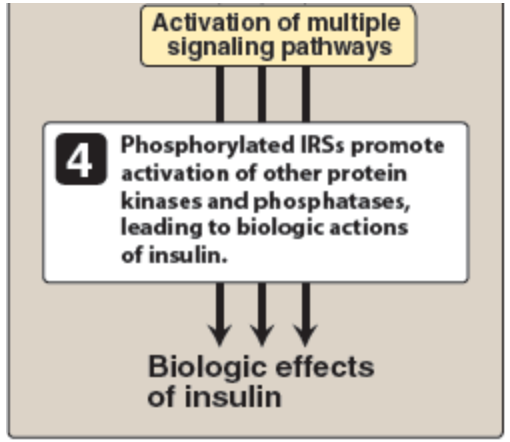

3
α Subunit of G_s protein dissociates and activates adenylyl cyclase.
β
γ
α
GTP
ATP
Active adenylyl cyclase
cAMP + PP_i
4
When hormone is no longer present, the receptor reverts to its resting state. GTP on the α subunit is hydrolyzed to GDP, and adenylyl cyclase is deactivated.
β
γ
α
GDP
P_i
Inactive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