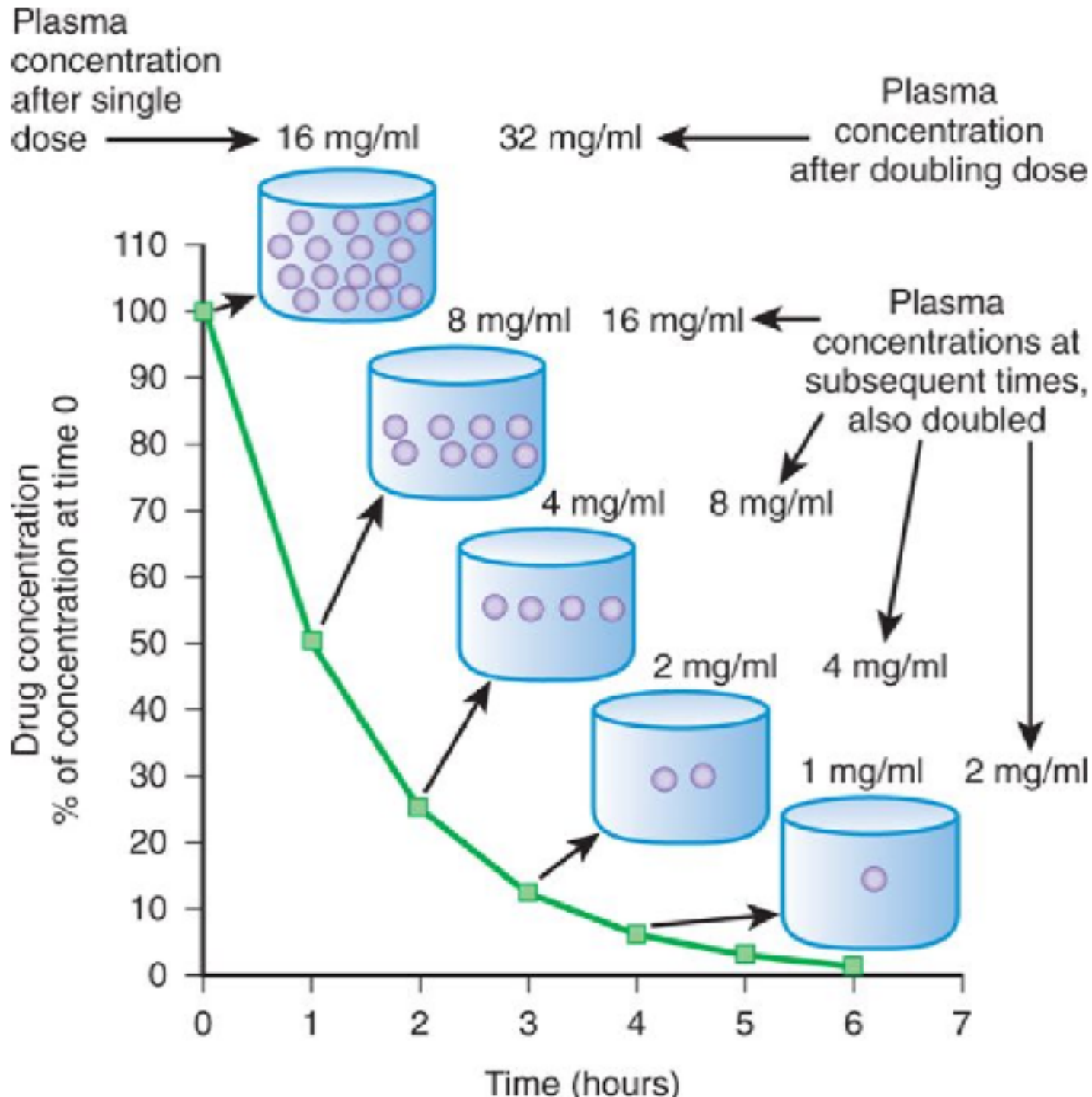
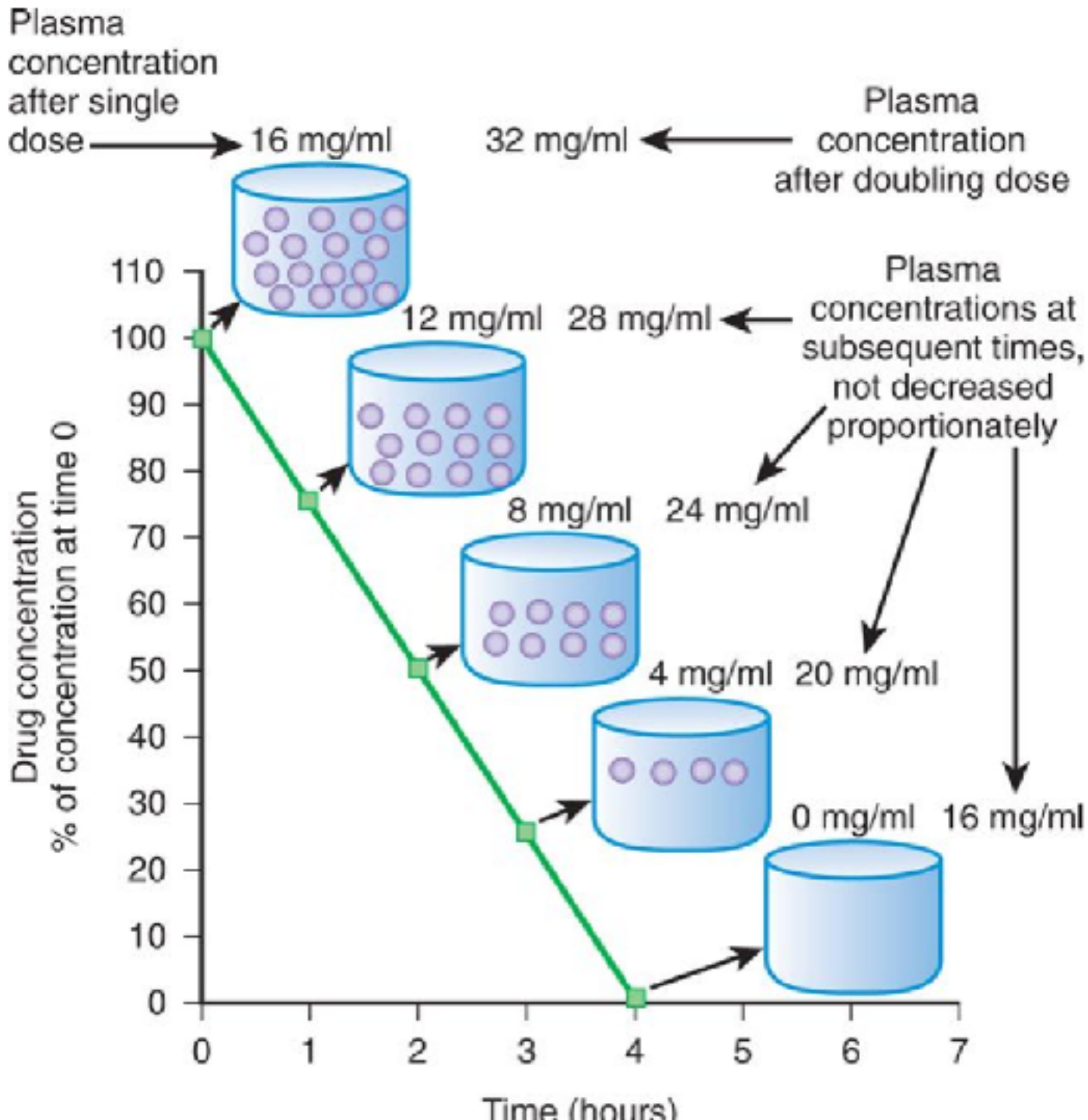
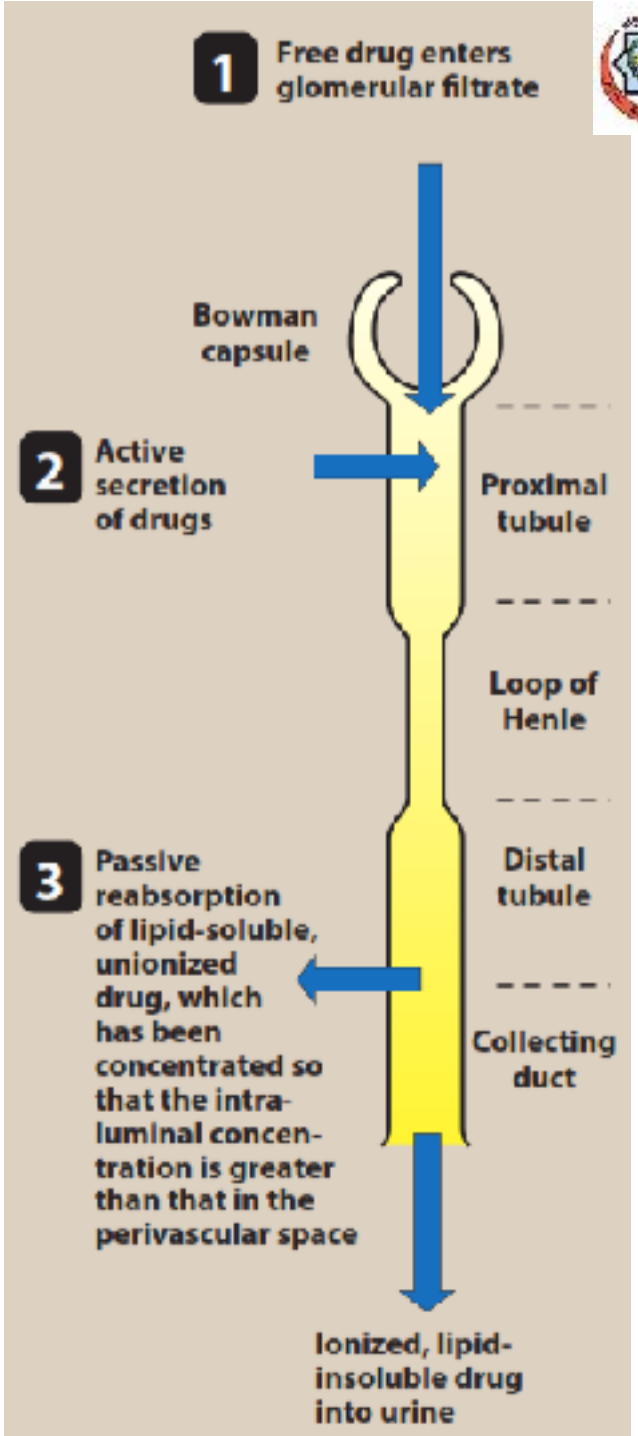

Plasma concentration after single dose
16 mg/ml
32 mg/ml
Plasma concentration after doubling dose
8 mg/ml
16 mg/ml
Plasma concentrations at subsequent times, also doubled
4 mg/ml
8 mg/ml
2 mg/ml
4 mg/ml
1 mg/ml
2 mg/ml
Drug concentration % of concentration at time 0
110
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
Time (hours)

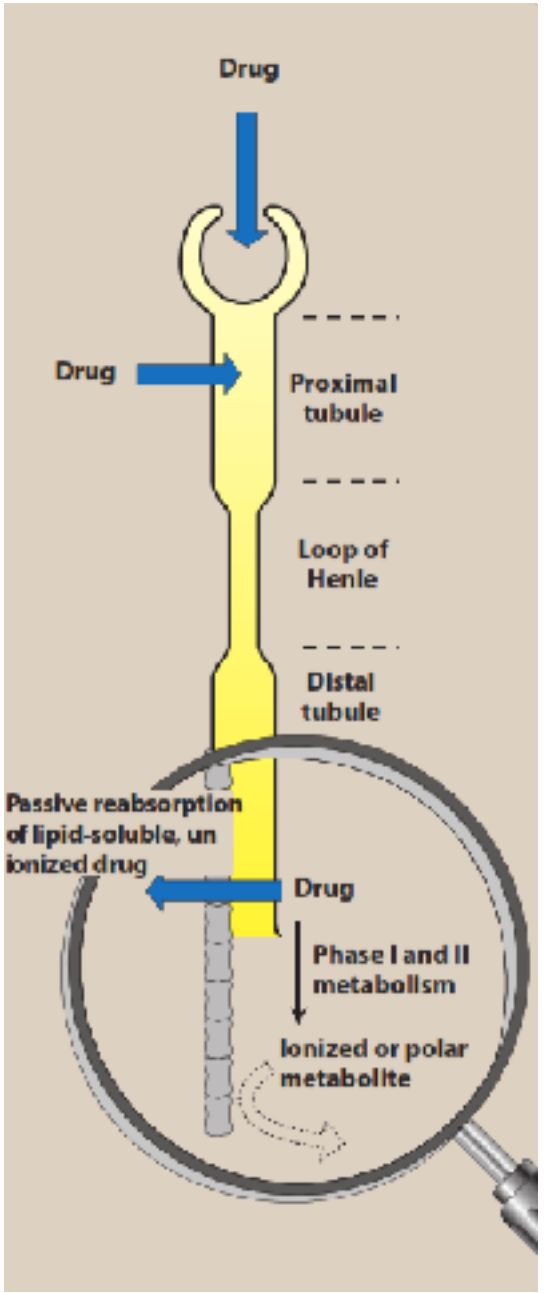

Plasma concentration after single dose
16 mg/ml
32 mg/ml
Plasma concentration after doubling dose
Plasma concentrations at subsequent times, not decreased proportionately
12 mg/ml
28 mg/ml
8 mg/ml
24 mg/ml
4 mg/ml
20 mg/ml
0 mg/ml
16 mg/ml
Drug concentration % of concentration at time 0
110
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
Time (hours)

Drug Clearance by the Kidney

1.Glomerular filtration:
(free D cleared by ???)
1.Proximal tubular secretion:
(WAs & WBs)
1.Distal tubular reabsorption:
(lipid soluble Ds)



Role of Drug Metabolism



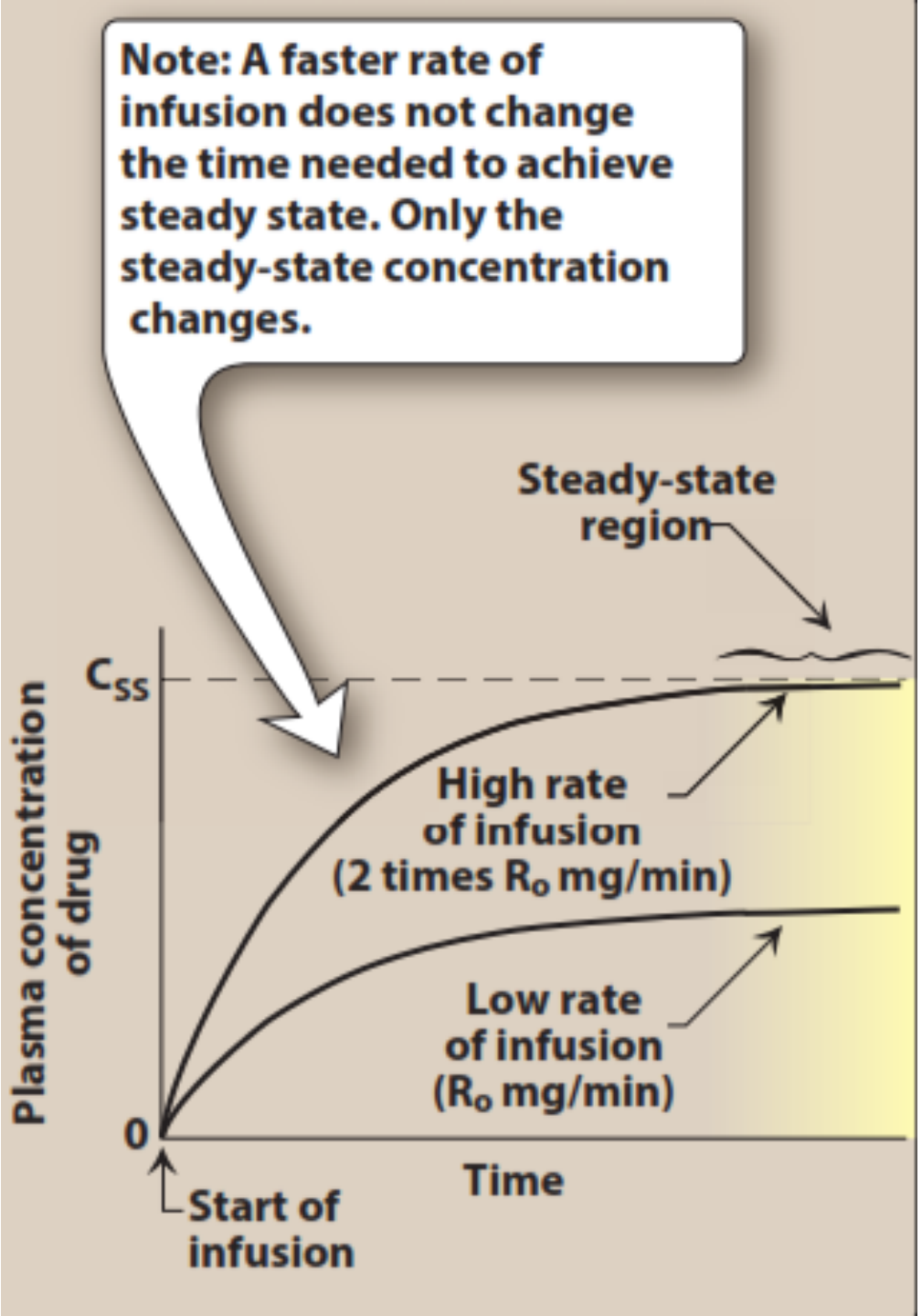
Clearance (continuation)

- *Clearance by other Routes*
- *Total Body Clearance*

$$CL_{total} = CL_{hepatic} + CL_{renal} + CL_{pulmonary} + CL_{other}$$

where $CL_{hepatic} + CL_{renal}$ are typically the most important.

- *Clinical Situations Resulting in Changes in* $t_{1/2}$



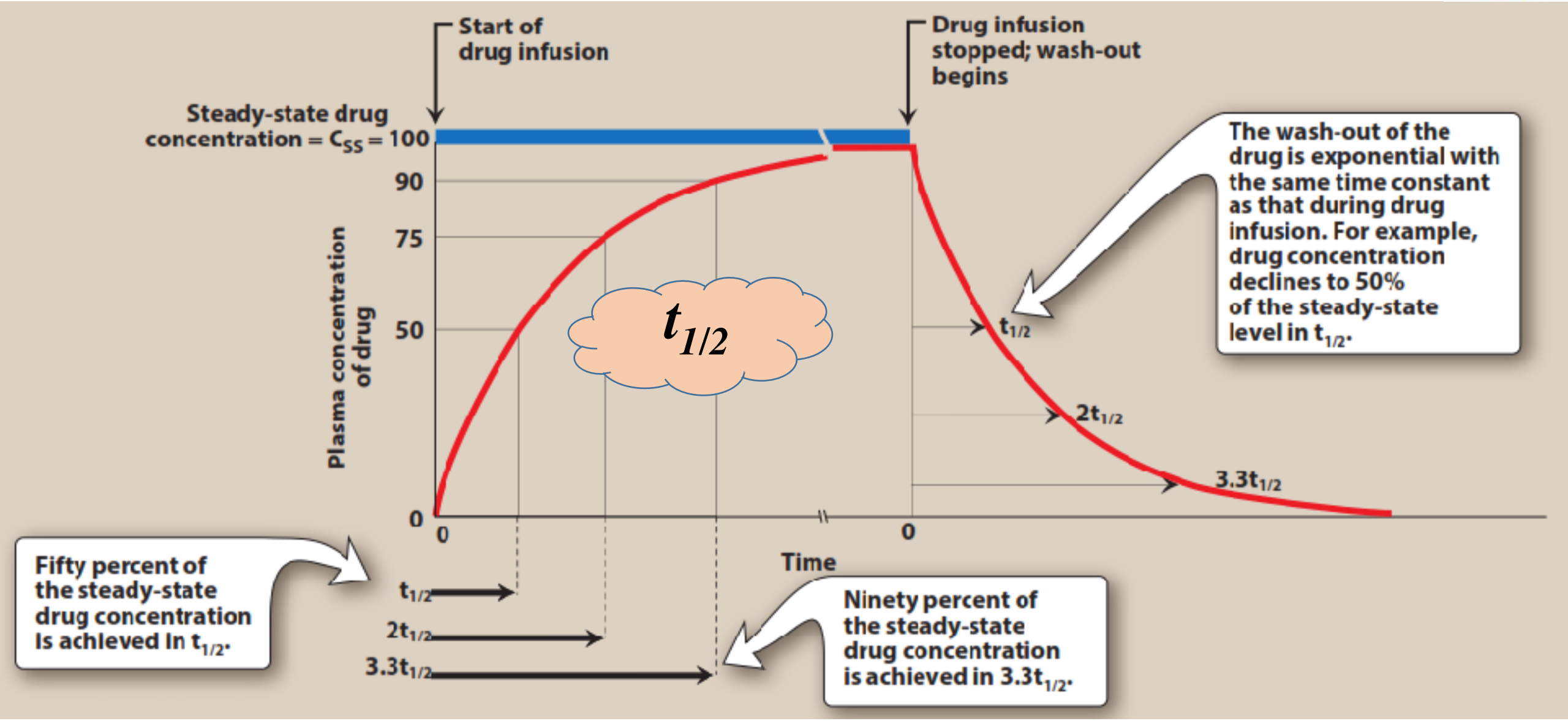
Design & Optimization of Dosage Regimen

Steady State Condition (Css)

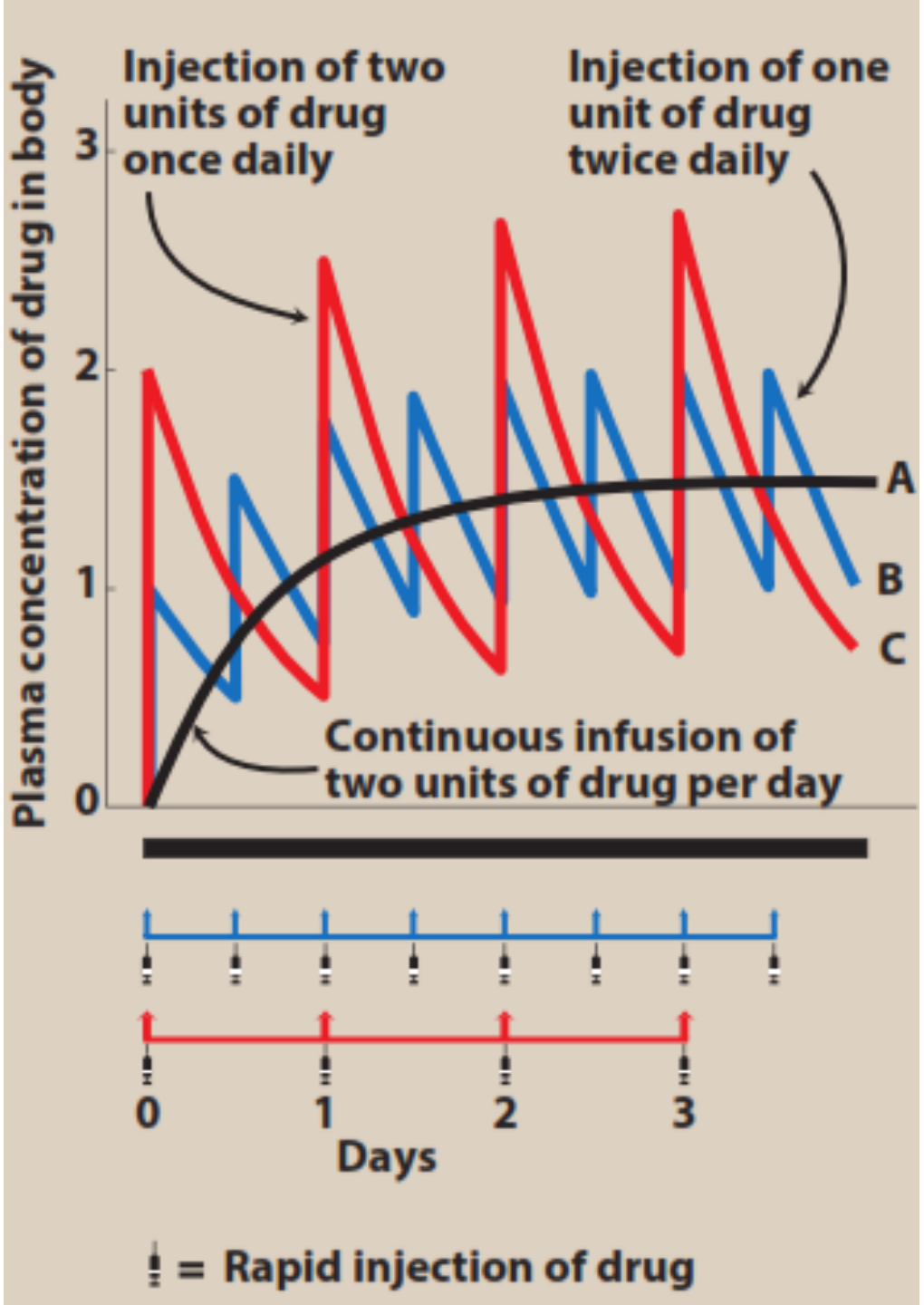
Css *is directly proportional to rate of infusion*

Css *is inversely proportional to CL*

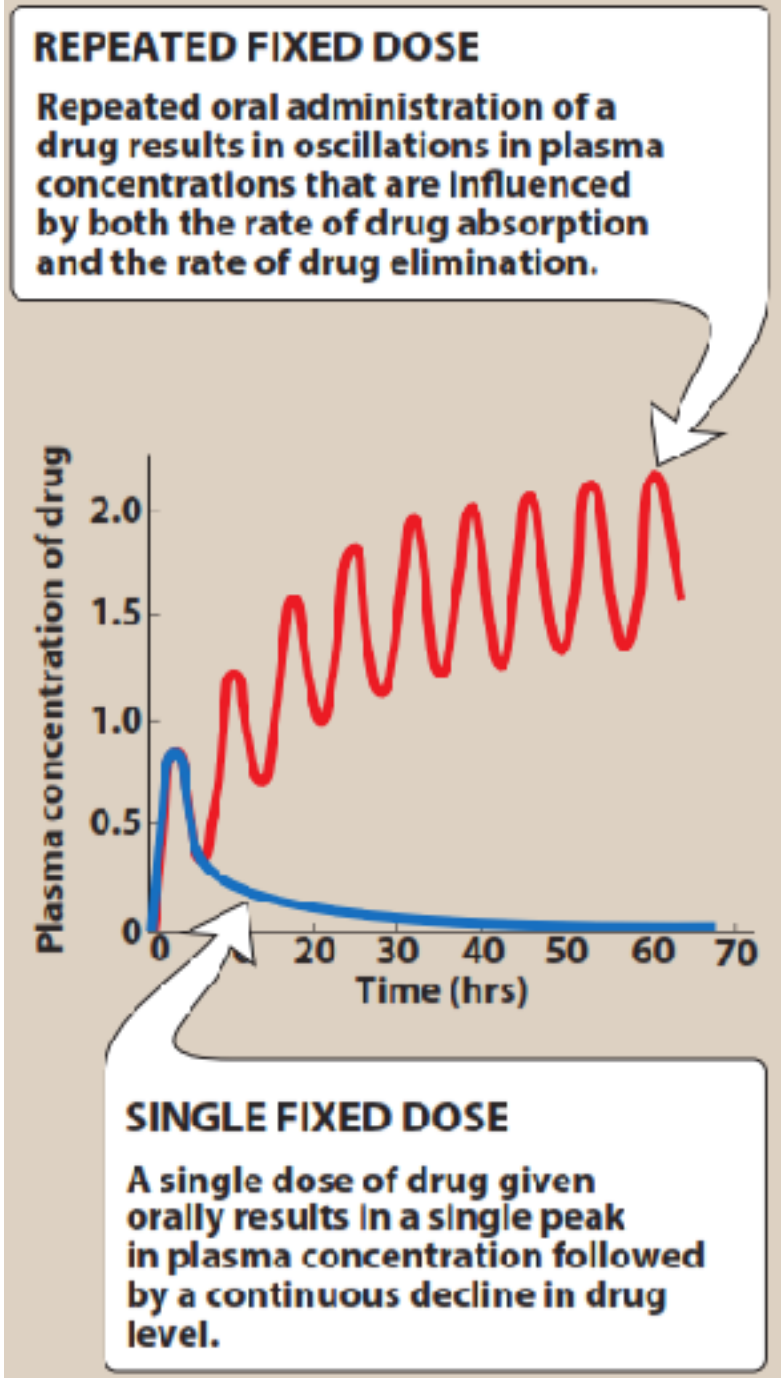
Time to Reach Steady State Concentration



Fixed Dose / Fixed Time Interval



Optimization of Dose



Maintenance dose:

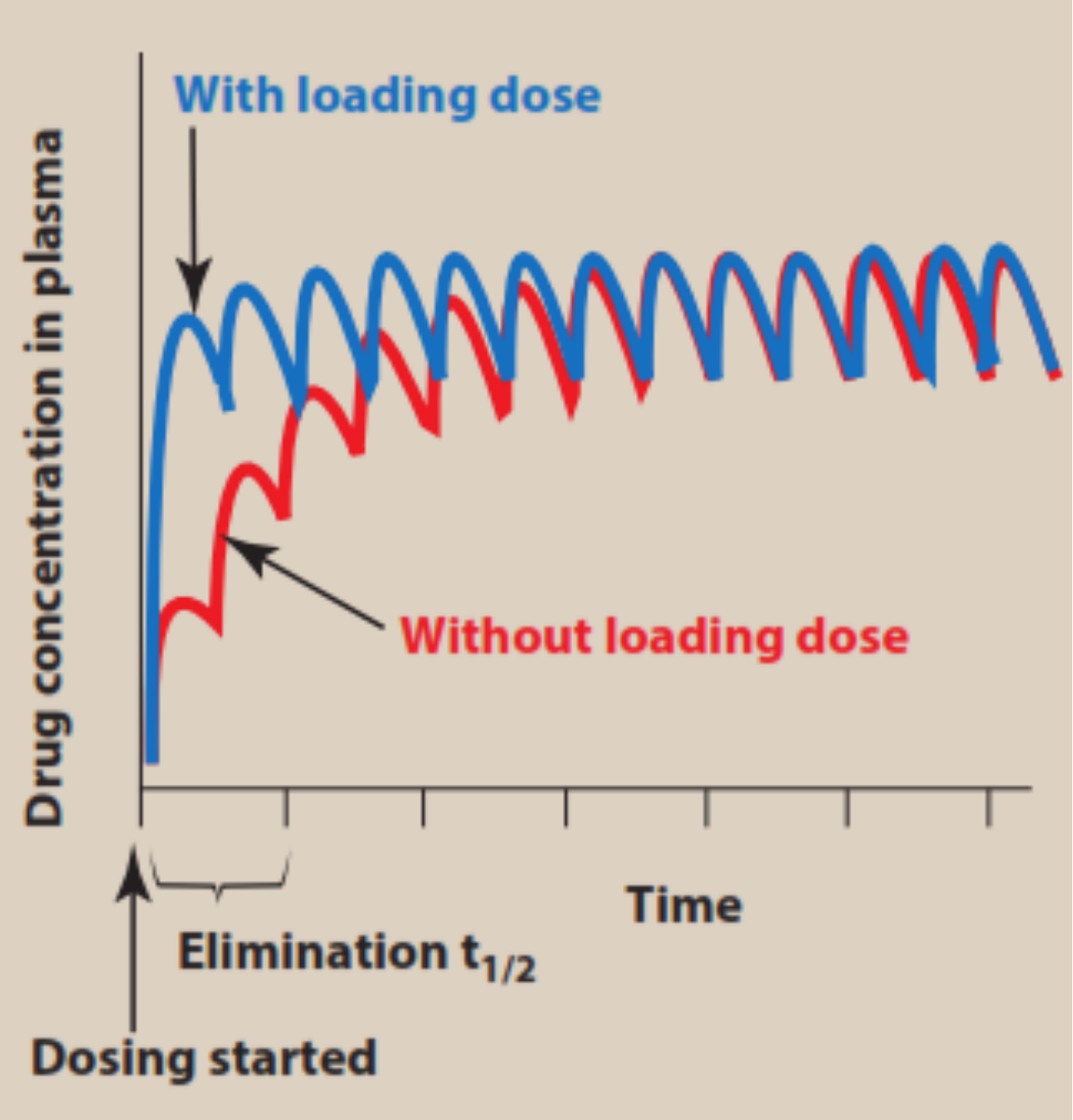
$$Dosing\,rate = \frac{(Target\ Cplasma)\ (CL)}{F}$$

Loading Dose :

$$Loading\ Dose = (V_d)\,x\ (desired\ Css)/F$$

For IV:

$$Loading\ Dose = (V_d)\,x\ (desired\ Css)$$


With loading dose
Drug concentration in plasma
Without loading dose
Time
Elimination $t_{1/2}$
Dosing started

Factors affecting drug absorption

Formulation

Stability to acid and enzymes

Motility of gut

Food in stomach

Degree of first-pass metabolism

Lipid solubility

Depends a lot on the pK of drug and pH of environment. Unionized drug is much more lipid soluble than ionized drug

The relative proportions are given by (for a weak base):

$$\log \frac{BH^+}{B} = pK_a - pH$$

Routes of administration

Oral–most common

Sublingual–veins from buccal cavity avoid liver

Intravenous injection avoids absorption barriers

For example a weak base (B) $pK_a = 7$

Buccal cavity

B

Stomach — pH 2

$H^+ + B \rightleftharpoons BH^+$

1 : 5000

No absorption

Most molecules ionized

Intestine — pH 8

$H^+ + B \rightleftharpoons BH^+$

1 : 10

90% molecules unionized

Portal vein

$B + H^+ \rightleftharpoons BH^+$

Liver

B

B

Biliary duct

First-pass metabolism

Volume of distribution V_D

Lipid-soluble drugs enter cells (e.g. ethanol)

Highly ionized drugs are confined to the extracellular fluid (e.g. tubocurarine)

Drugs that are highly protein-bound or high molecular weight (heparin) are retained in circulation

Intra-cellular water

Interstitial water

$B + H^+ \rightleftharpoons BH^+$

Renal glomerulus

$B + H^+ \rightleftharpoons BH^+$

PB

$B + P \rightleftharpoons$ PB

Protein-bound drug

$B \quad BH^+ \rightleftharpoons BH^+$

Vascular compartment

B

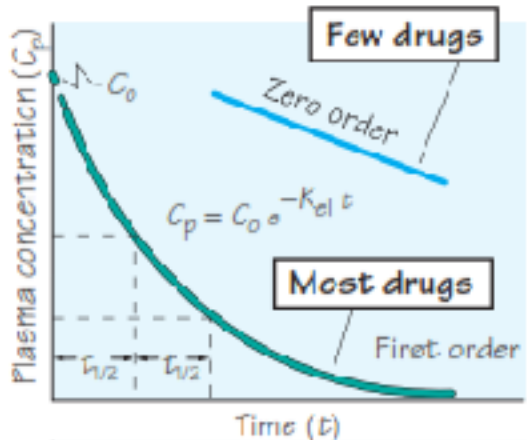
BH^+

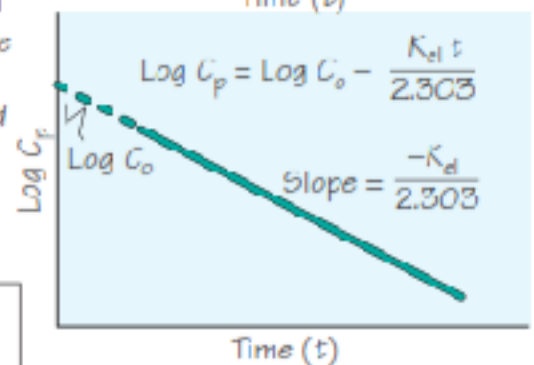
Renal tubule

Much unionized drug reabsorbed

Most ionized drug excreted

Urine





Absorption

Distribution

Excretion

Drug-Receptor Interactions and Pharmacodynamics

D-R Interact.ions and Pharmacodynamics

➢ *Pharmacodynamics*

Describes the actions of drugs on the body and the influence of drug concentration on the magnitude of the response

➢ *Signal Transduction*

✓ *Ligands*

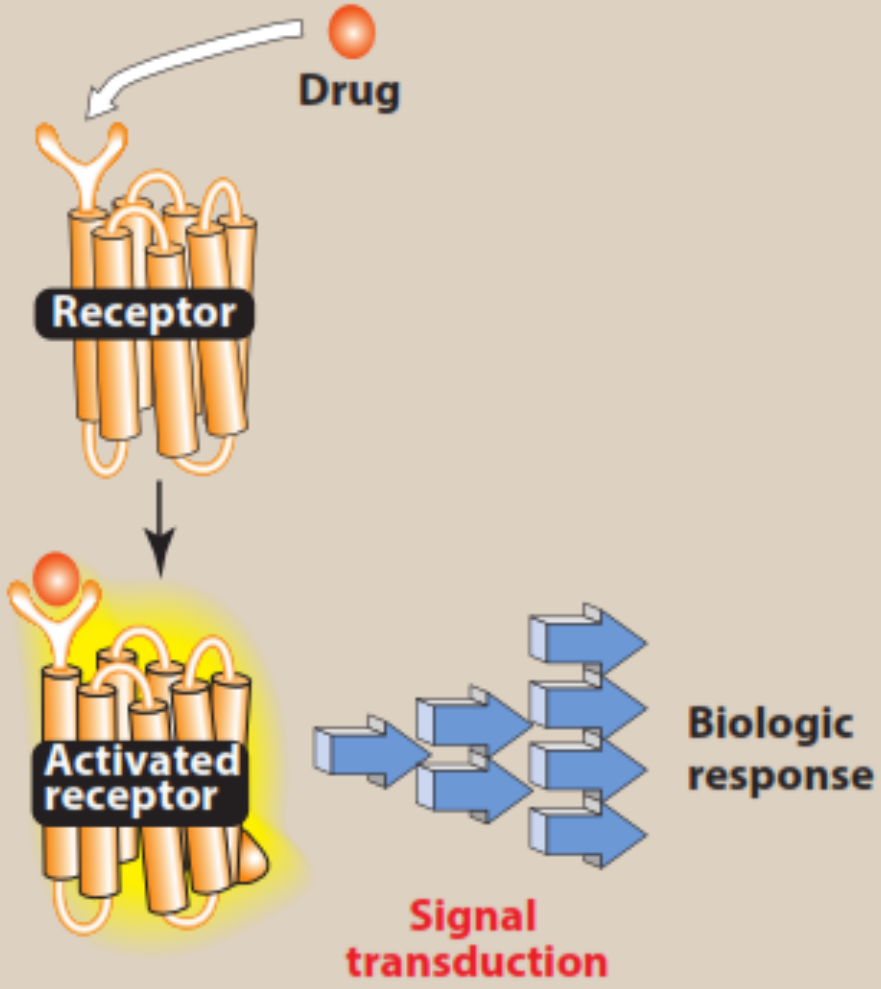
✓ *Second Messenger*

Drug-Receptor Complex

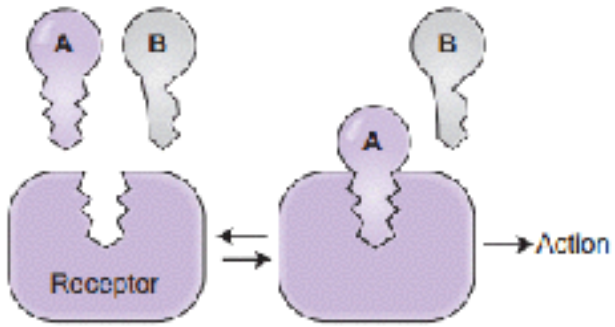
Drug + Receptor ⇌ Drug-Receptor Complex ——— Biologic Effect

1 **Unoccupied receptor does not influence intracellular processes.**

2 **Receptor with bound agonist is activated. It has altered physical and chemical properties, which leads to interaction with cellular molecules to cause a biologic response.**



Receptor?????



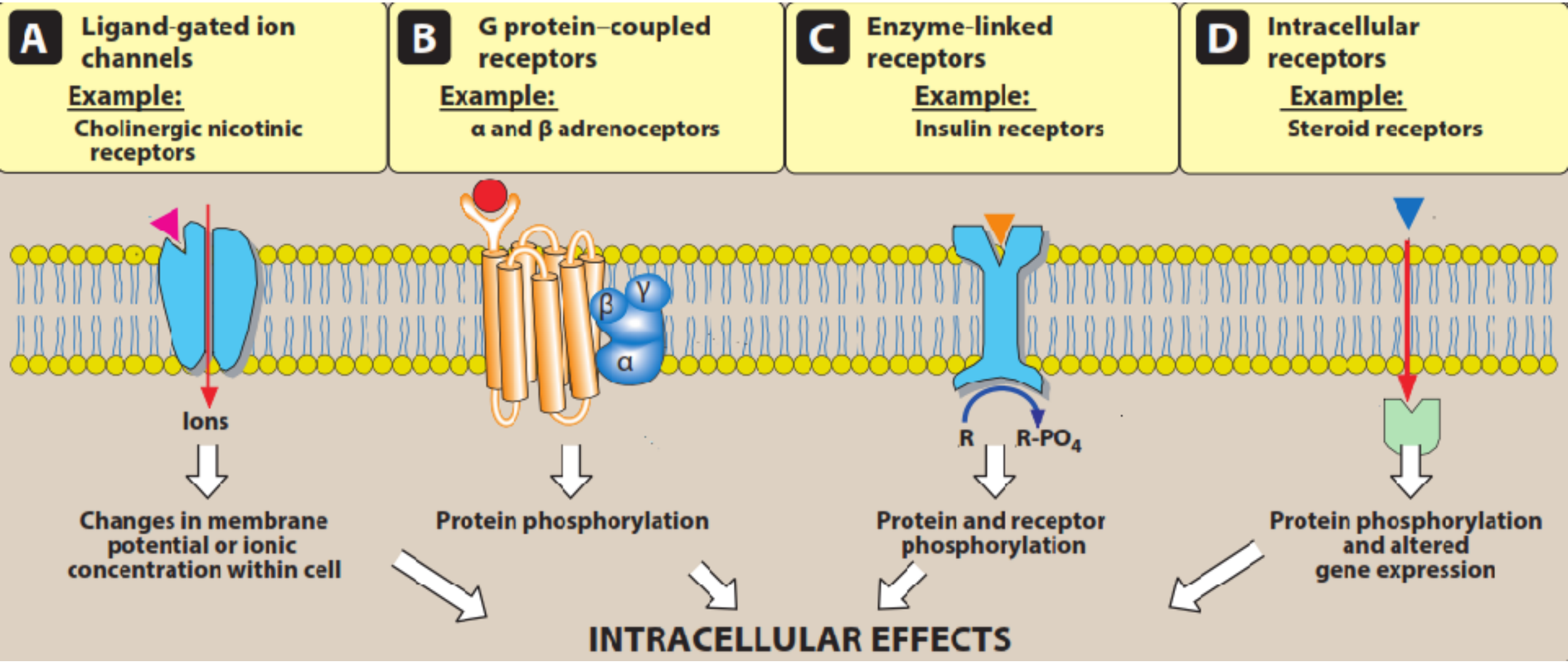
Drug **A** binds to receptor
Drug **B** cannot bind to receptor

Receptor States

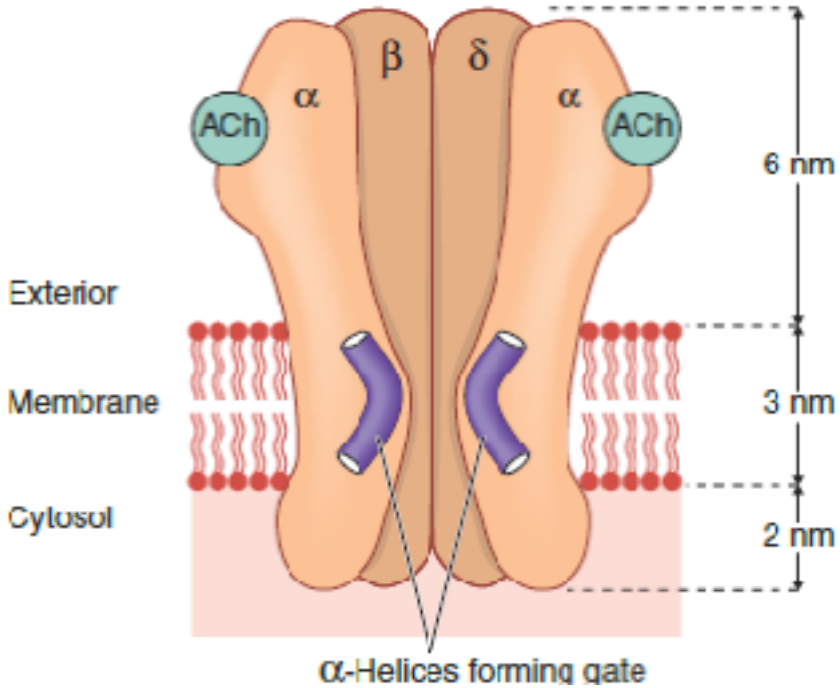
- *R (inactive)* $\rightleftharpoons$ *R *(active)*

- *Agonist ???*
- *Antagonist ???*
- *Partial agonist ???*

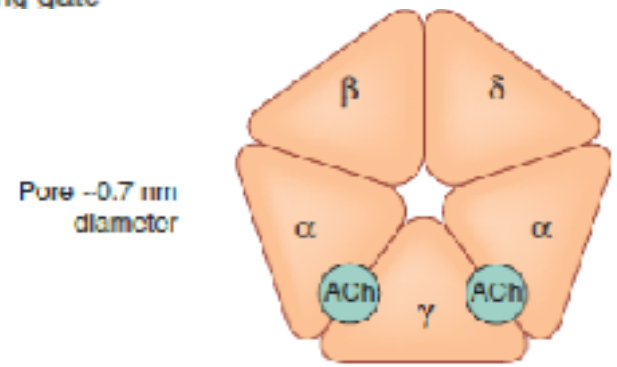
Receptor Families



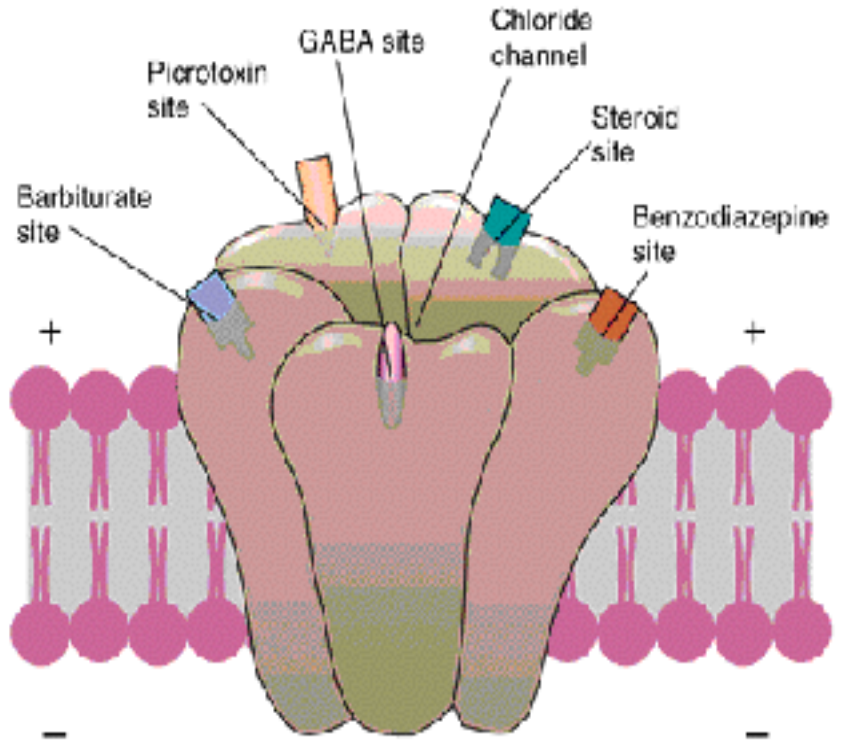
Transmembrane ligand-gated ion channels



Schematic illustration of ACh receptors

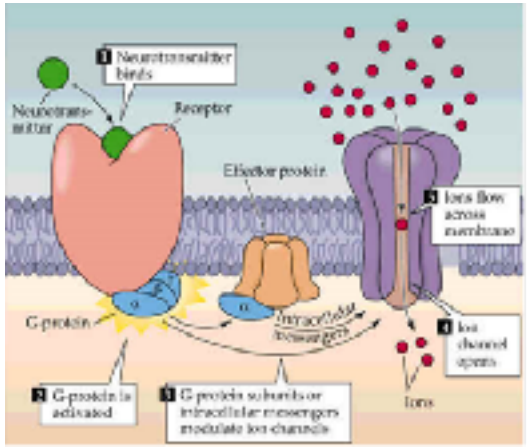


Schematic Illustration of a $GABA_A$ Receptor, with Its Binding Sites

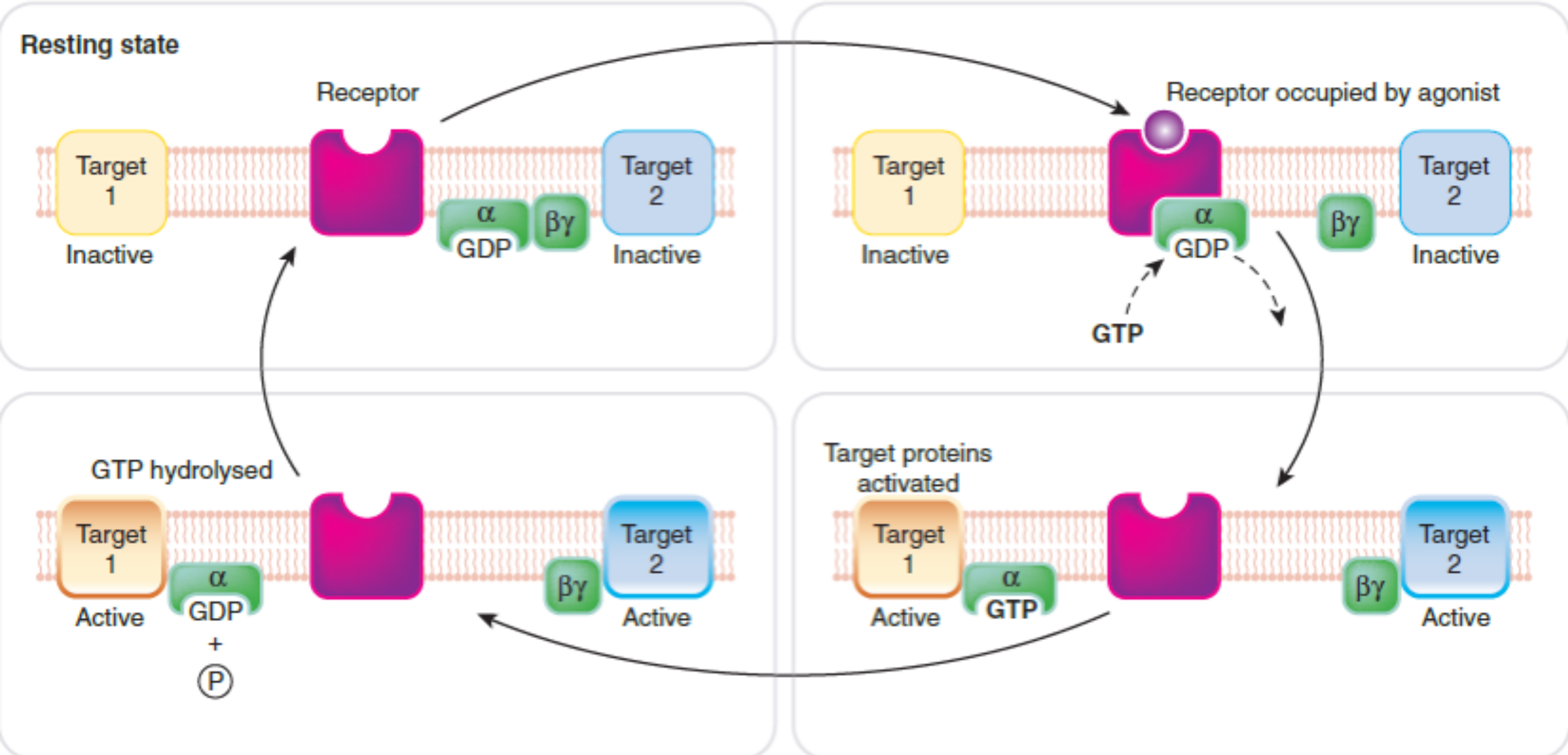


Transmembrane G protein-coupled receptors

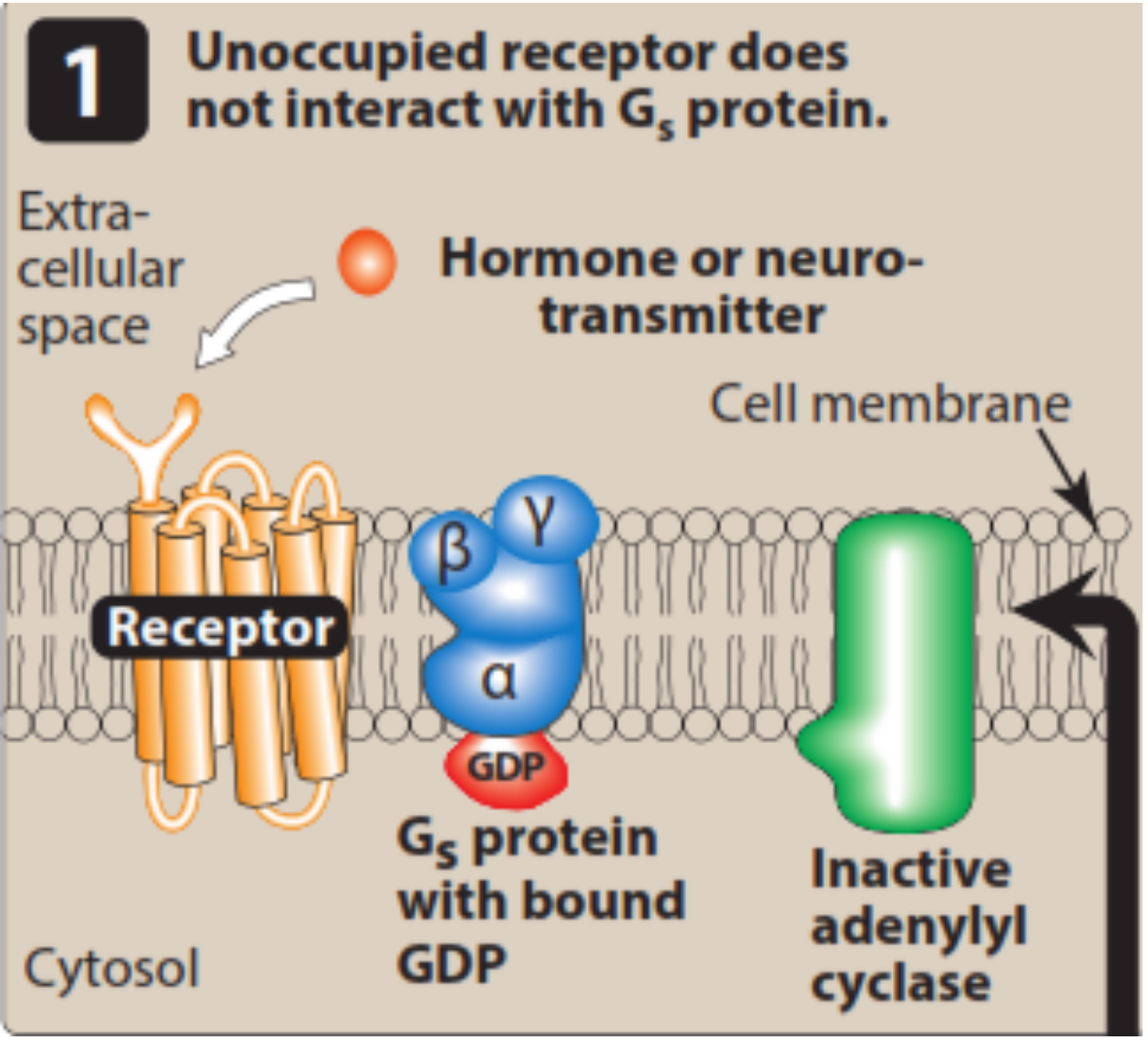
- ✓ *EC domain*
- ✓ *IC domain interacvts with G ptn or effector molecule*
- ✓ *Many kinds of G ptns (Gs, Gi, Gq)*
- ✓ *All composed of* α, β & γ subunits
- ✓ *The responses lasts for several seconds to minutes*

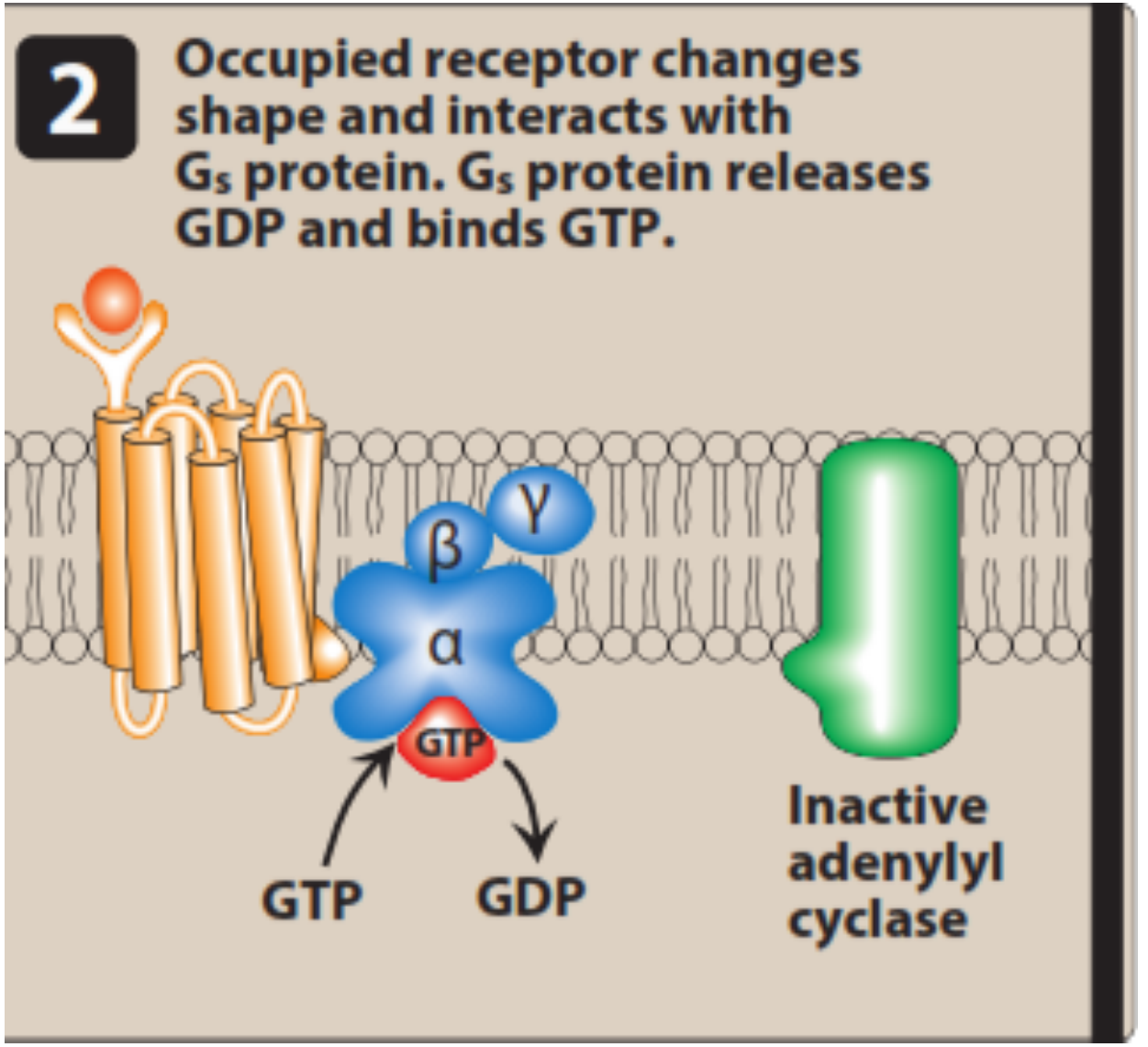


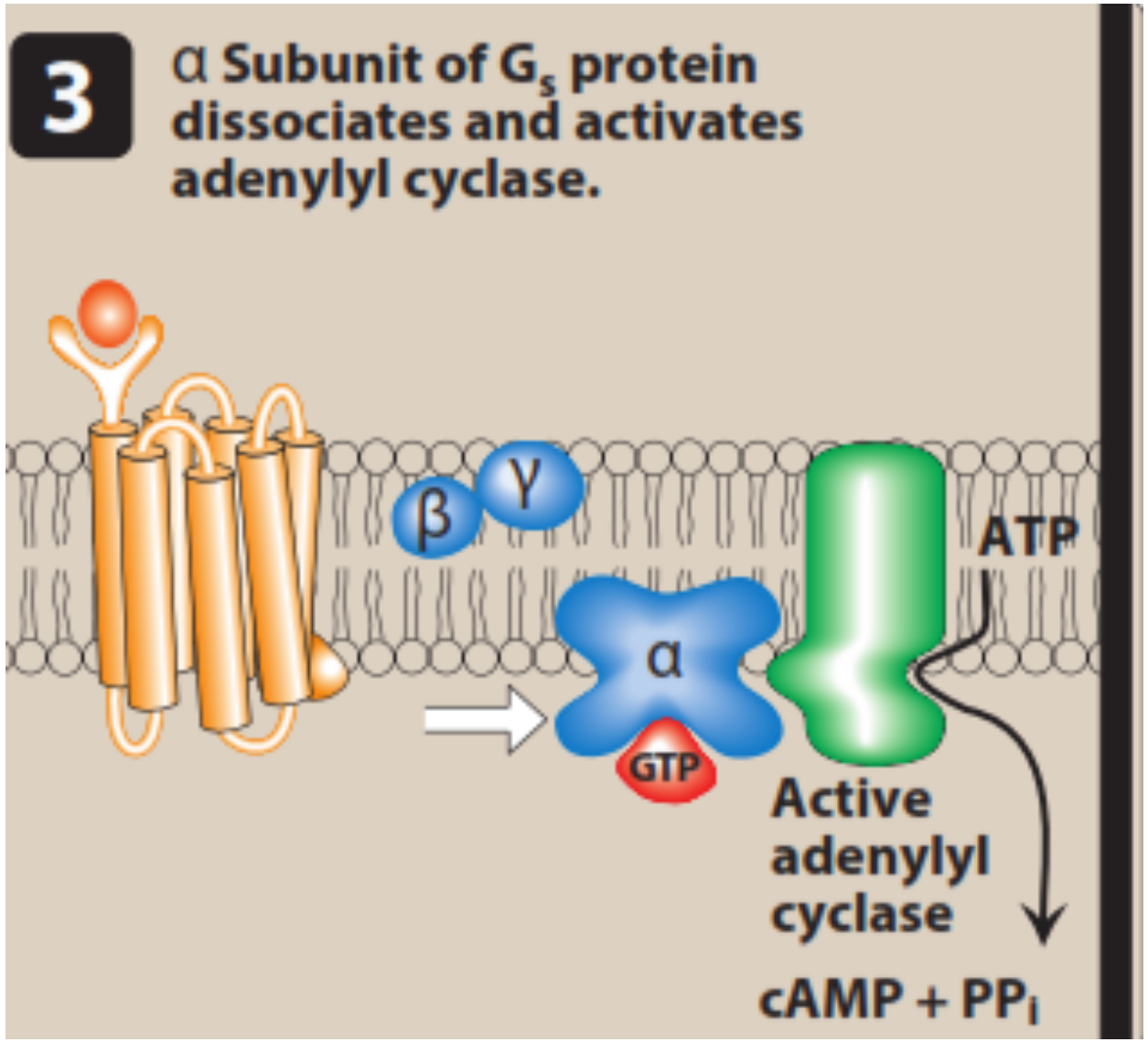
Transmembrane G protein-coupled receptors (cont.)

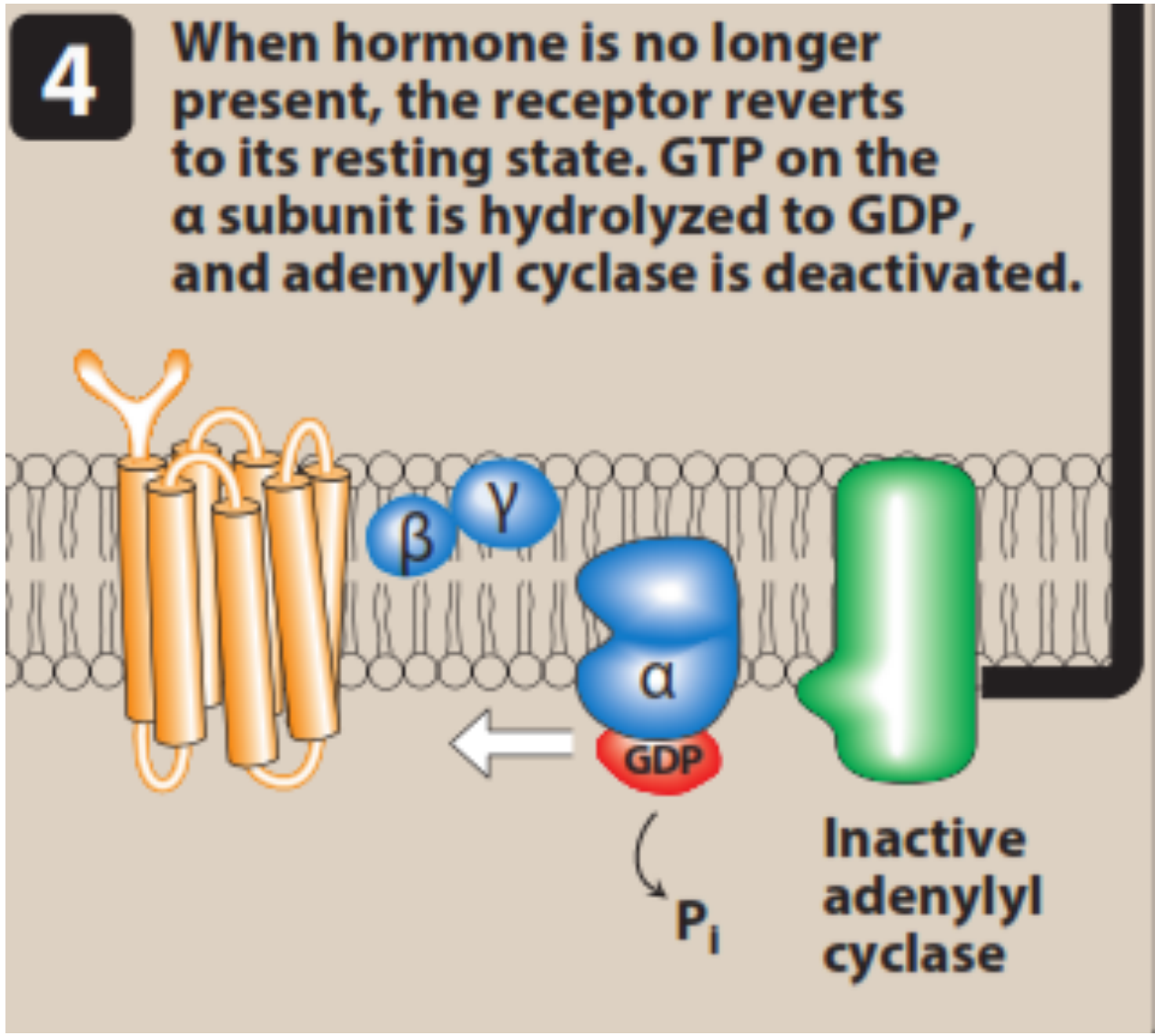


Transmembrane G protein-coupled receptors (cont.)



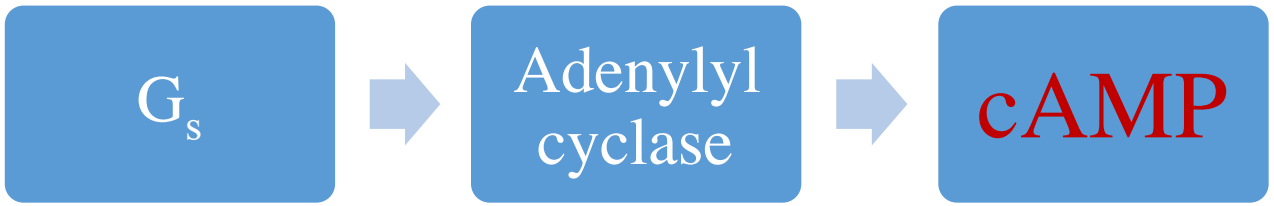



3
α Subunit of G_s protein dissociates and activates adenylyl cyclase.
β
γ
α
GTP
ATP
Active adenylyl cyclase
cAMP + PP_i

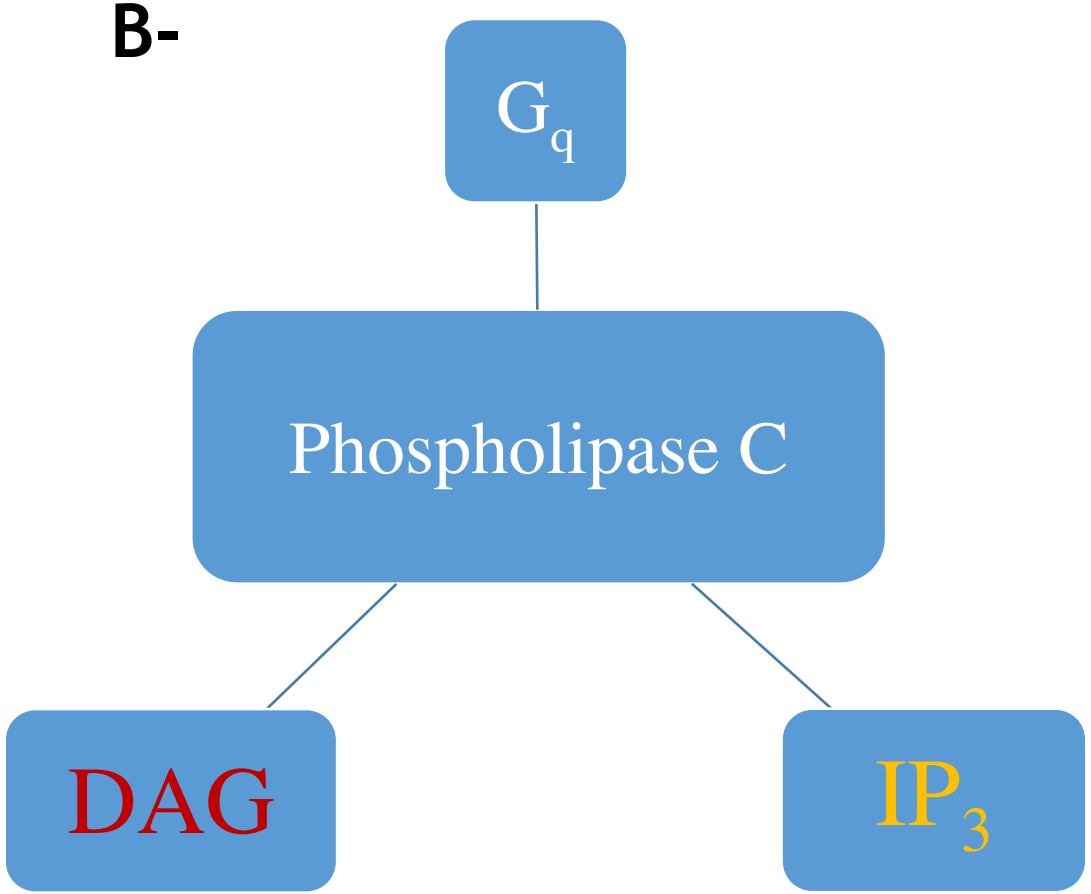

4
When hormone is no longer present, the receptor reverts to its resting state. GTP on the α subunit is hydrolyzed to GDP, and adenylyl cyclase is deactivated.
β
γ
α
GDP
P_i
Inactive adenylyl cyclase

G proteins

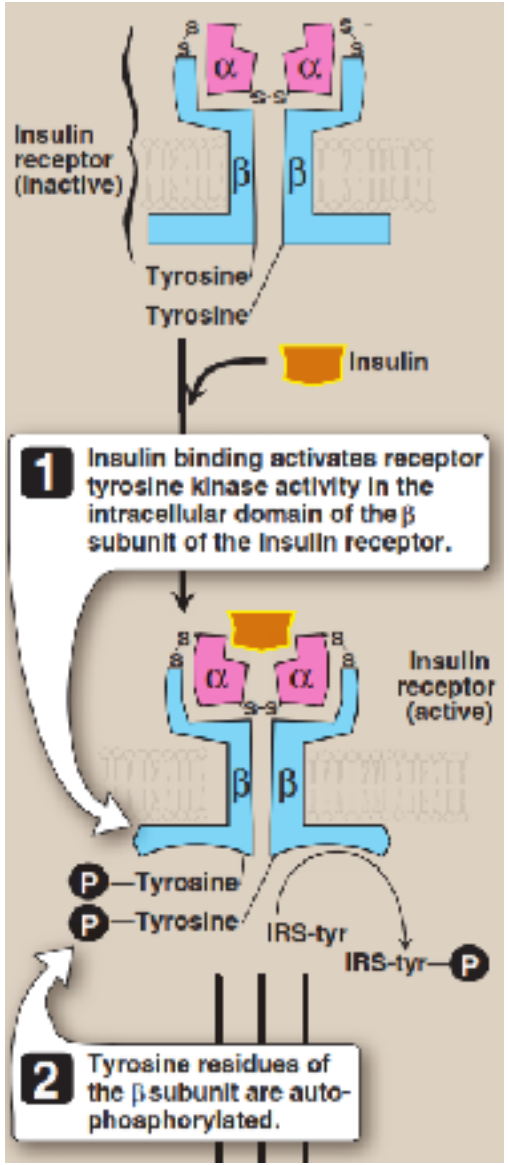
A-



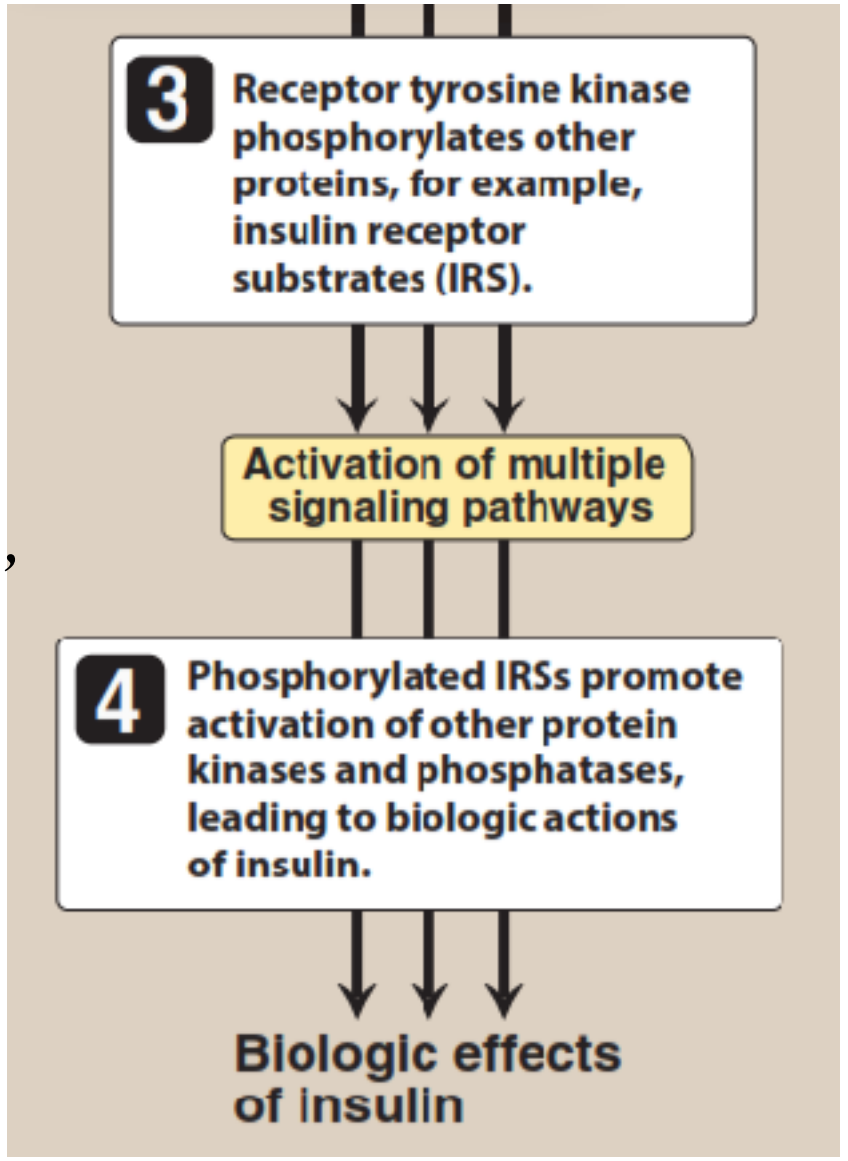
B-



Enzyme-linked receptors (Insulin Receptors)



- *Dimers or multisubunits*
- *Lasts min to hrs*
- *Ex., epidermal growth factor(EGF), platelet-derived growth factor (PDGF), atrial natriuretic peptide (ANP), insulin & others*



Intracellular receptors

- *Takes hours to days to give response*
- *Examples: steroid H, structural pts, Es, RNA & ribosomes*