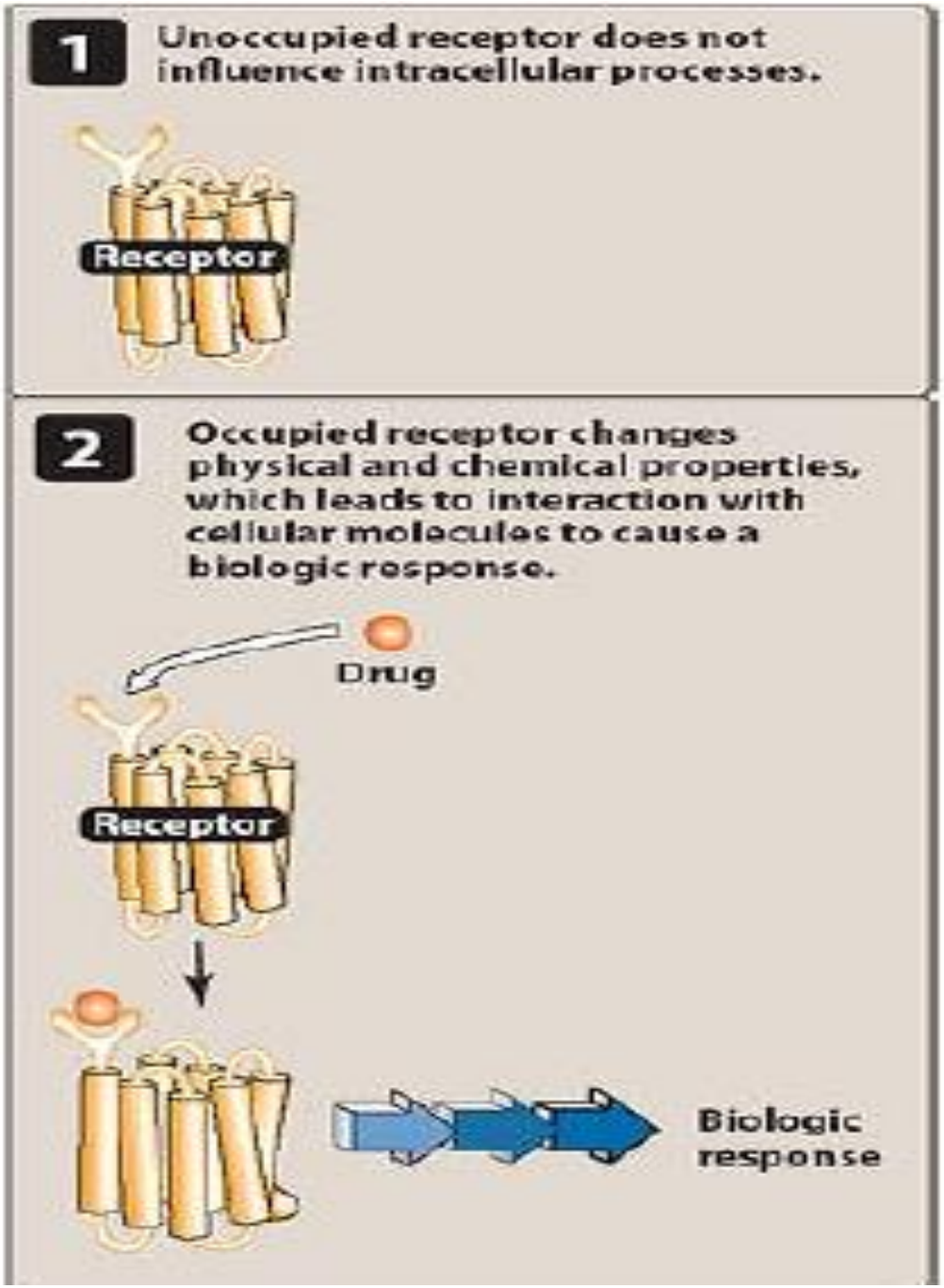
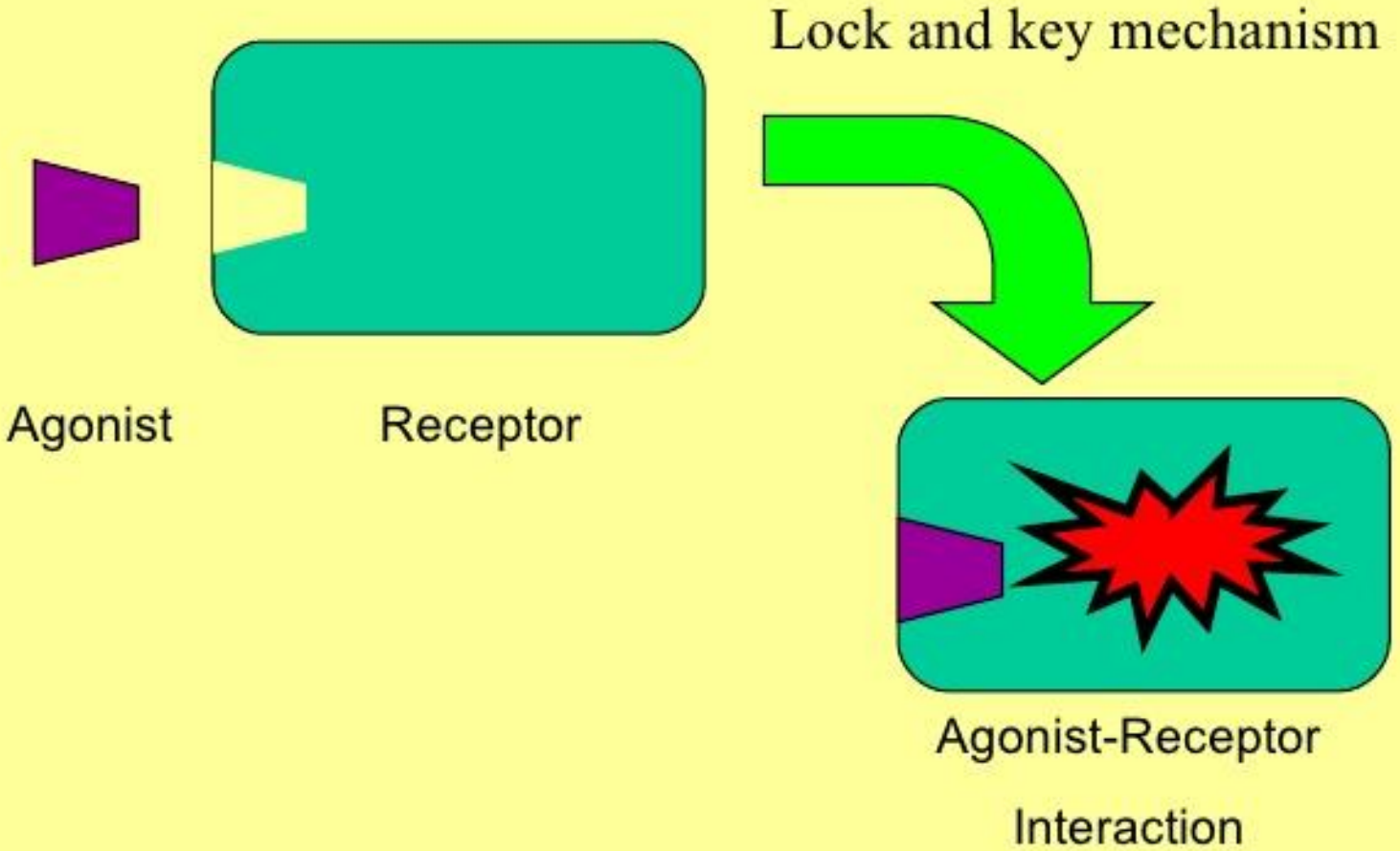
PHARMACODYNAMIC


1
Unoccupied receptor does not influence intracellular processes.
Receptor
2
Occupied receptor changes physical and chemical properties, which leads to interaction with cellular molecules to cause a biologic response.
Drug
Receptor
Biologic response

Receptor
Ligand

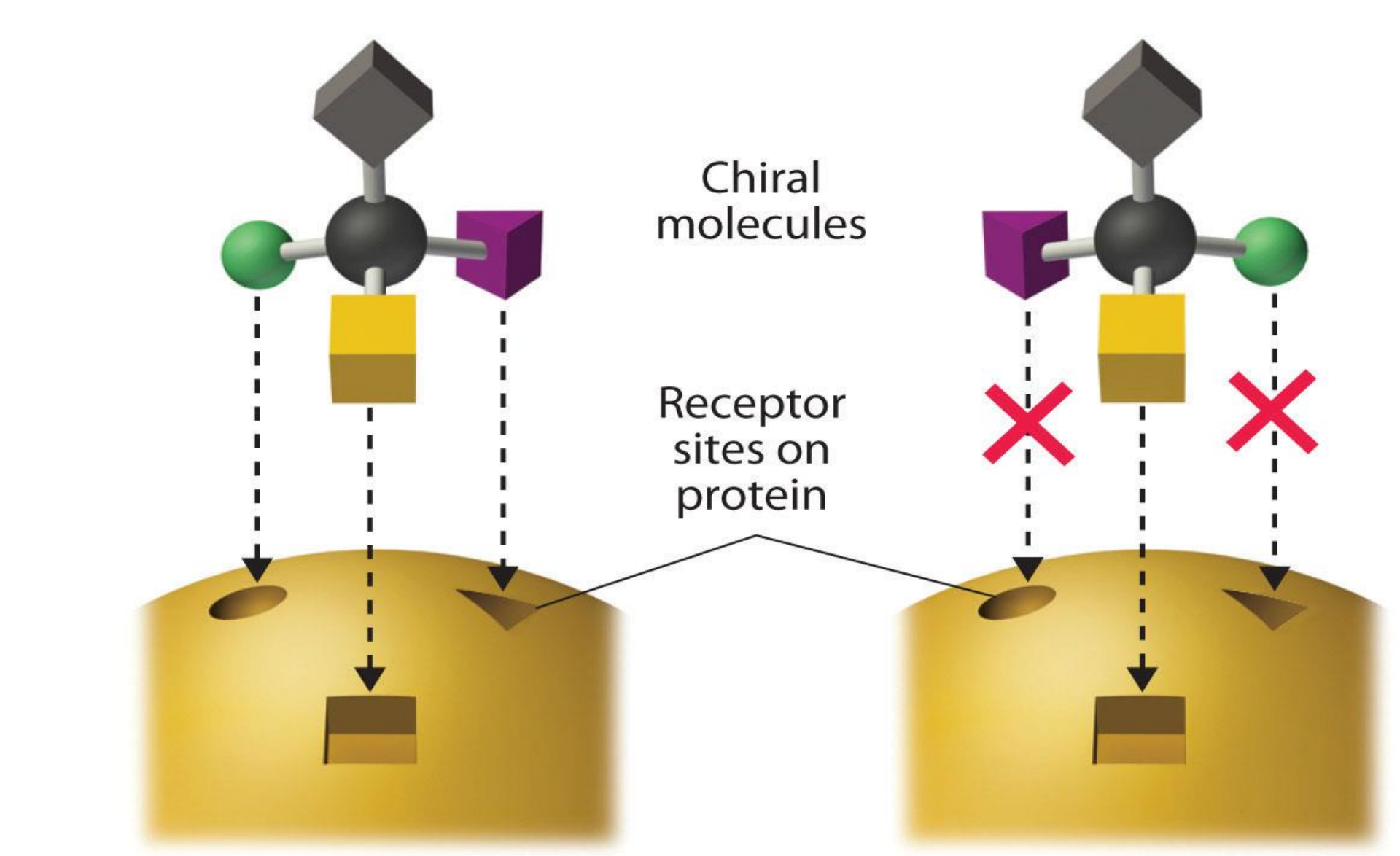
Receptor Interactions



ENZYME

GOOD Substrate

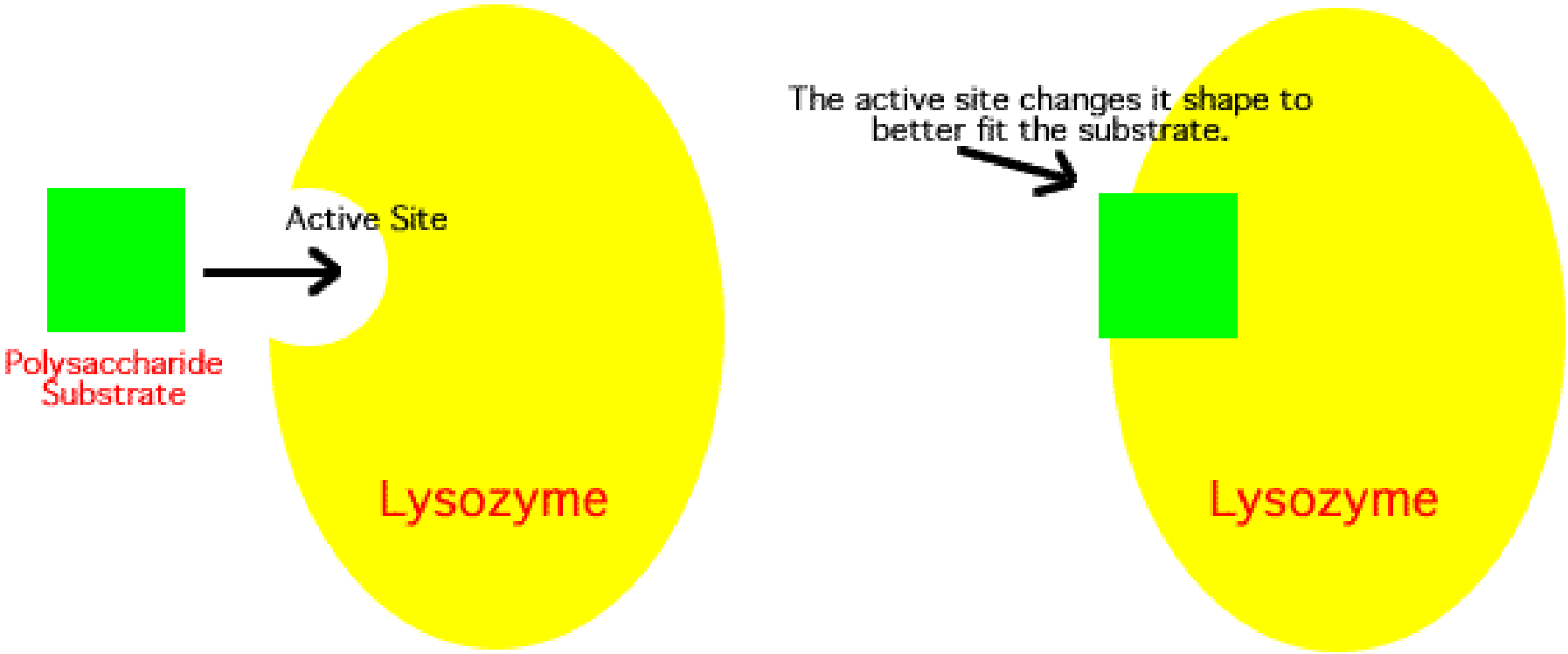
BAD Substrate



(a) Molecule fits receptor site, leading to a response

(b) Molecule does not fit receptor site; no response

An Example of Induced Fit: The Enzyme Lysozyme



The enzyme Lysozyme helps kill bacteria by binding to the polysaccharide coating of the bacteria. The fit is not perfect, so the shape of the active site changes to fit the polysaccharide substrate. This change of shape of the active site is called induced fit. By initiating this "induced fit", the enzyme breaks the polysaccharide, ultimately helping kill the bacteria.

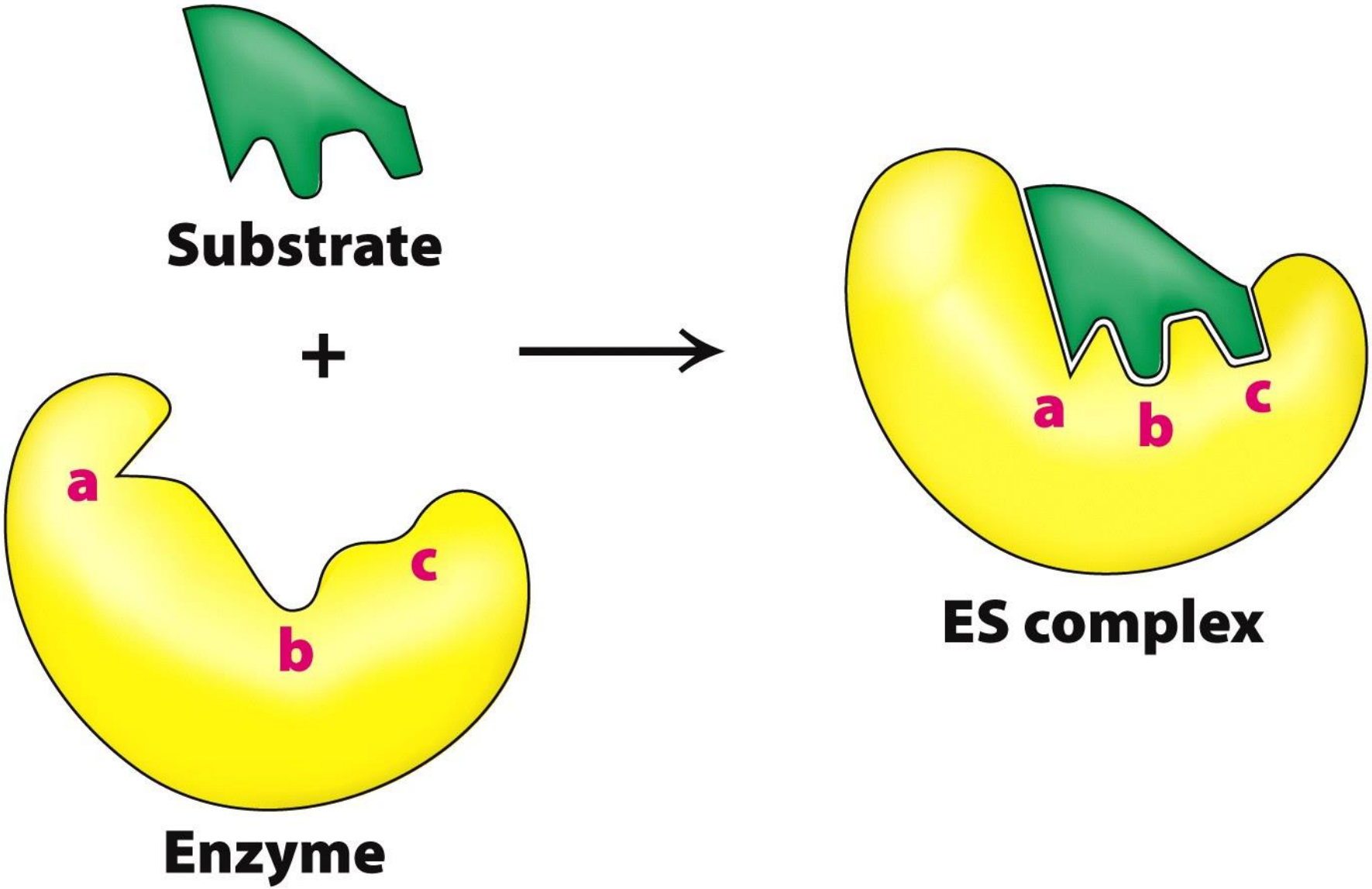
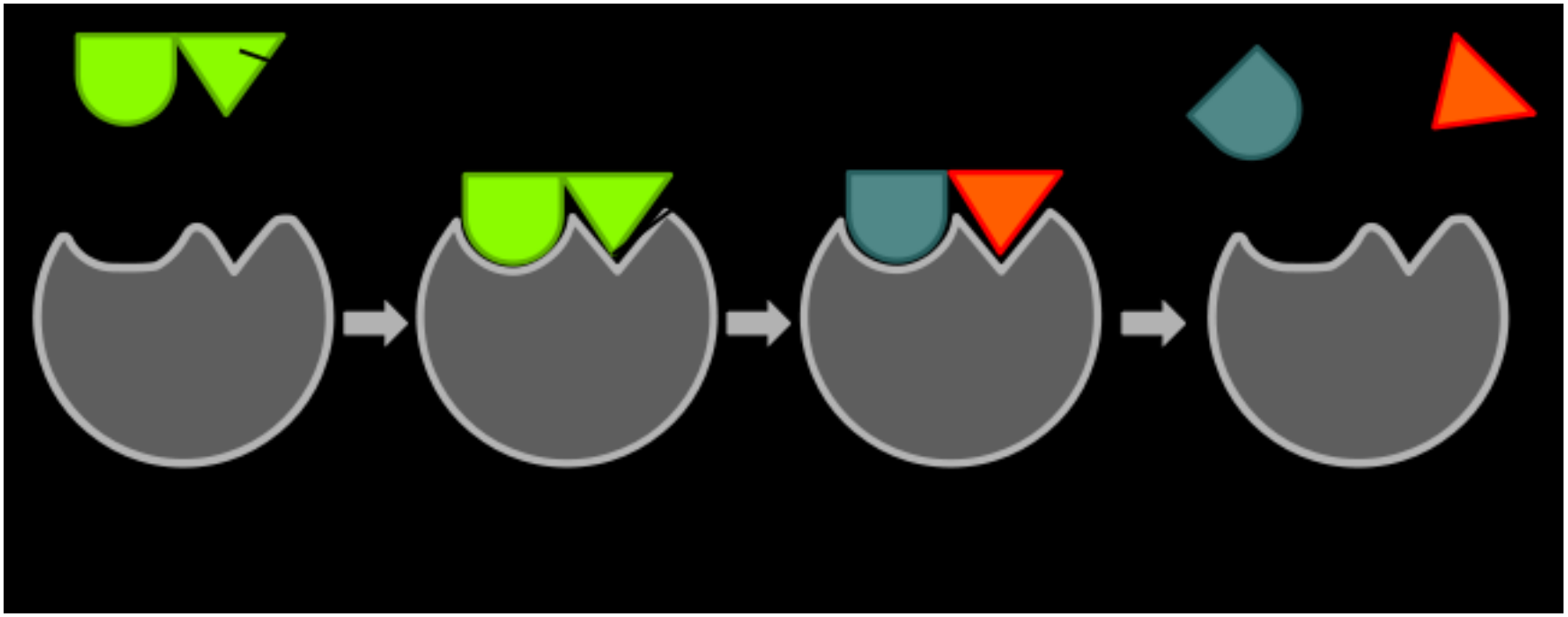
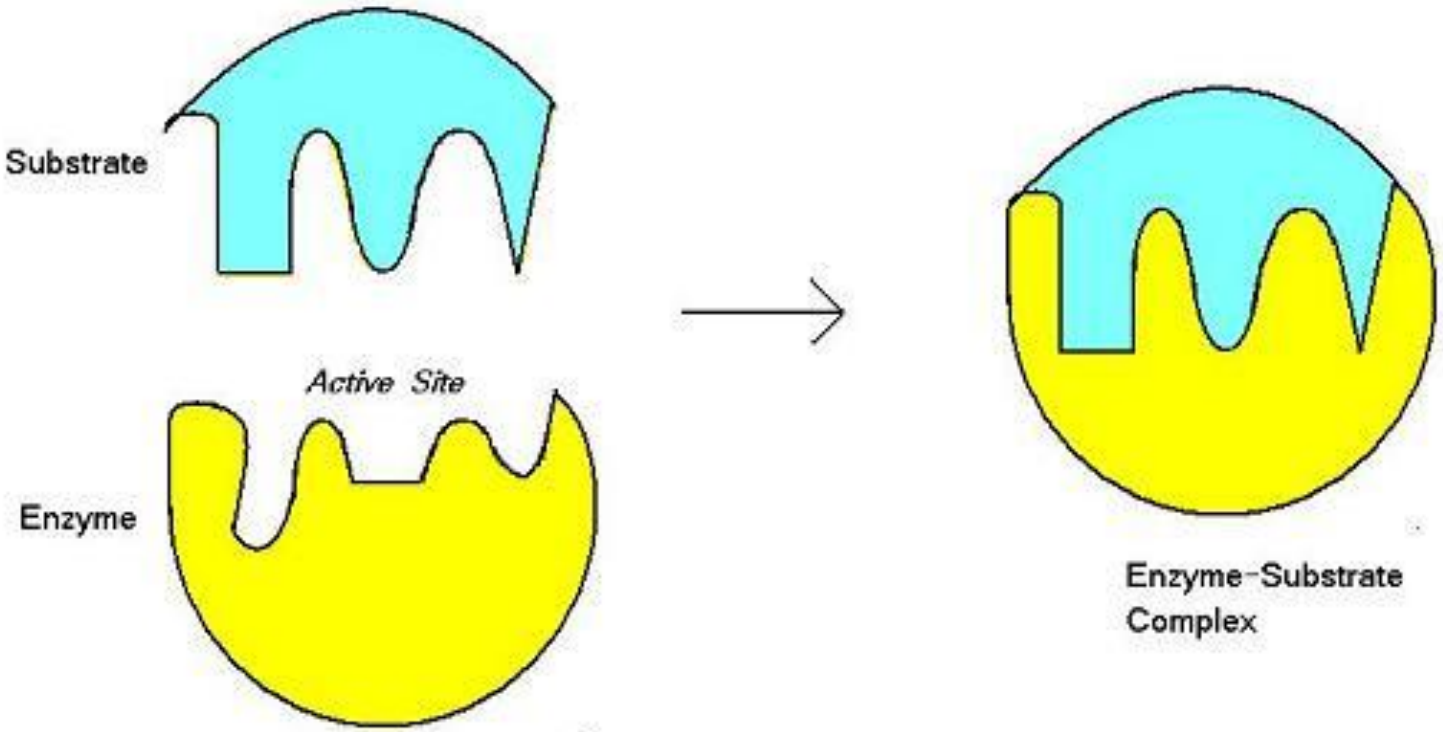
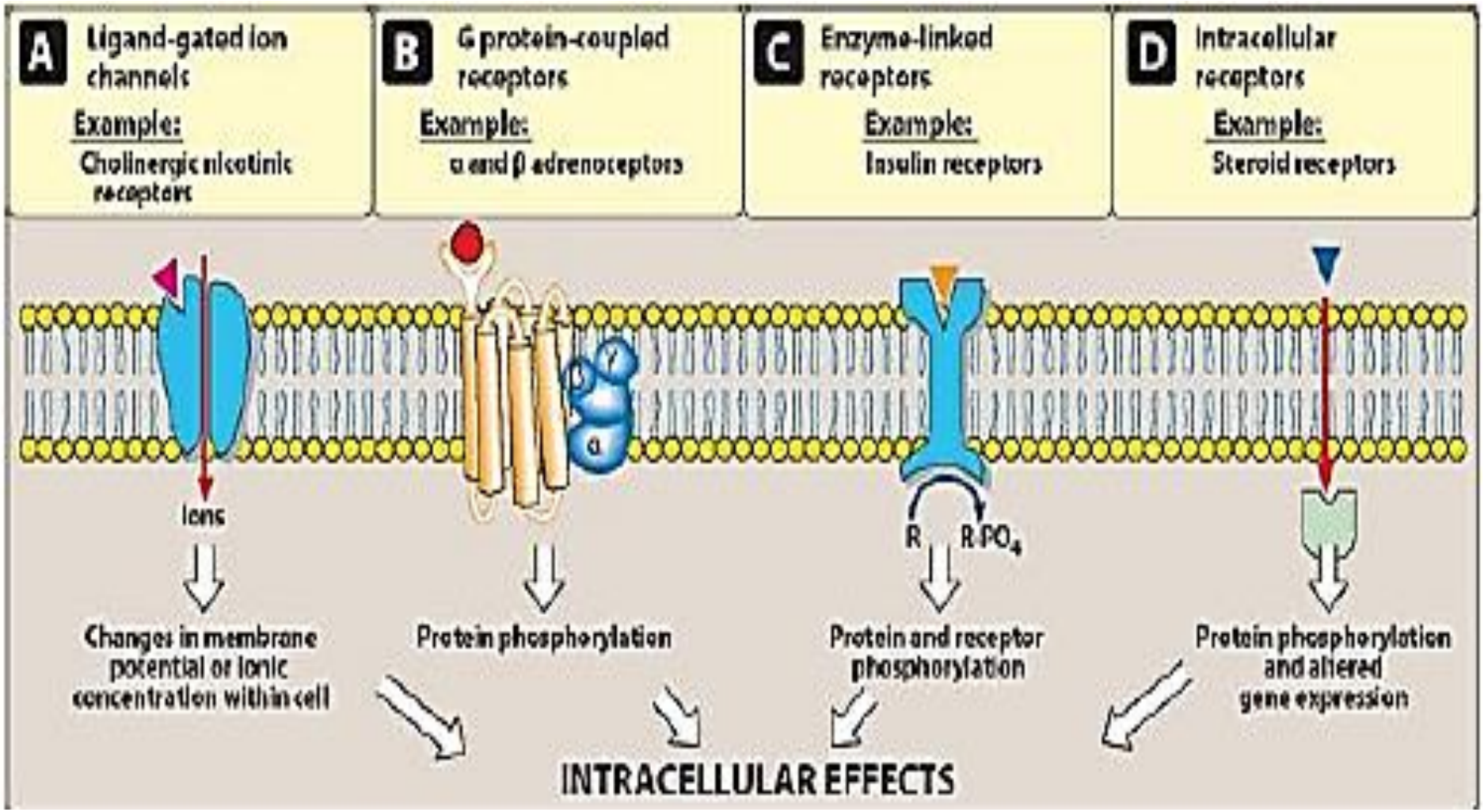


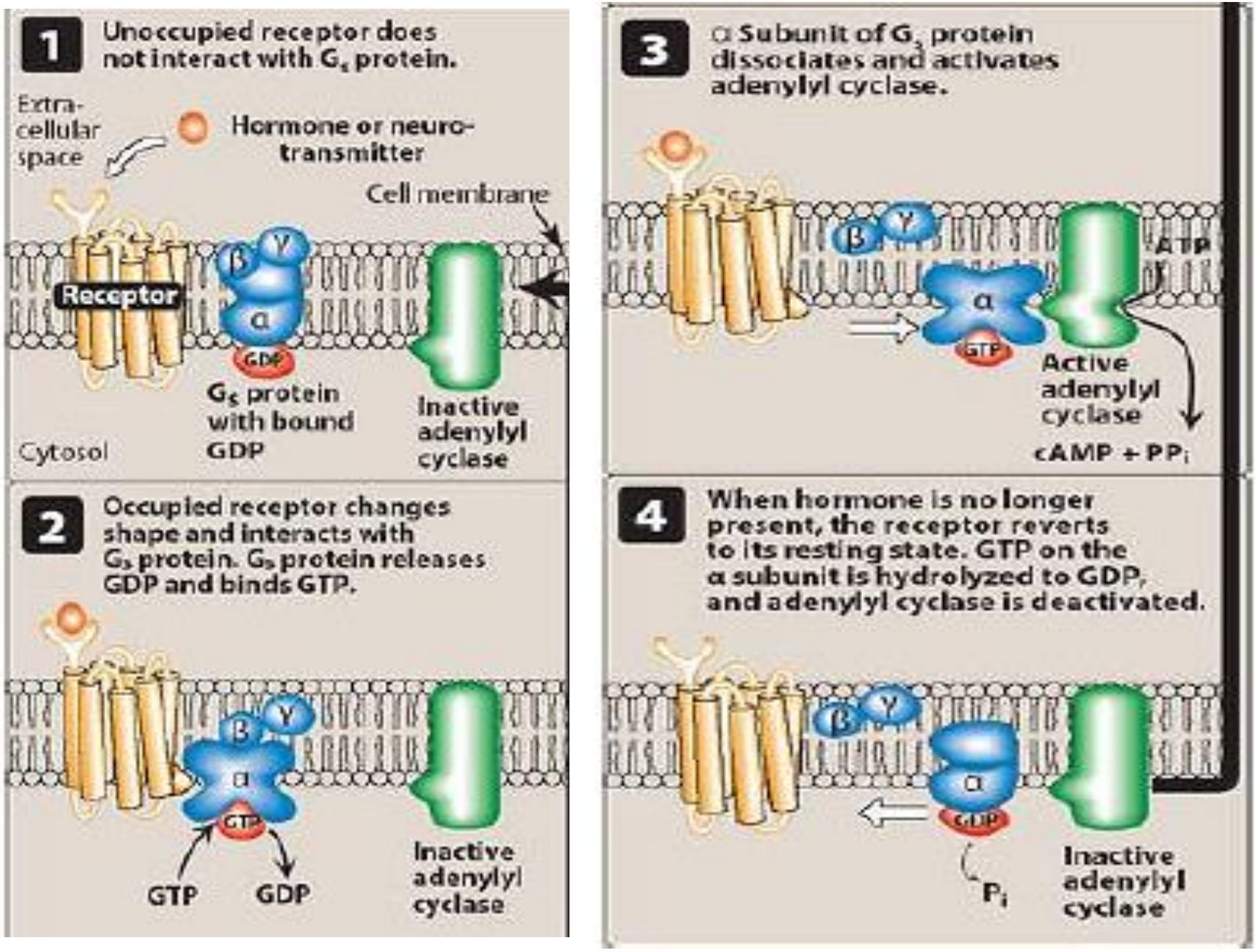
Figure 8.9
***Biochemistry*, Seventh Edition**

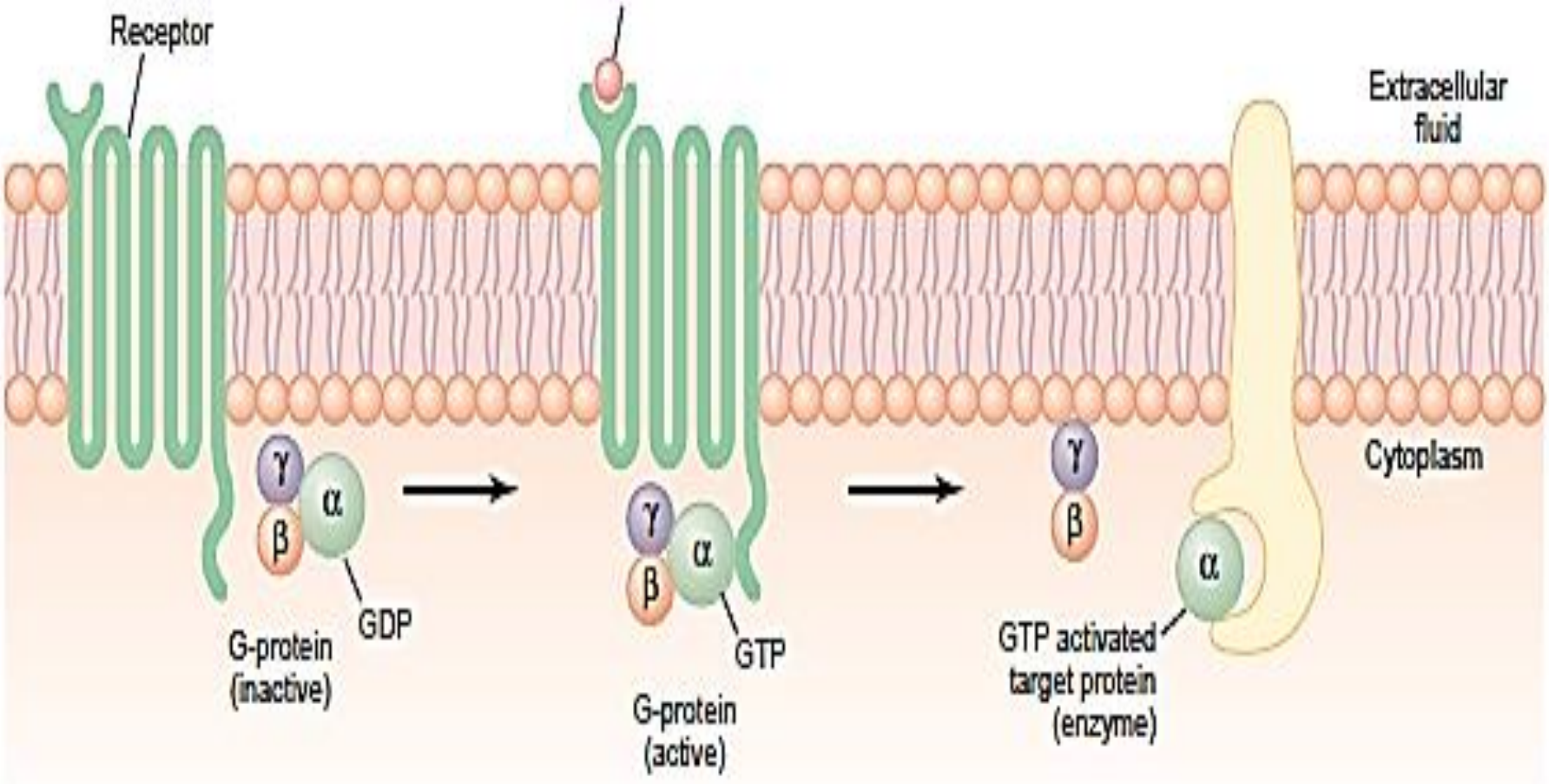


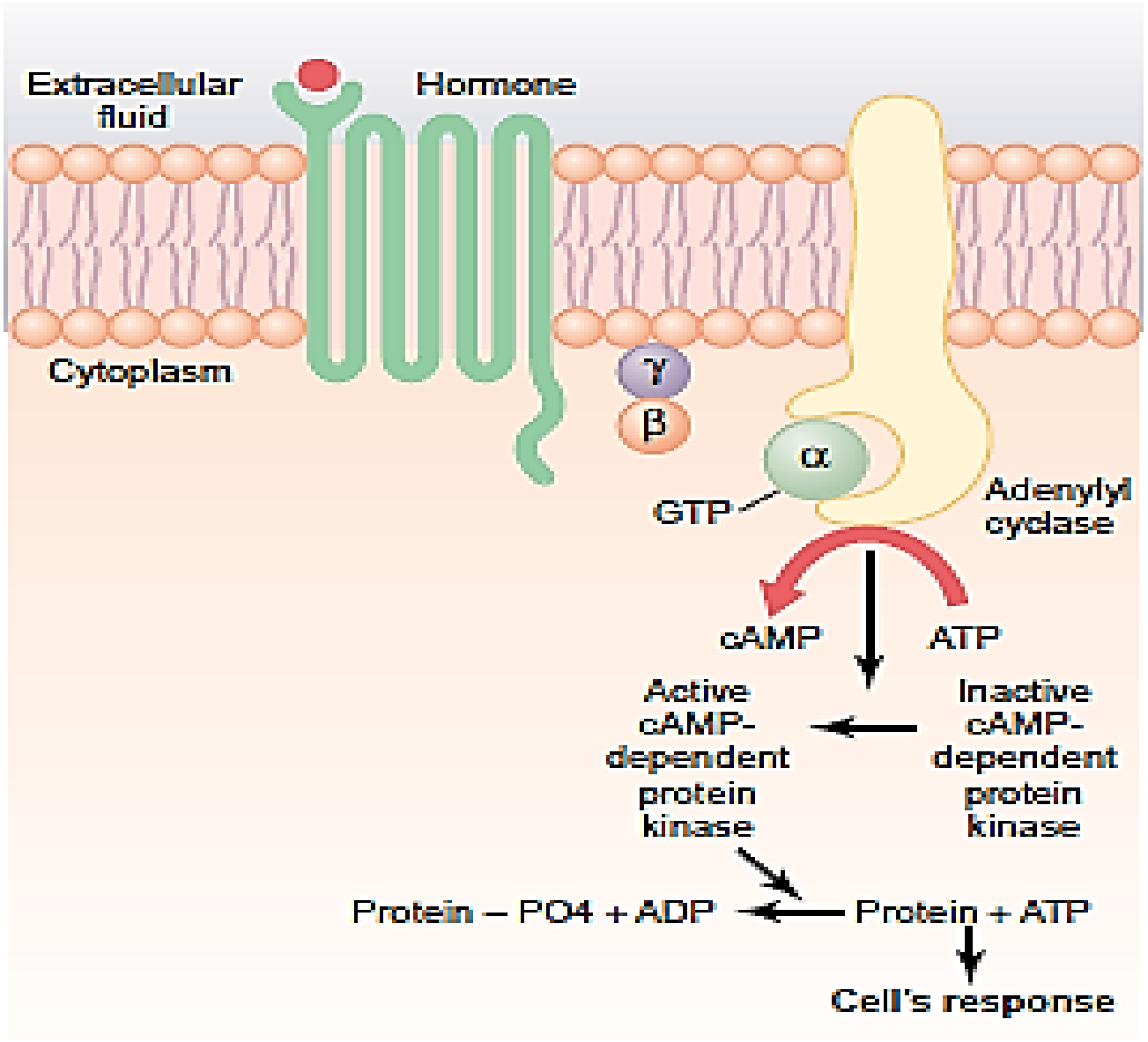


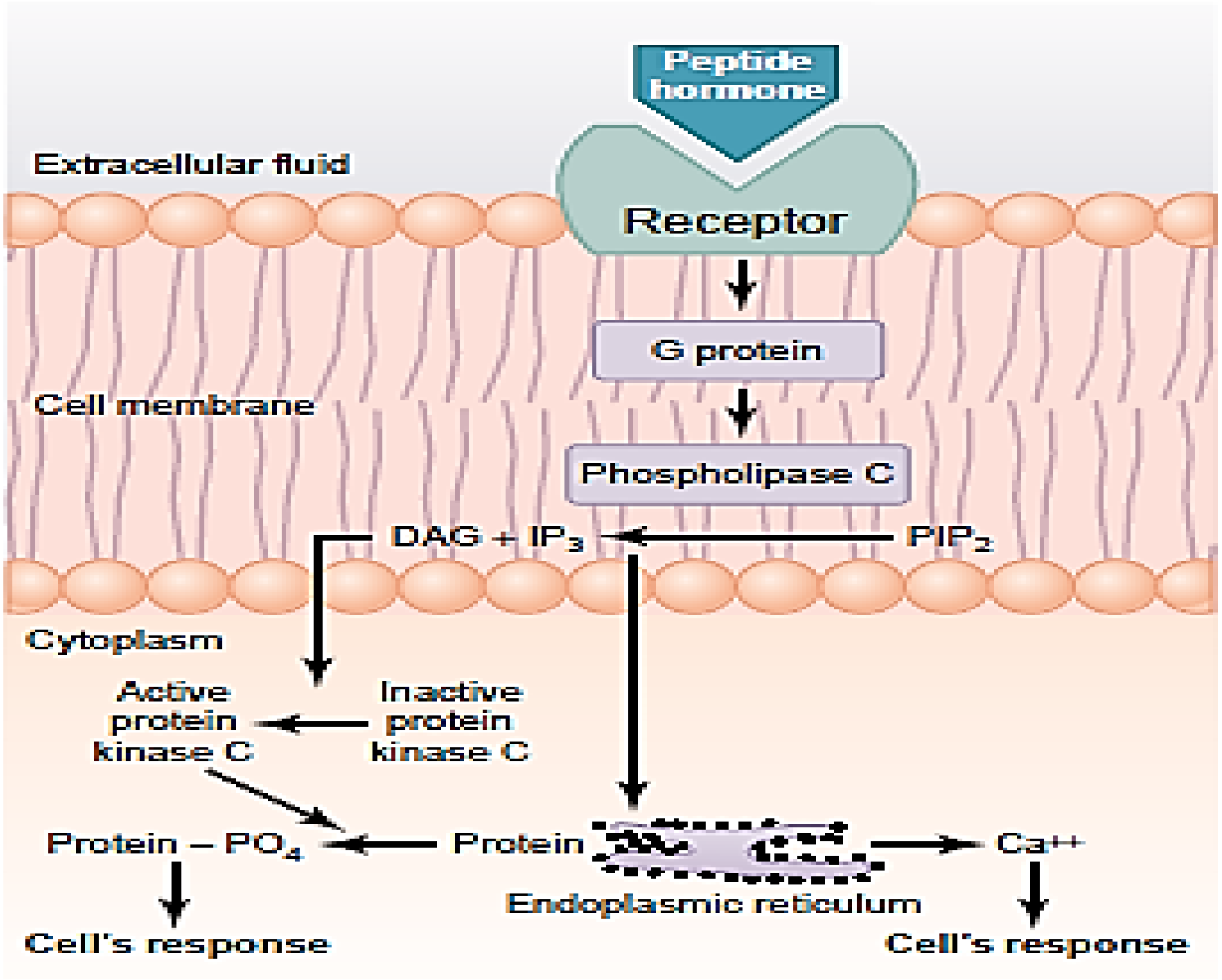
Induced-fit Model. - The enzyme active site forms a complementary shape to the substrate after binding.

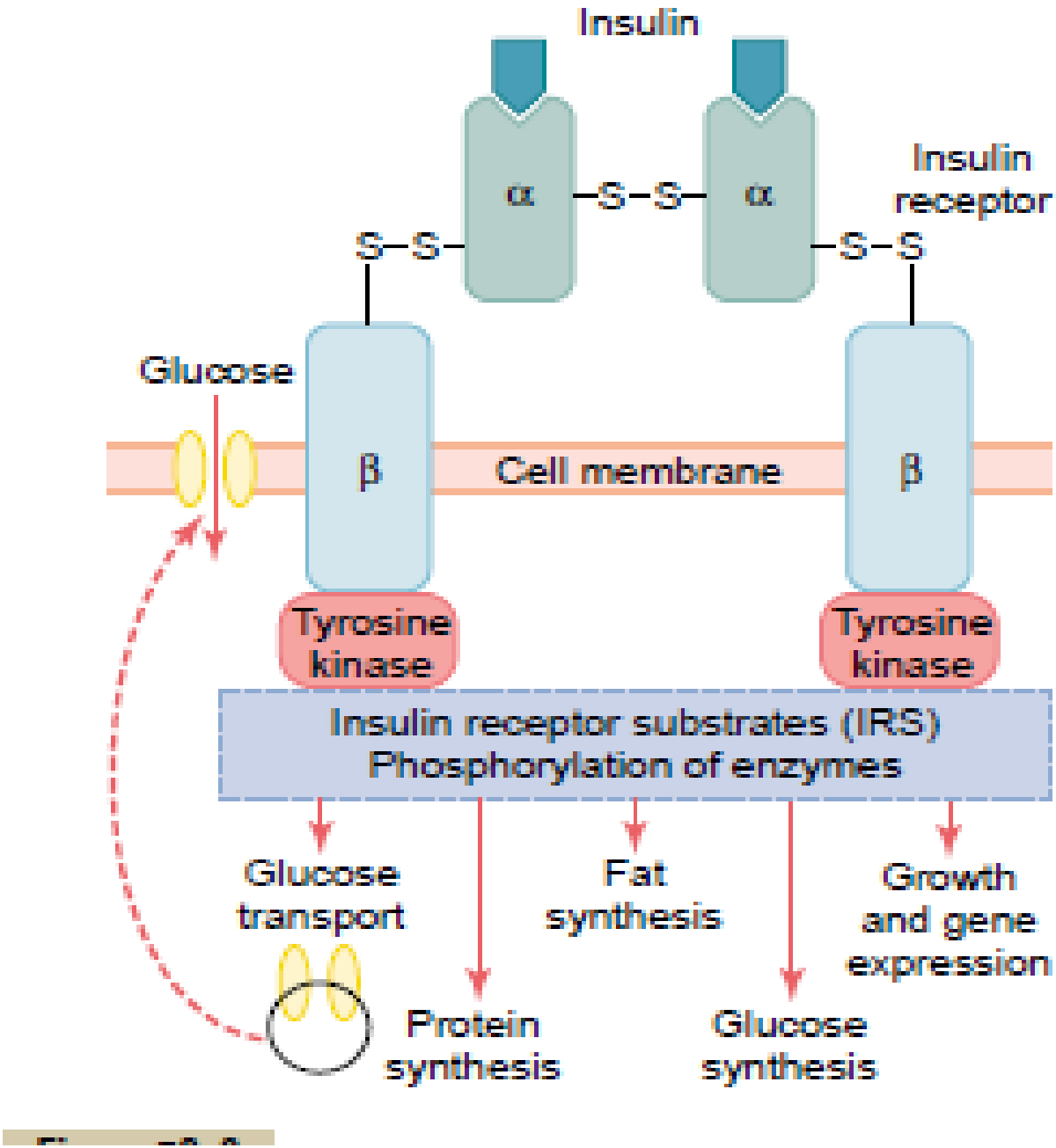

A
Ligand-gated ion channels
Example:
Cholinergic nicotinic receptors
B
G protein-coupled receptors
Example:
α and β adrenoceptors
C
Enzyme-linked receptors
Example:
Insulin receptors
D
Intracellular receptors
Example:
Steroid receptors
Ions
R
R·PO4
Changes in membrane potential or ionic concentration within cell
Protein phosphorylation
Protein and receptor phosphorylation
Protein phosphorylation and altered gene expression
INTRACELLULAR EFFECTS

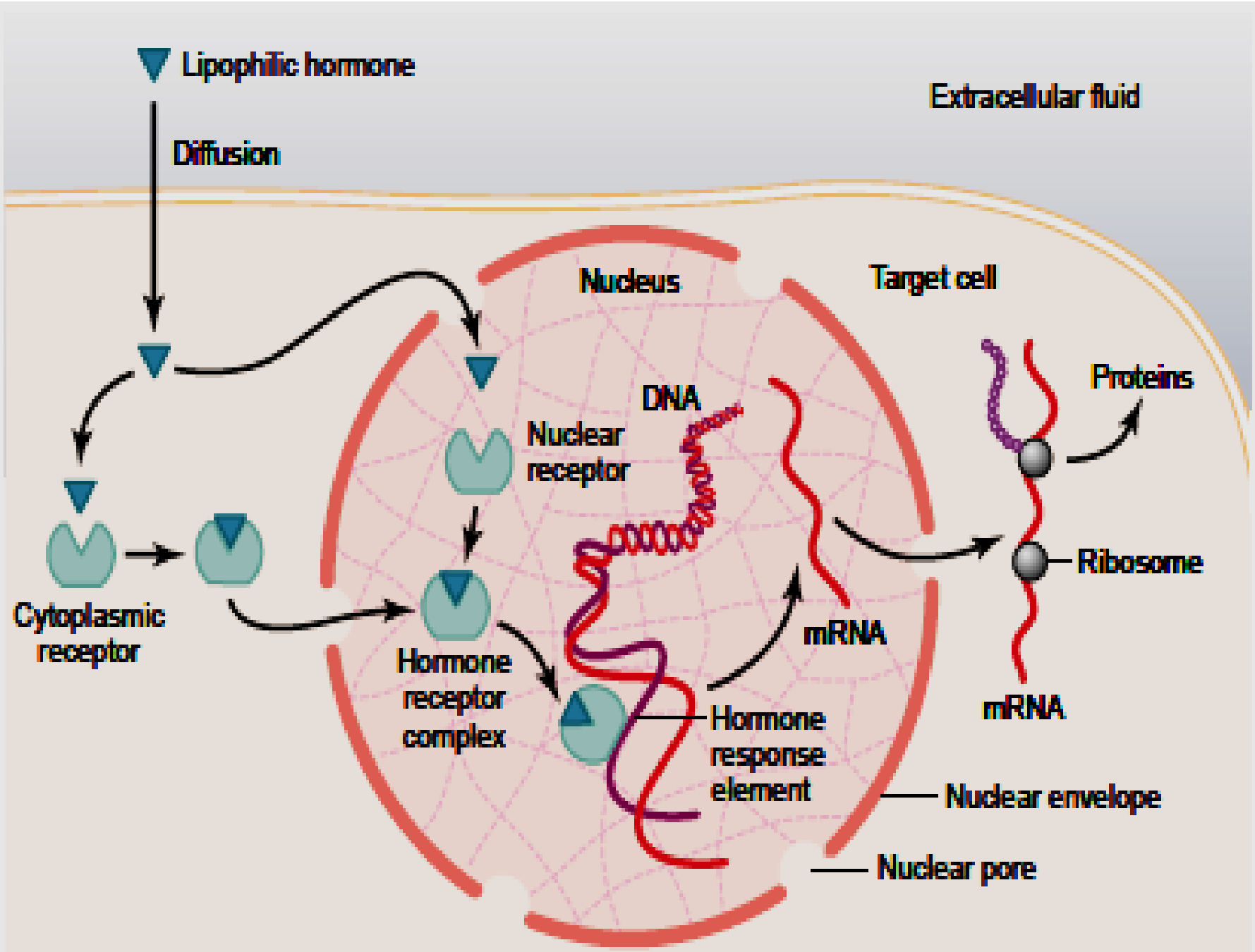

1
Unoccupied receptor does not interact with G_s protein.
Extra-cellular space
Hormone or neuro-transmitter
Cell membrane
Receptor
β
γ
α
GDP
G_s protein with bound GDP
Inactive adenylyl cyclase
Cytosol
2
Occupied receptor changes shape and interacts with G_s protein. G_s protein releases GDP and binds GTP.
GTP
GTP
GDP
Inactive adenylyl cyclase
3
α Subunit of G_s protein dissociates and activates adenylyl cyclase.
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.
GDP
P_i
Inactive adenylyl cyclase

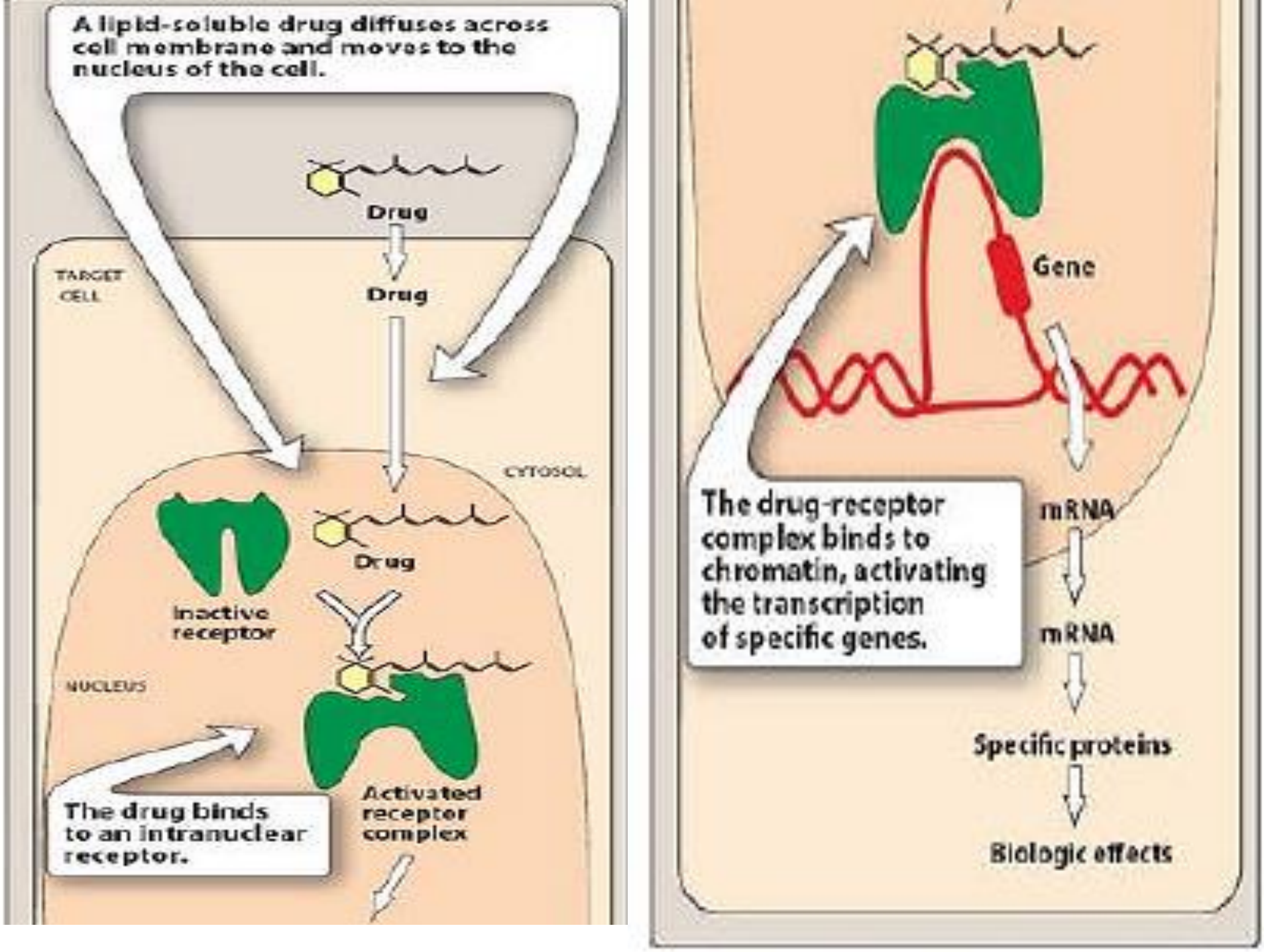

Receptor
Extracellular fluid
Cytoplasm
γ
β
α
GDP
G-protein (inactive)
γ
β
α
GTP
G-protein (active)
γ
β
α
GTP activated target protein (enzyme)


Extracellular fluid
Hormone
Cytoplasm
γ
β
α
GTP
Adenylyl cyclase
cAMP
ATP
Active cAMP-dependent protein kinase
Inactive cAMP-dependent protein kinase
Protein – PO4 + ADP
Protein + ATP
Cell's response

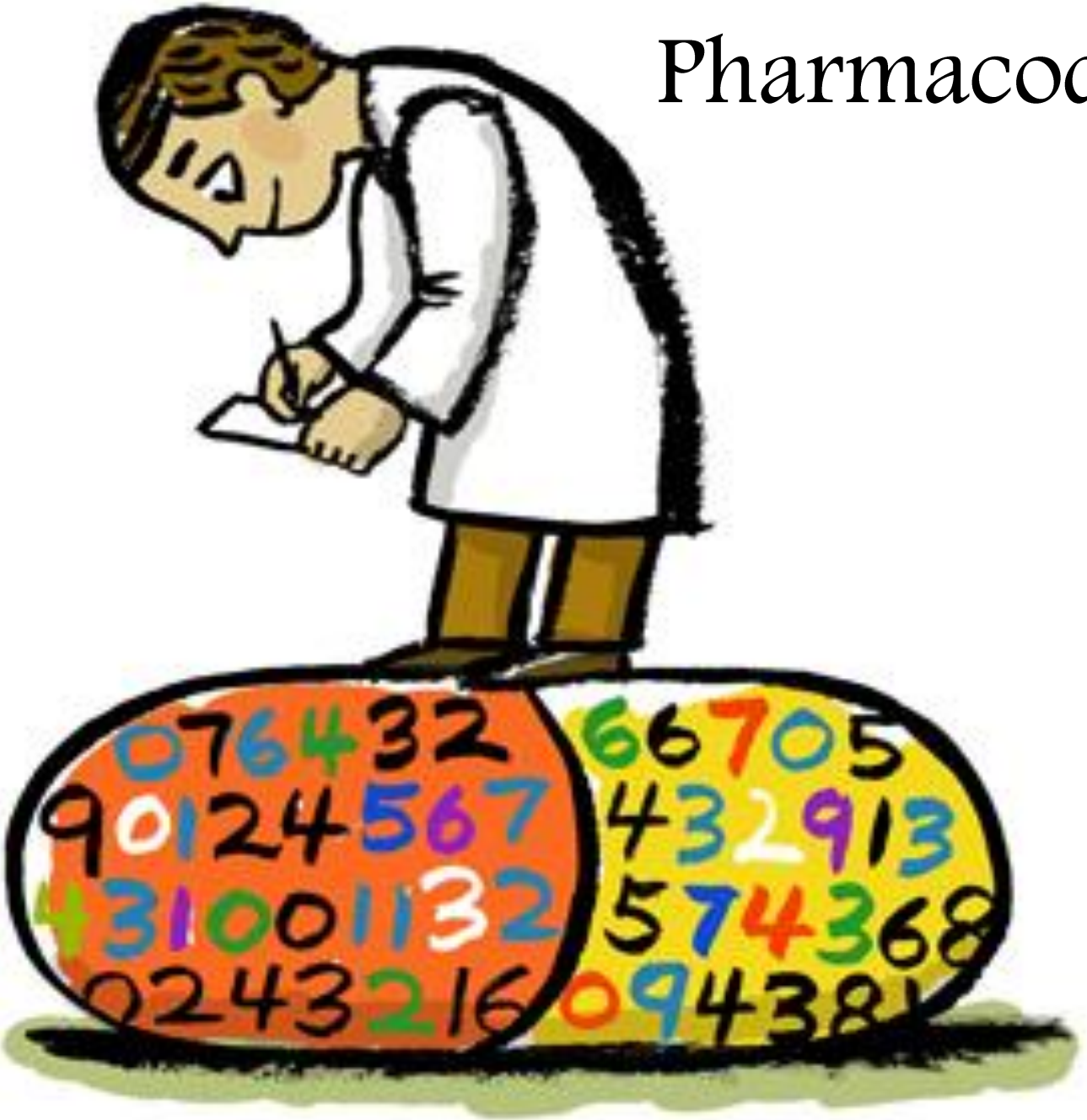

Peptide hormone
Extracellular fluid
Receptor
G protein
Cell membrane
Phospholipase C
DAG + IP3
PIP2
Cytoplasm
Active protein kinase C
Inactive protein kinase C
Protein – PO4
Protein
Ca++
Endoplasmic reticulum
Cell's response
Cell's response

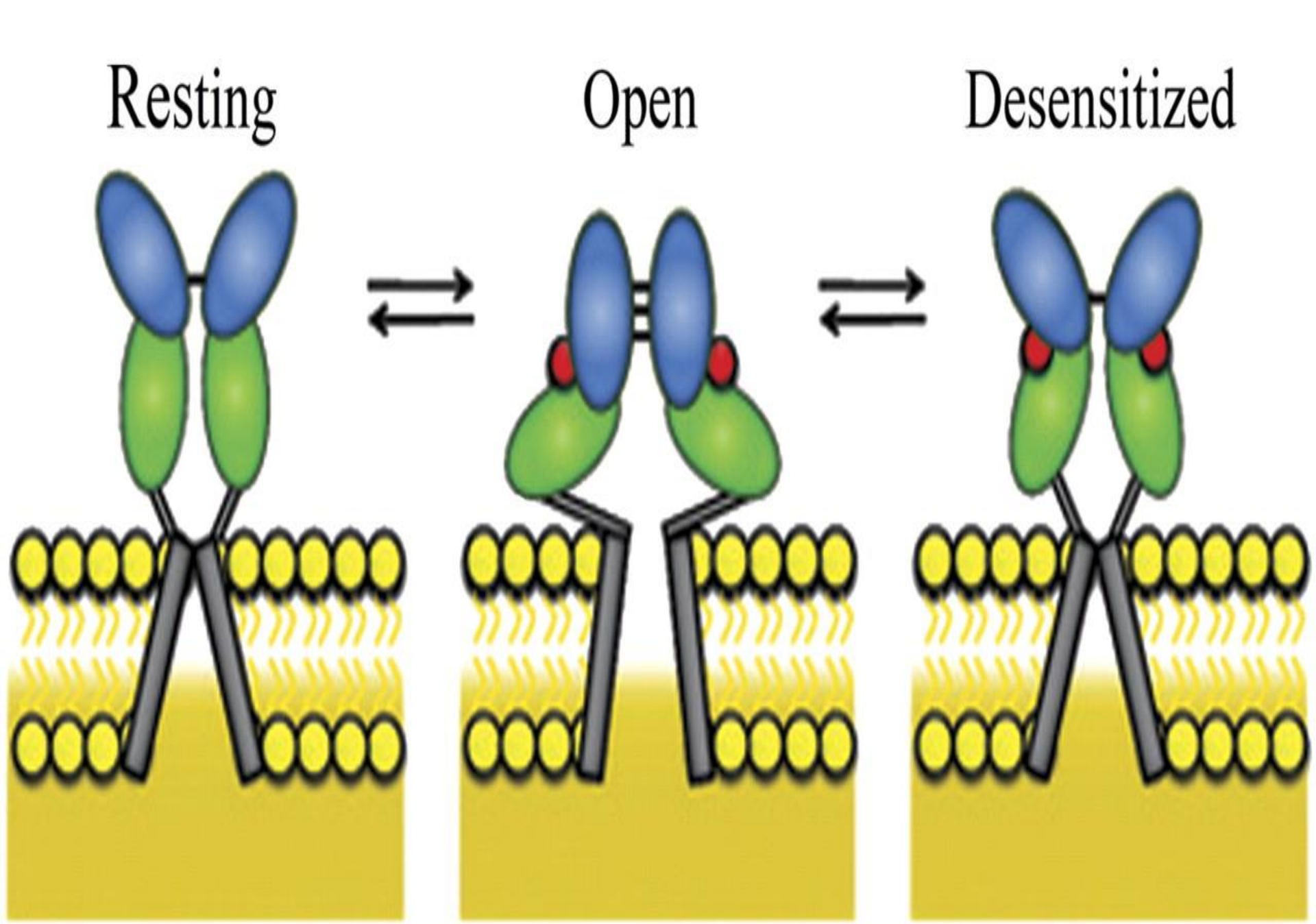

Insulin
α
S–S
α
Insulin receptor
S–S
S–S
Glucose
β
Cell membrane
β
Tyrosine kinase
Tyrosine kinase
Insulin receptor substrates (IRS)
Phosphorylation of enzymes
Glucose transport
Protein synthesis
Fat synthesis
Glucose synthesis
Growth and gene expression

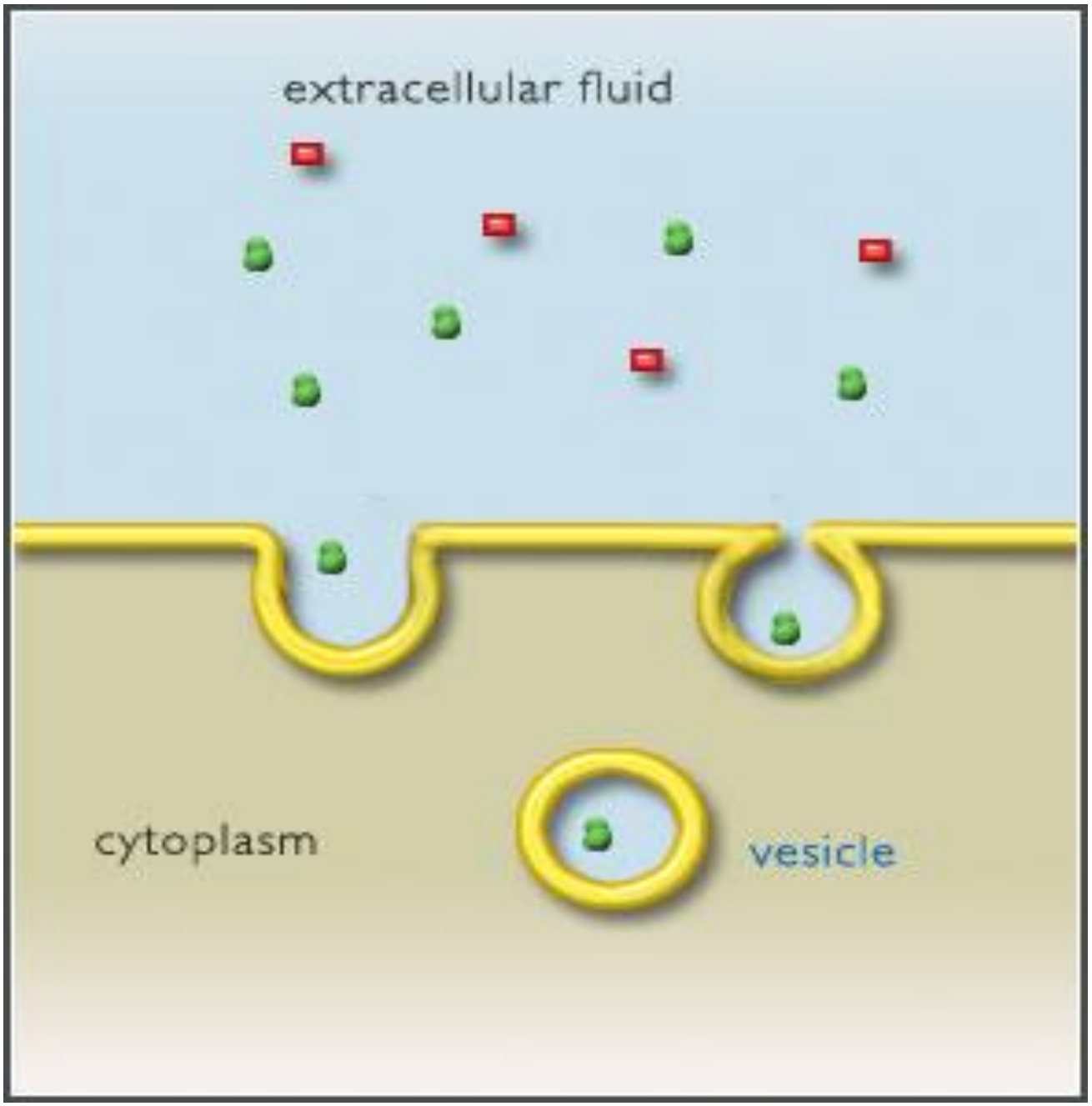

Lipophilic hormone
Diffusion
Extracellular fluid
Nucleus
Target cell
DNA
Nuclear receptor
Proteins
Ribosome
Cytoplasmic receptor
Hormone receptor complex
mRNA
mRNA
Hormone response element
Nuclear envelope
Nuclear pore

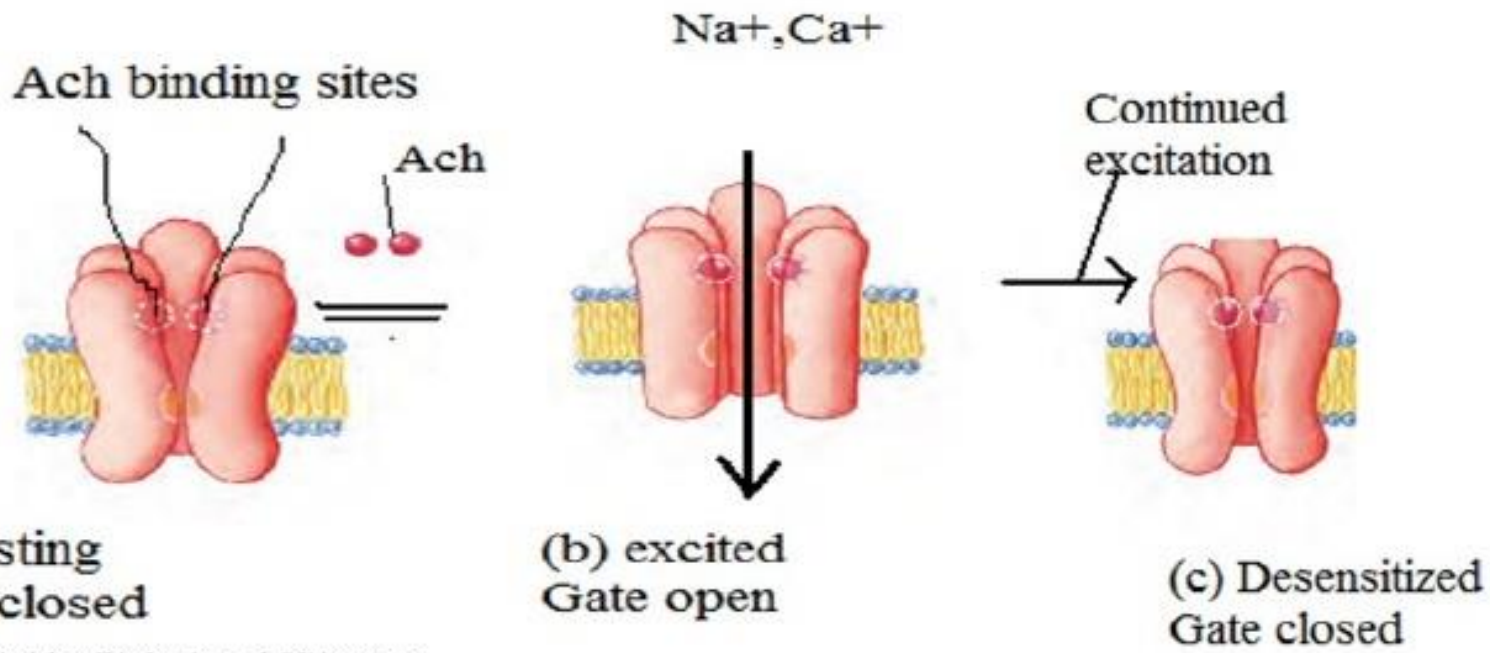

A lipid-soluble drug diffuses across cell membrane and moves to the nucleus of the cell.
Drug
Drug
TARGET CELL
CYTOSOL
Drug
Inactive receptor
NUCLEUS
The drug binds to an intranuclear receptor.
Activated receptor complex
Gene
The drug-receptor complex binds to chromatin, activating the transcription of specific genes.
mRNA
mRNA
Specific proteins
Biologic effects

Pharmacodynamics



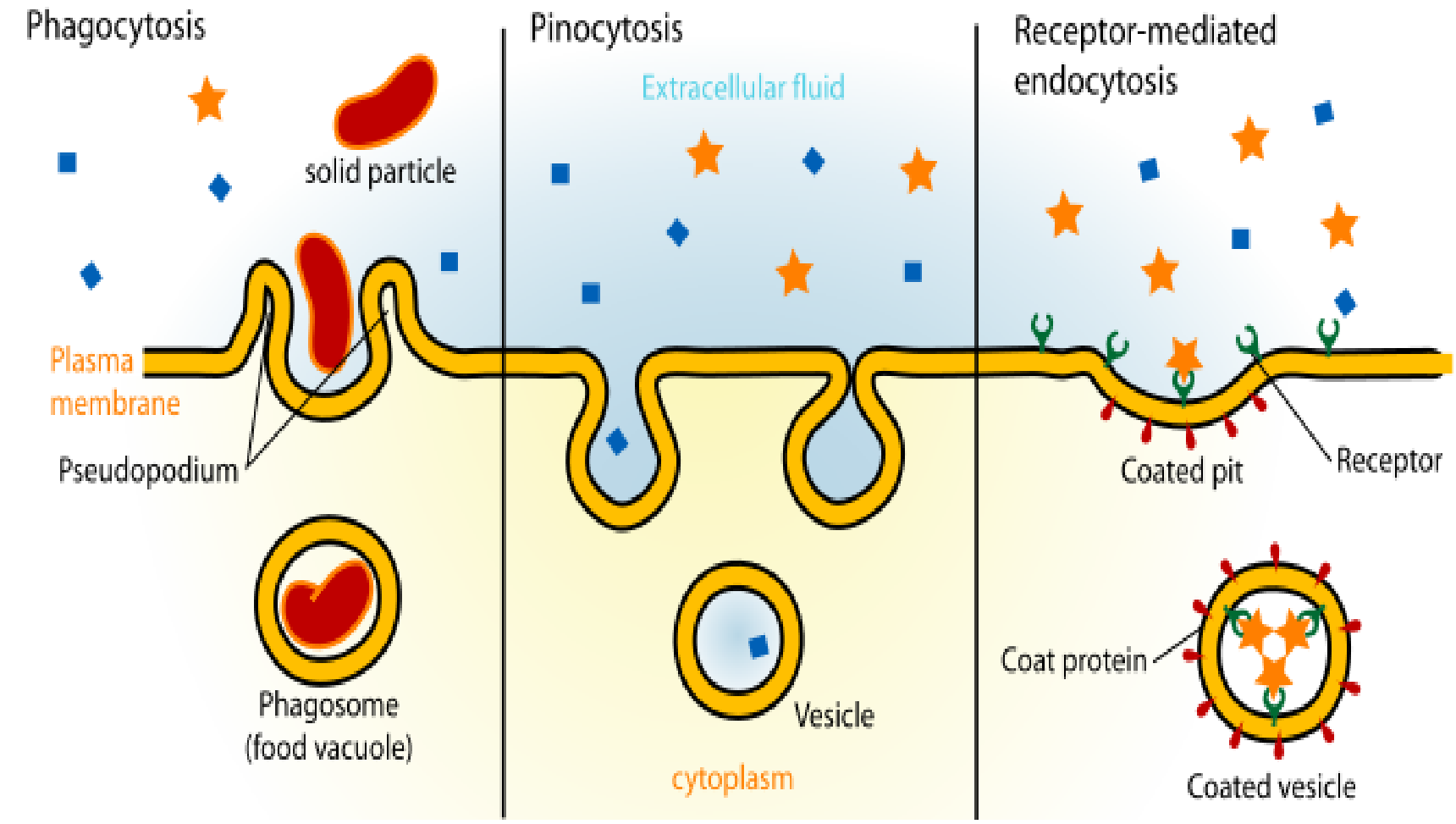

Resting
Open
Desensitized

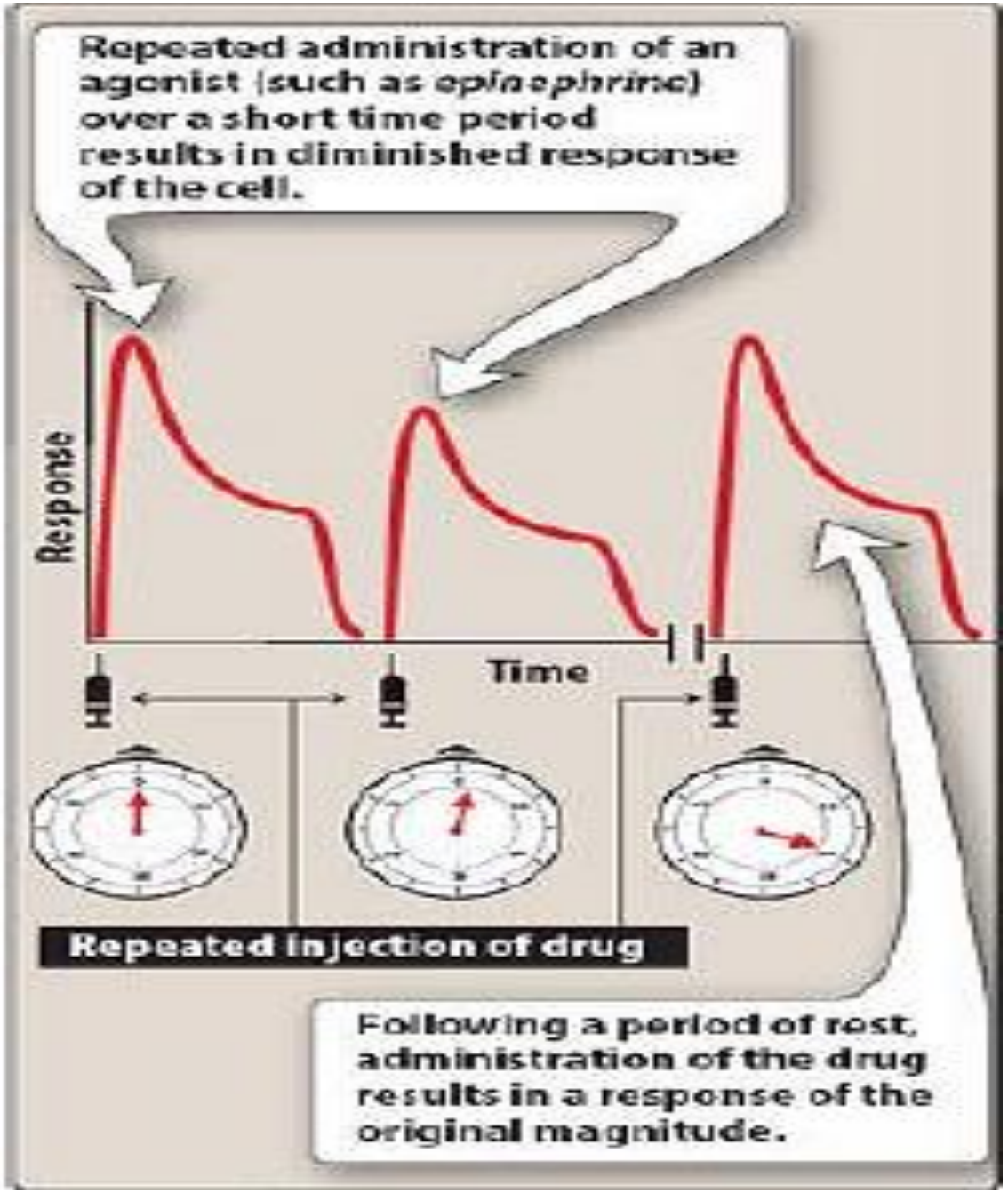

extracellular fluid
cytoplasm
vesicle

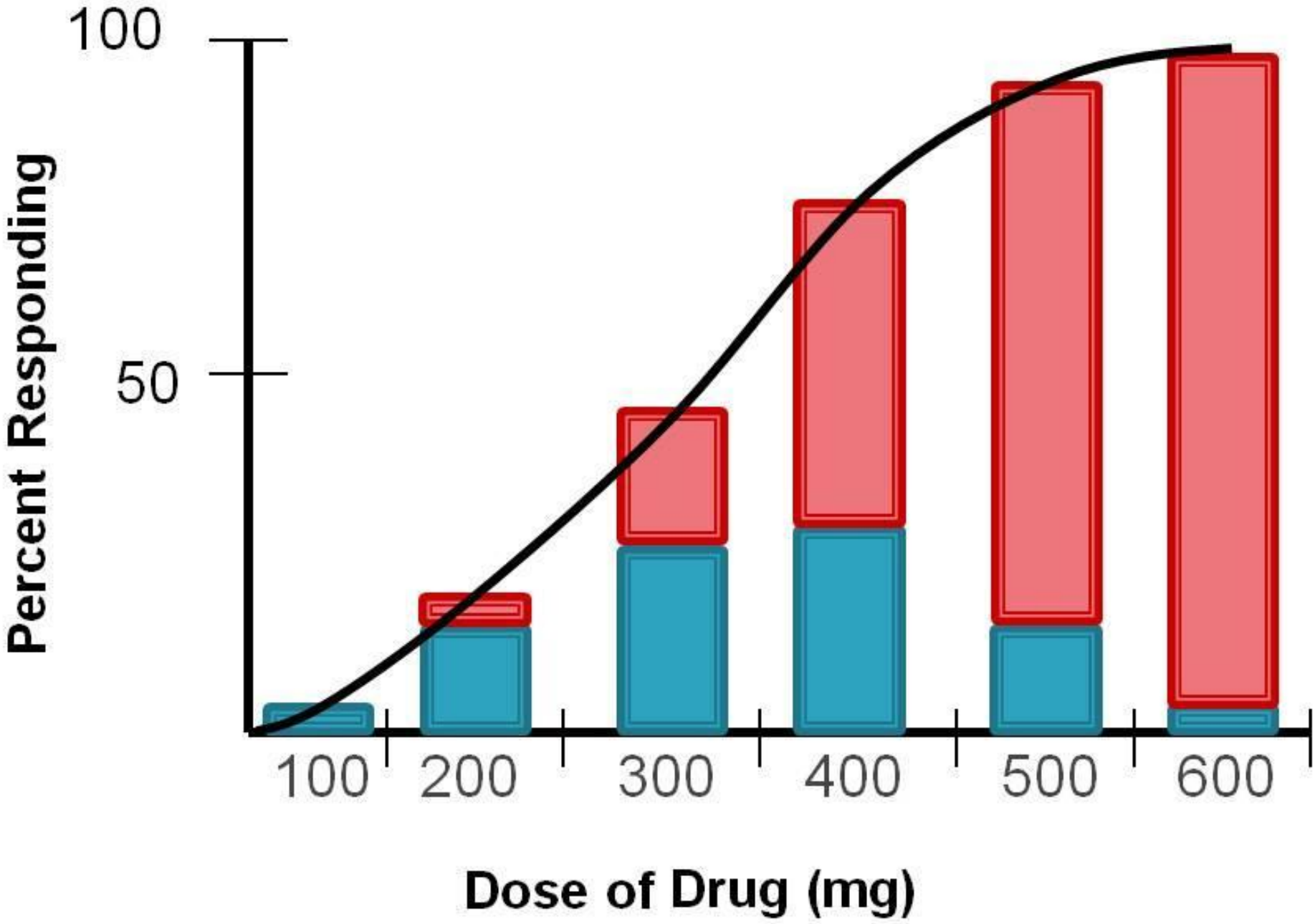


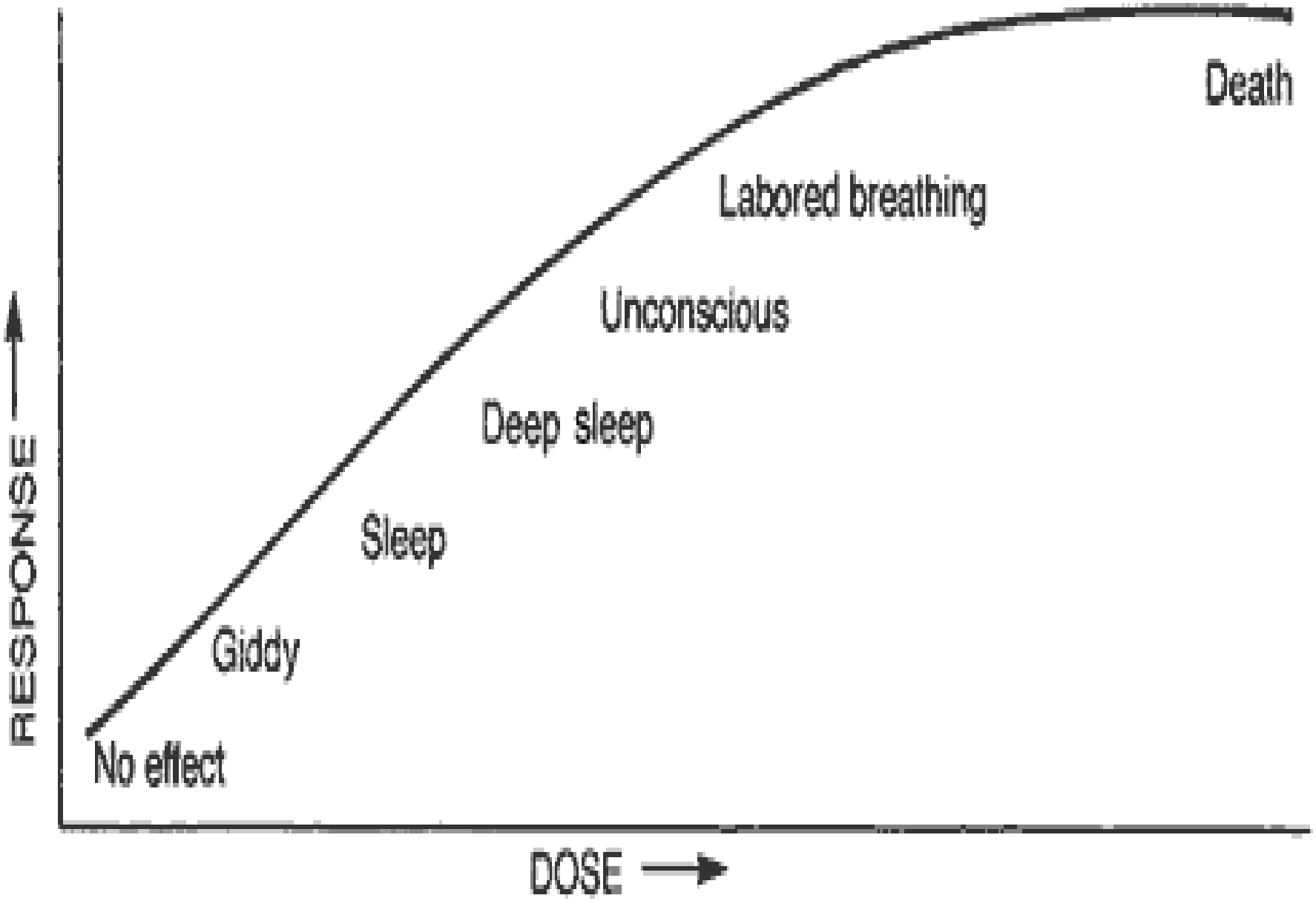
Lehninger principles of biochemistry 4th Edition pg.427

Endocytosis

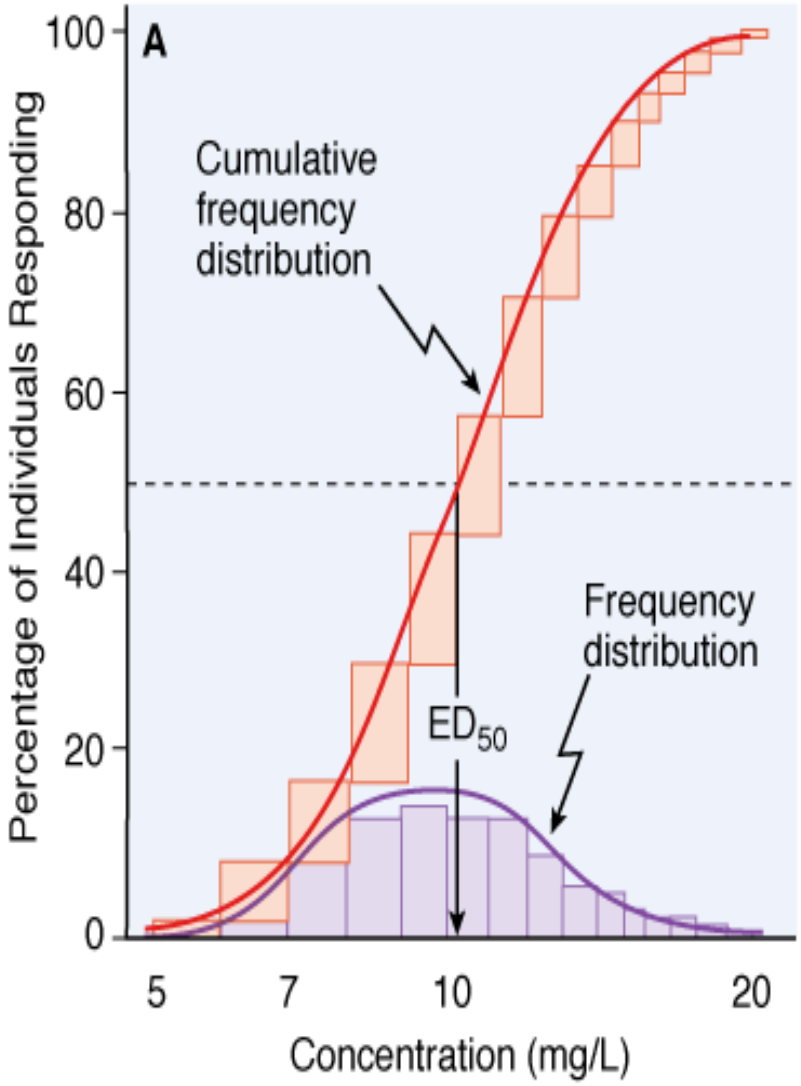


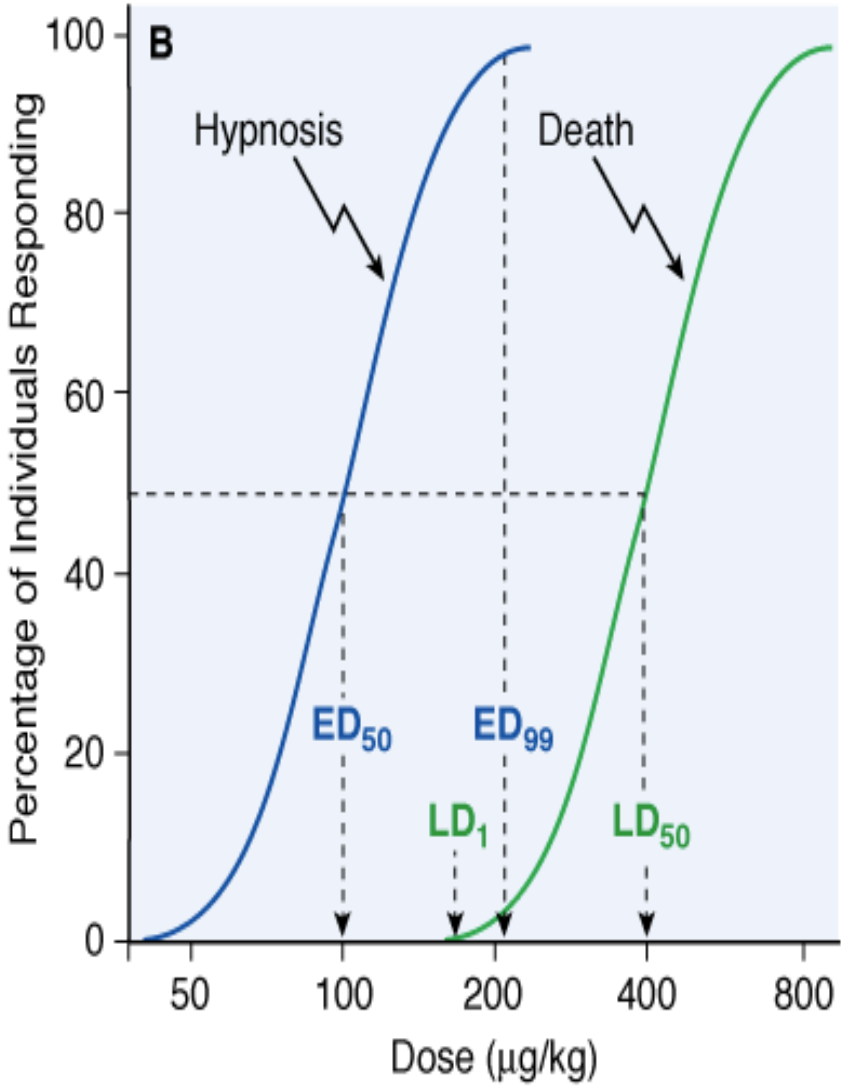

Repeated administration of an agonist (such as *epinephrine*) over a short time period results in diminished response of the cell.
Response
Time
Repeated injection of drug
Following a period of rest, administration of the drug results in a response of the original magnitude.

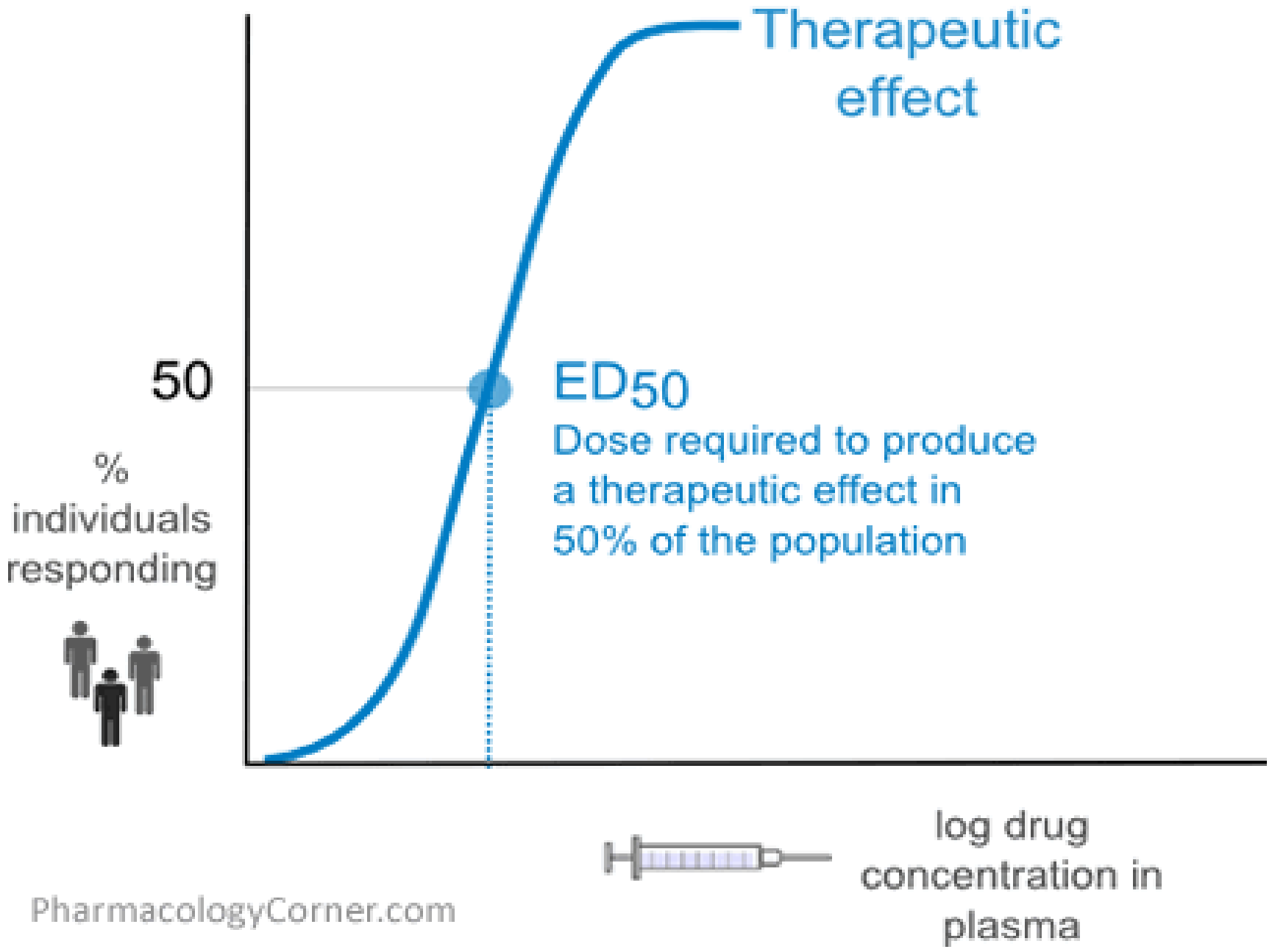

100
50
Percent Responding
100
200
300
400
500
600
Dose of Drug (mg)

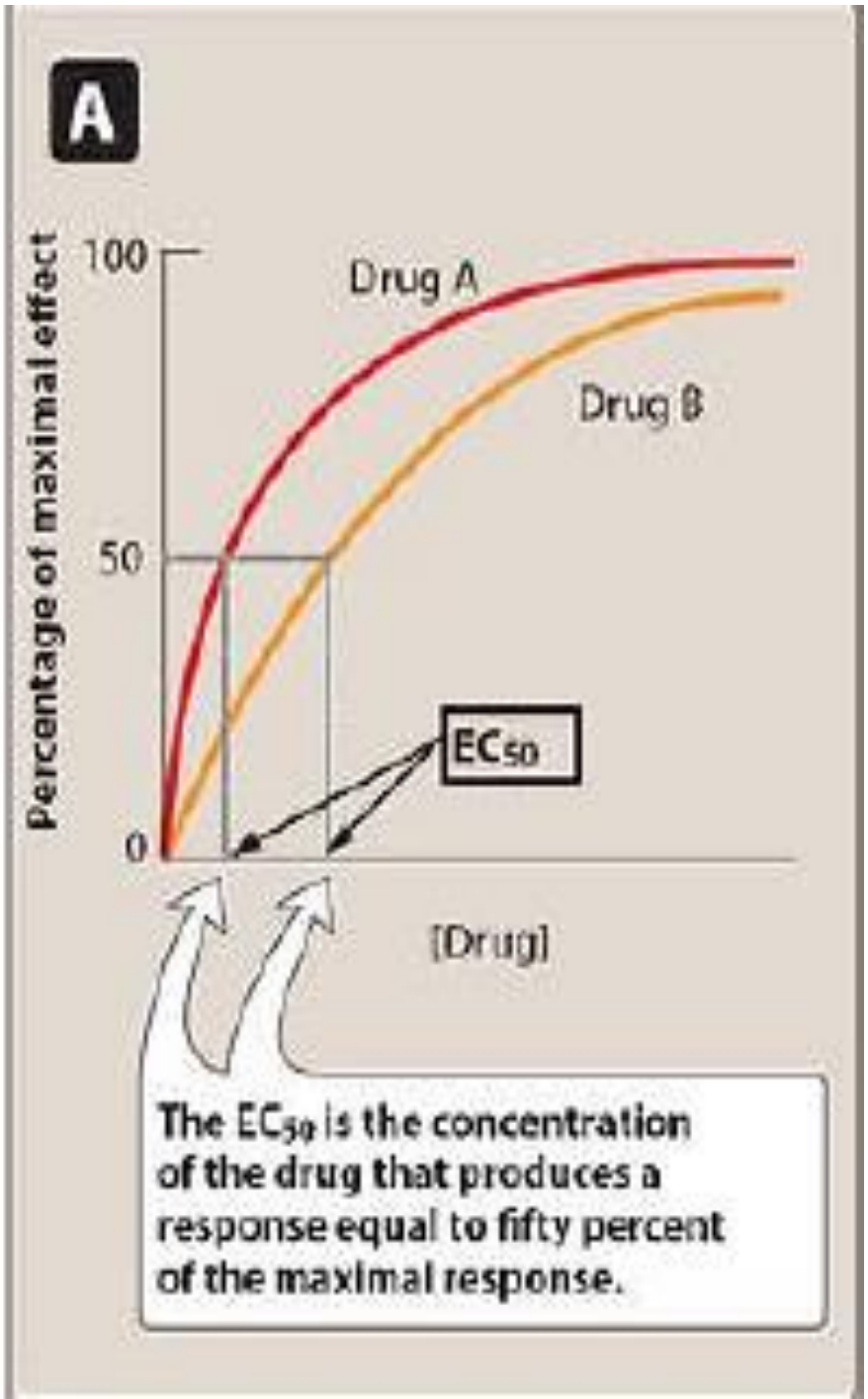

Death
Labored breathing
Unconscious
Deep sleep
Sleep
Giddy
No effect
RESPONSE
DOSE

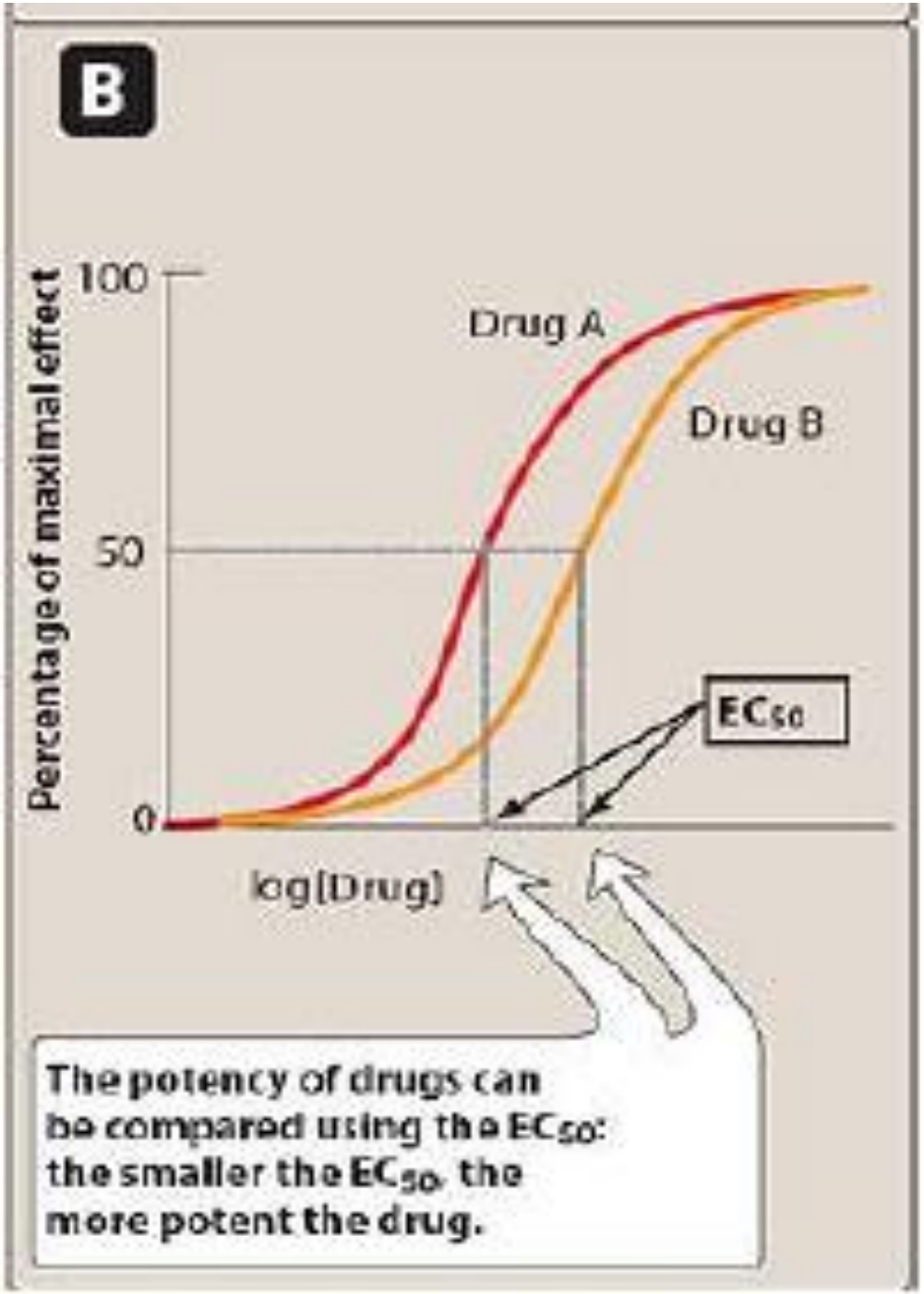
Therapeutic Index: $\frac{LD_{50}}{ED_{50}} = \frac{400}{100} = 4$






Therapeutic effect
50
ED50
Dose required to produce a therapeutic effect in 50% of the population
% individuals responding
log drug concentration in plasma
PharmacologyCorner.com

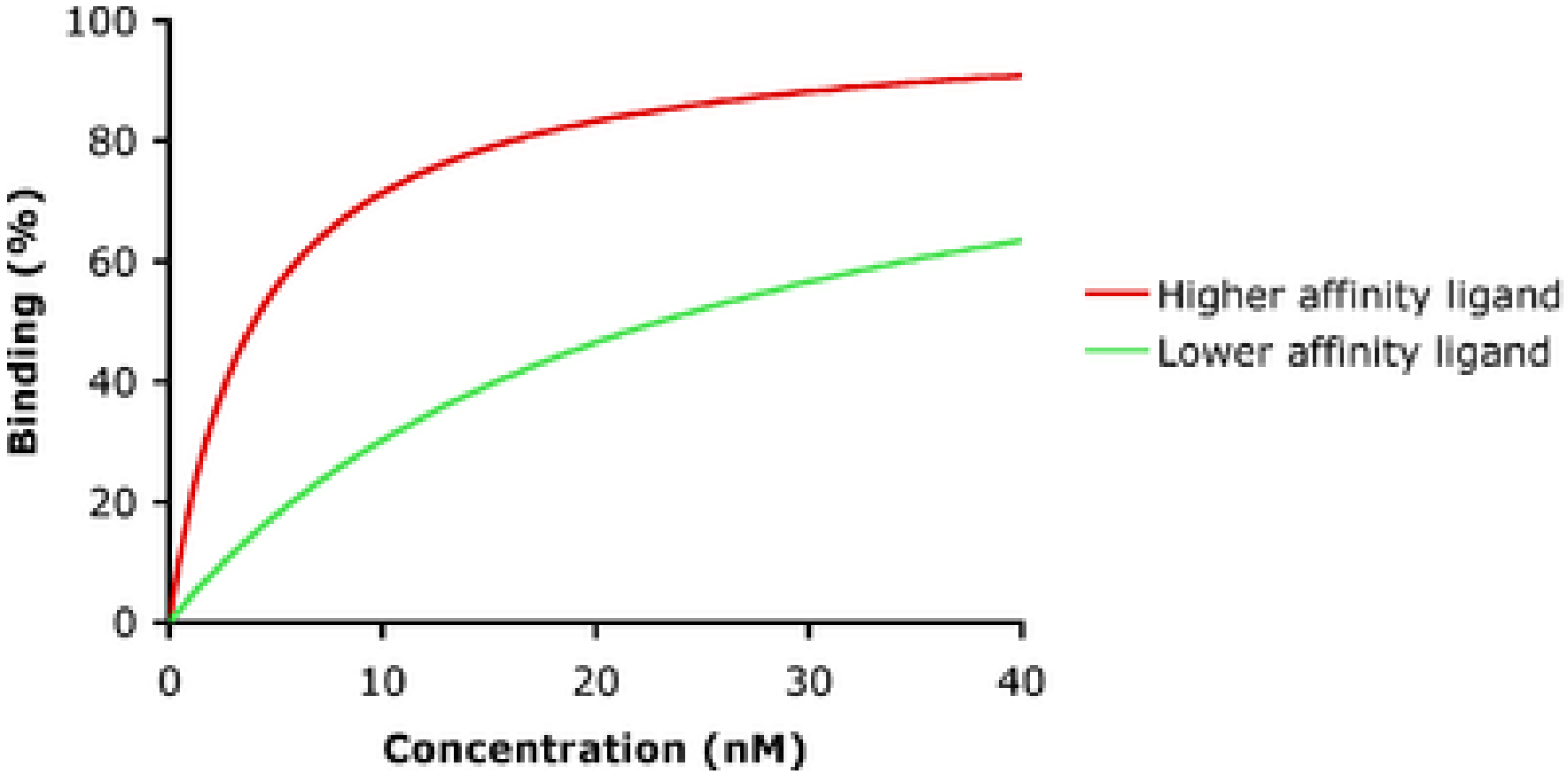

A
100
50
0
Percentage of maximal effect
Drug A
Drug B
EC50
[Drug]
The EC50 is the concentration of the drug that produces a response equal to fifty percent of the maximal response.

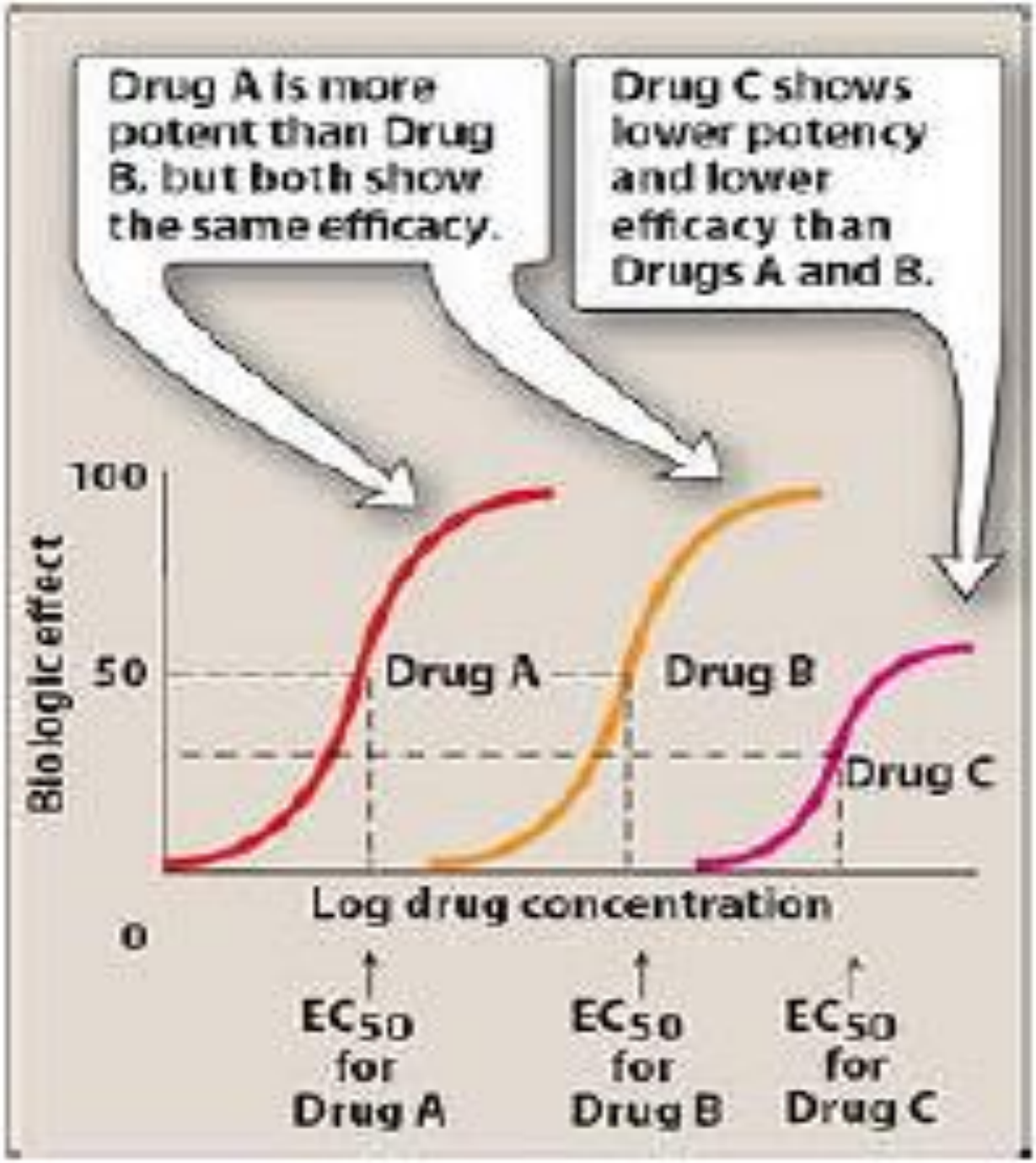

B
100
50
0
Percentage of maximal effect
Drug A
Drug B
EC50
log[Drug]
The potency of drugs can be compared using the EC50: the smaller the EC50, the more potent the drug.

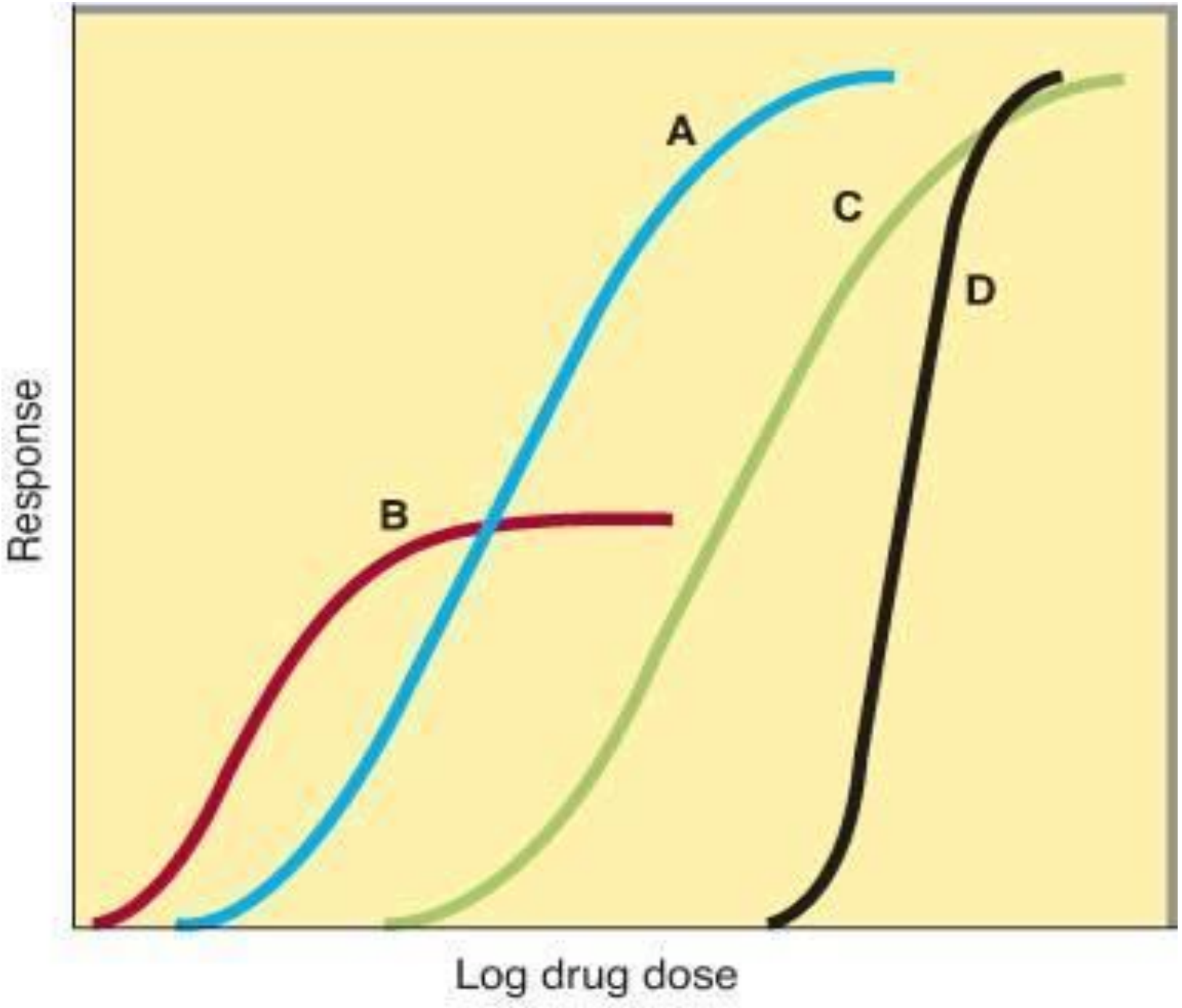
Drug - Receptor Binding

Affinity – measure of propensity of a drug to bind receptor; the attractiveness of drug and receptor

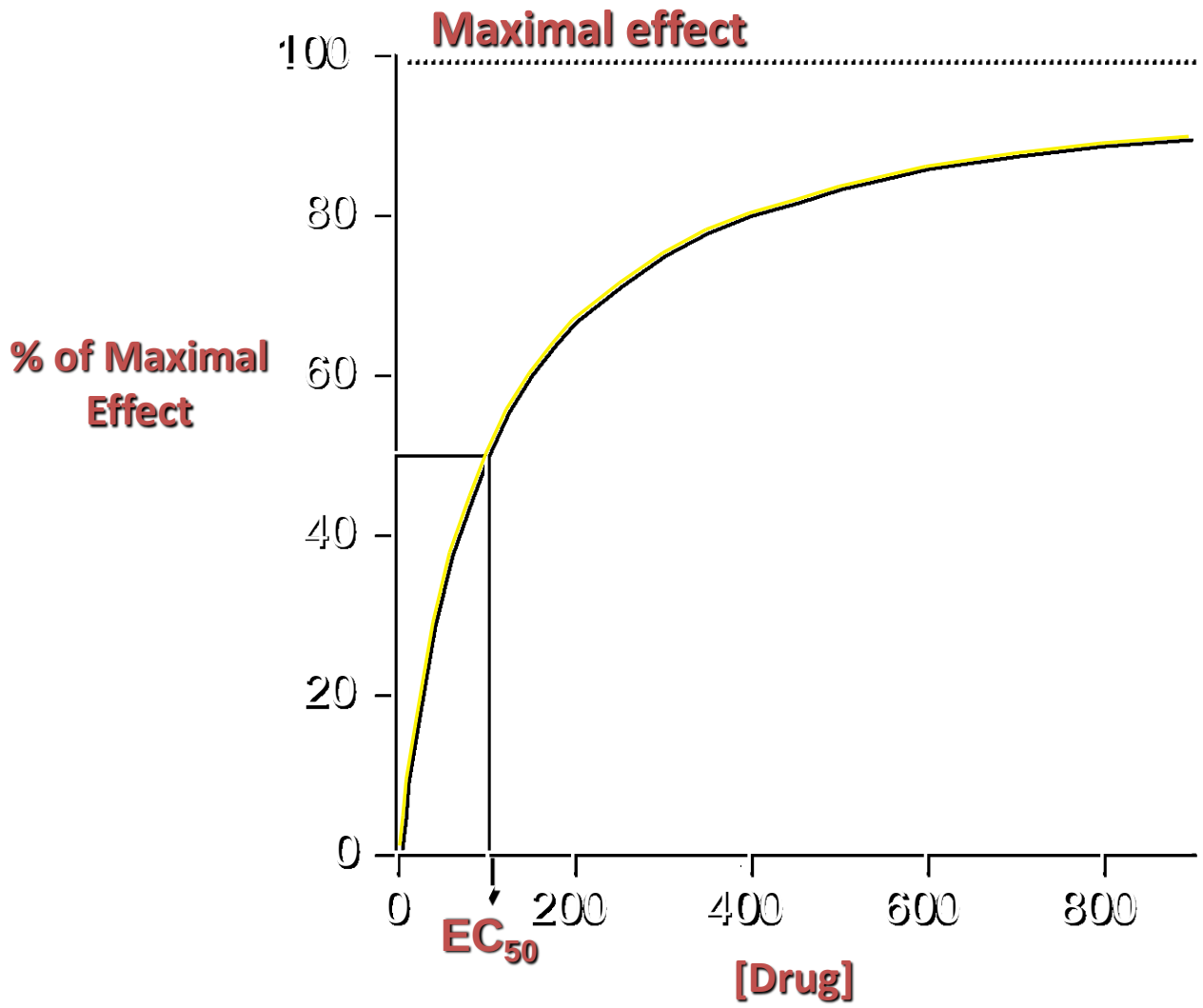
- Covalent bonds are stable and essentially irreversible

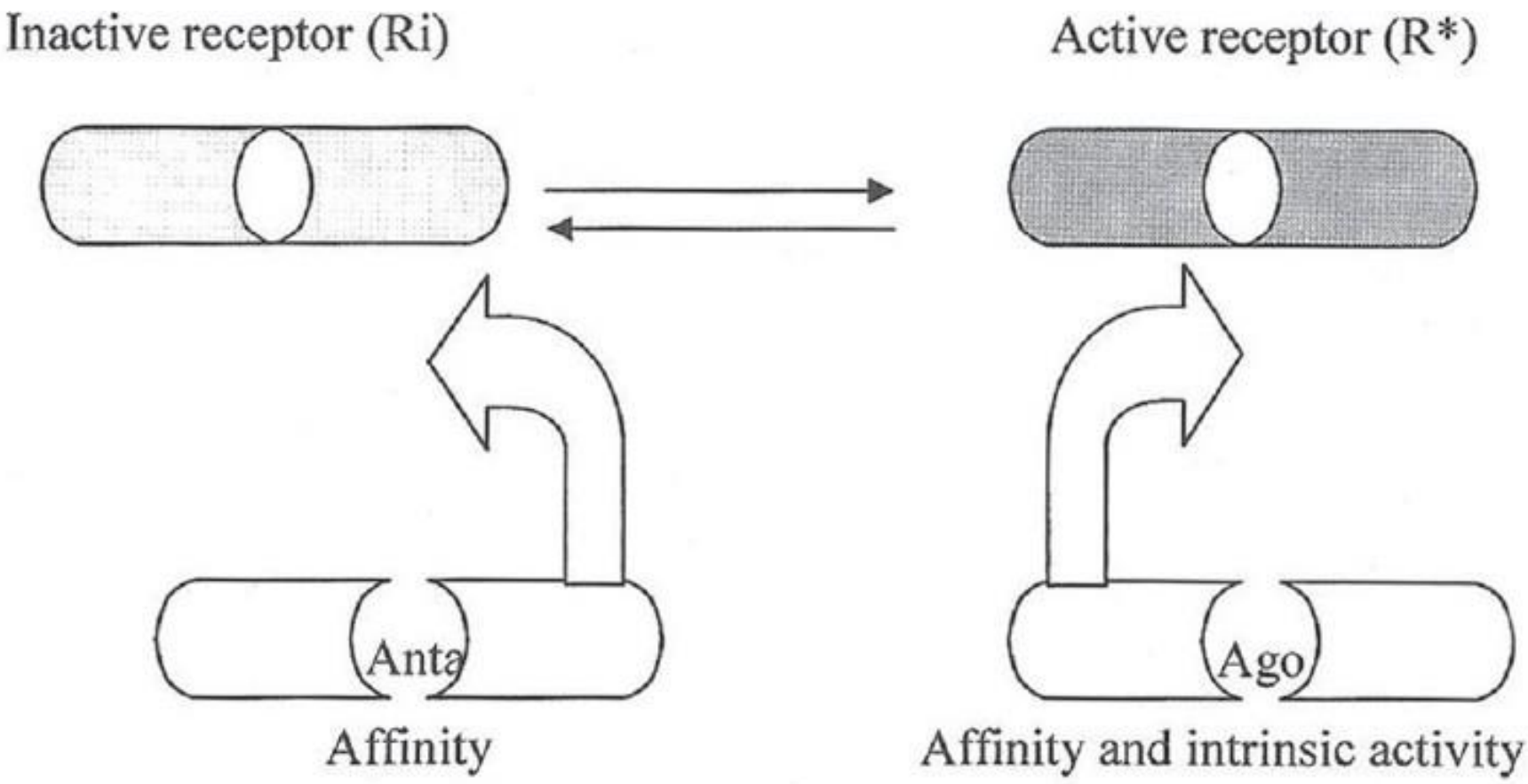

100
80
60
40
20
0
Binding (%)
0
10
20
30
40
Concentration (nM)
Higher affinity ligand
Lower affinity ligand


Drug A is more potent than Drug B, but both show the same efficacy.
Drug C shows lower potency and lower efficacy than Drugs A and B.
100
50
0
Biologic effect
Drug A
Drug B
Drug C
Log drug concentration
EC50 for Drug A
EC50 for Drug B
EC50 for Drug C

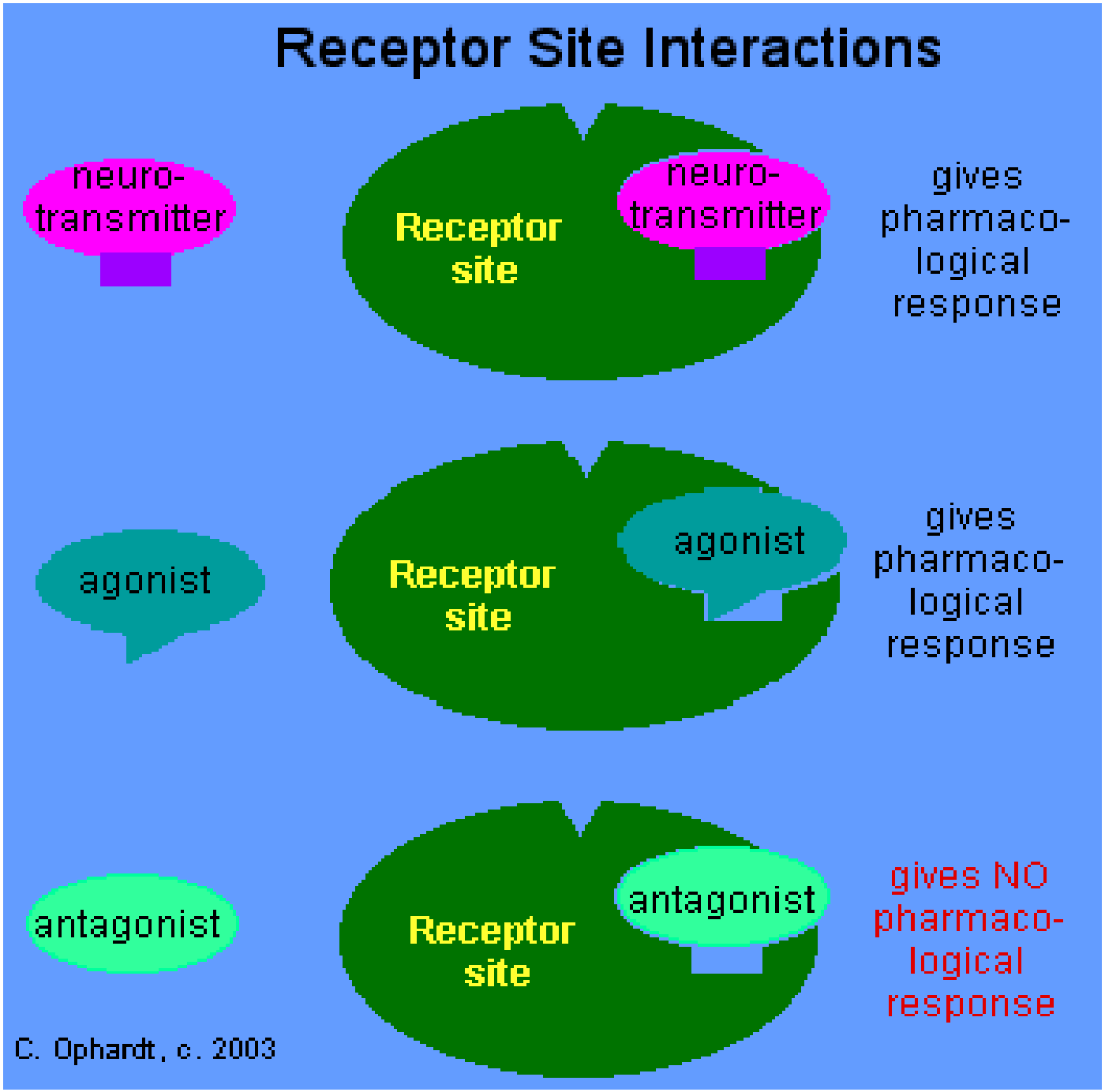

A
B
C
D
Response
Log drug dose

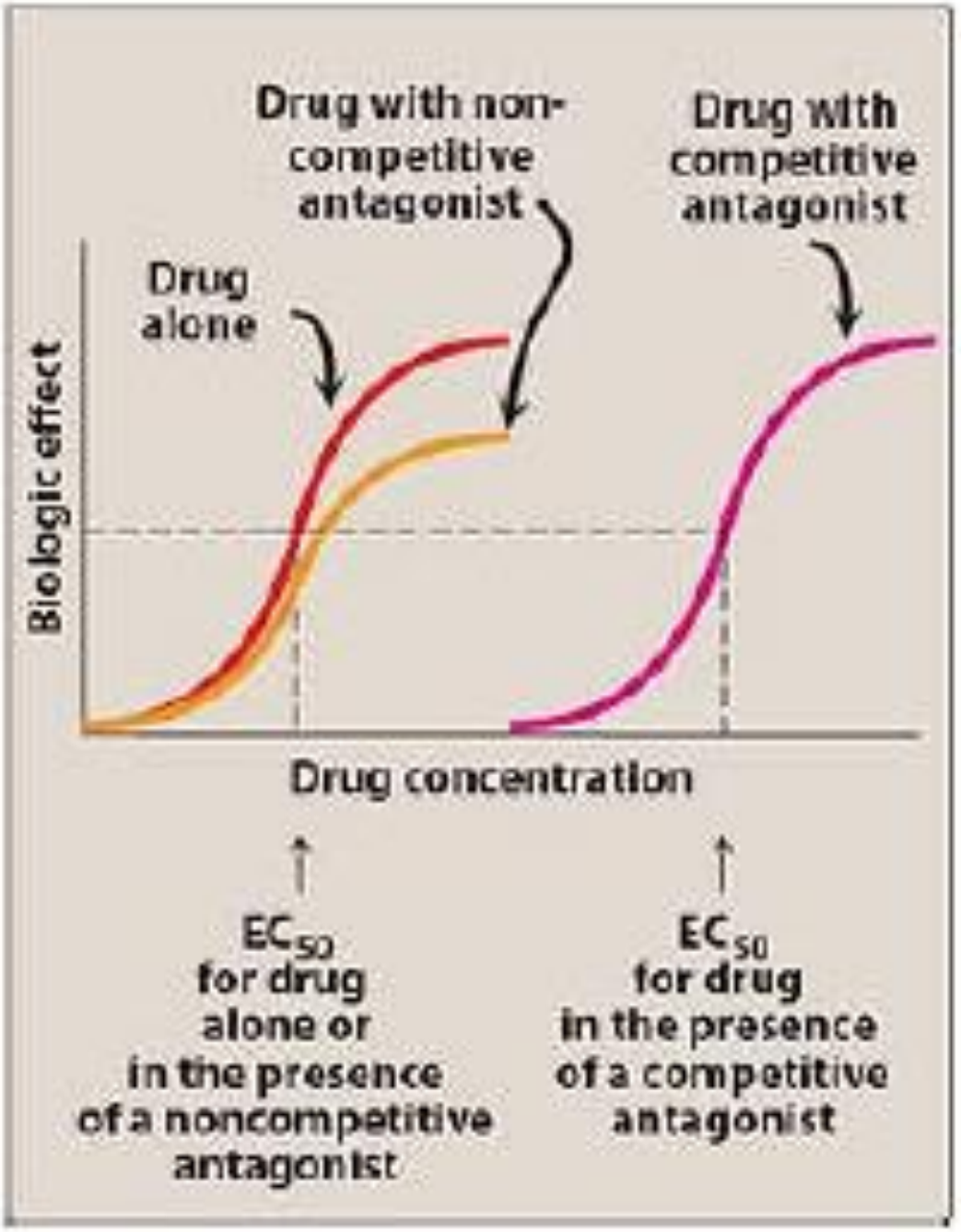
Graded Dose-Effect Curve

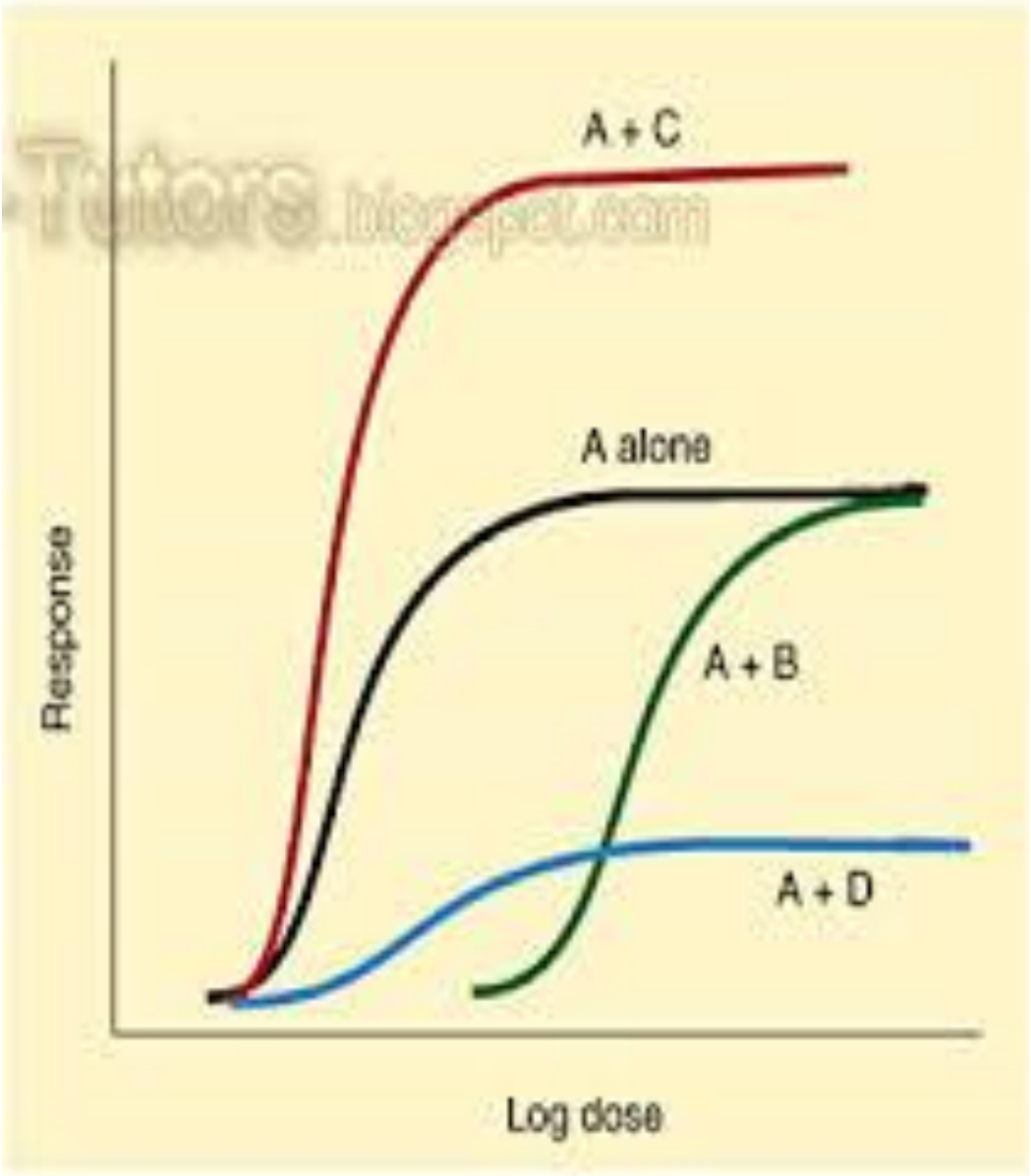




A receptor remains in dynamic equilibrium in two states Ri and R*. A ligand that binds and shifts the equilibrium to R* state is called agonist. A ligand that binds but does not shift the equilibrium to active state is called antagonist. Ligand binding is an equilibrium process.

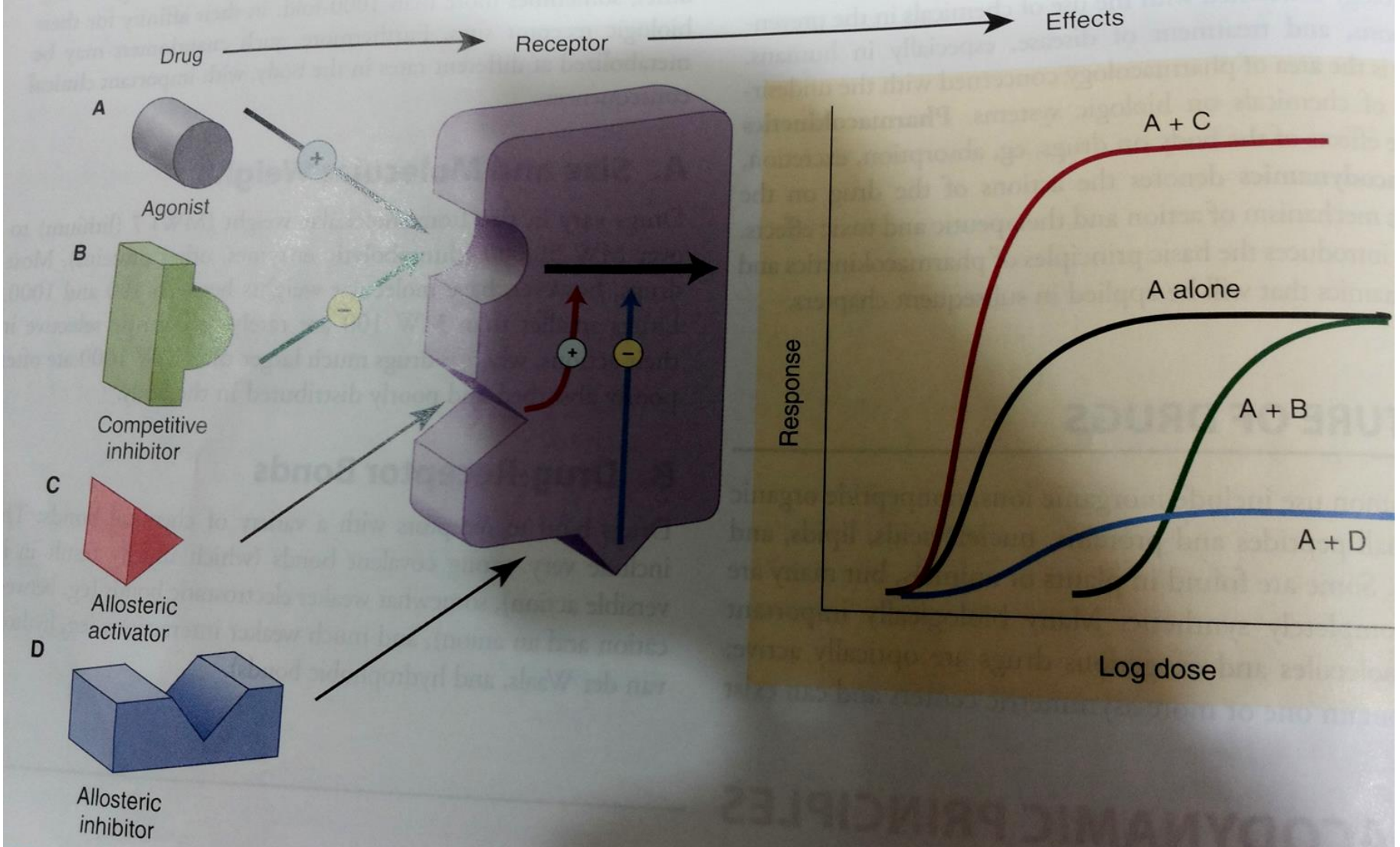

Receptor Site Interactions
neuro-transmitter
Receptor site
neuro-transmitter
gives pharmaco-logical response
agonist
Receptor site
agonist
gives pharmaco-logical response
antagonist
Receptor site
antagonist
gives NO pharmaco-logical response
C. Ophardt, c. 2003


Drug with non-competitive antagonist
Drug with competitive antagonist
Drug alone
Biologic effect
Drug concentration
EC50 for drug alone or in the presence of a noncompetitive antagonist
EC50 for drug in the presence of a competitive antagonist


A + C
A alone
A + B
A + D
Response
Log dose

response curves that provide information about the nature of the drug-receptor interaction. Dose-response phenomena are discussed

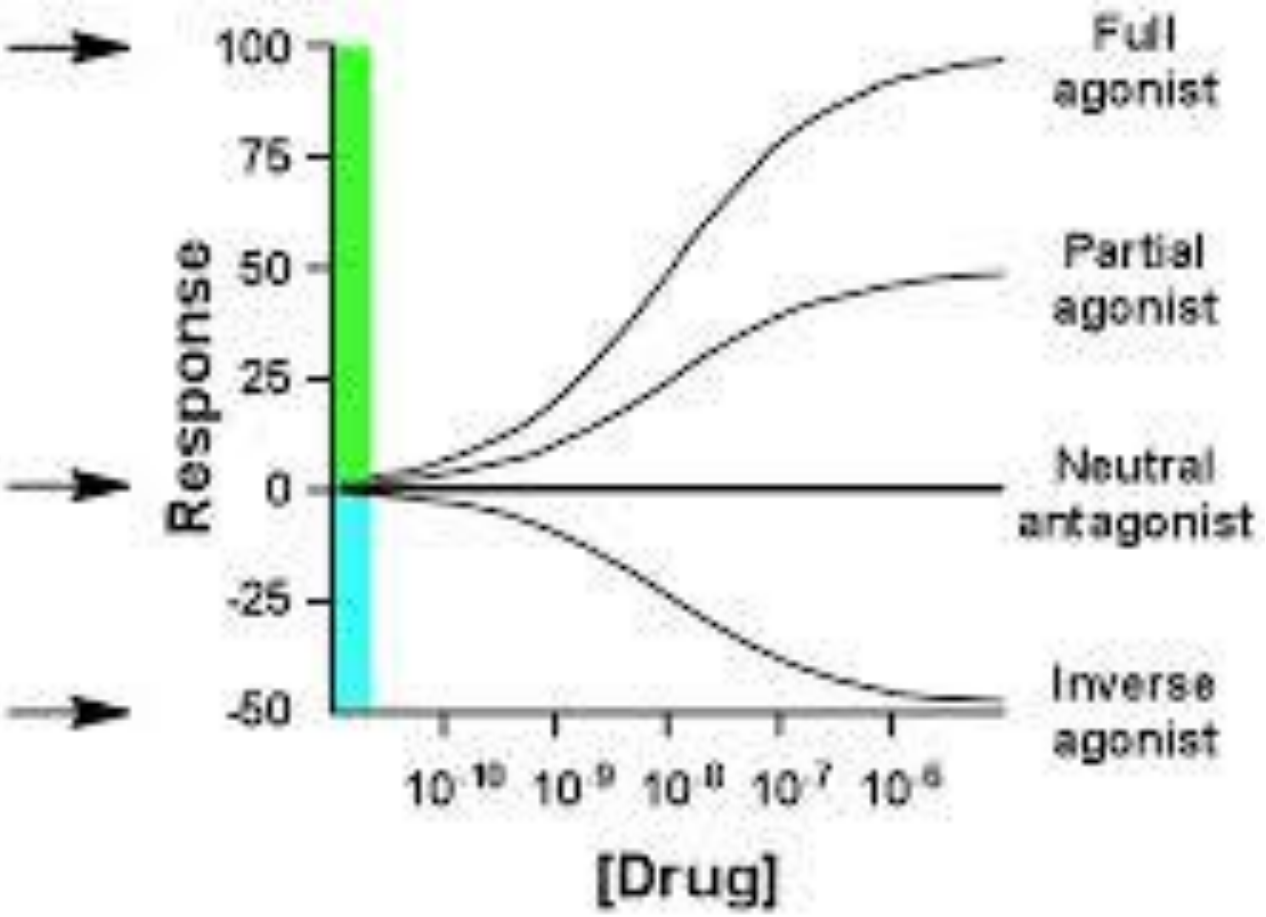
molecules, such as plasminogen.

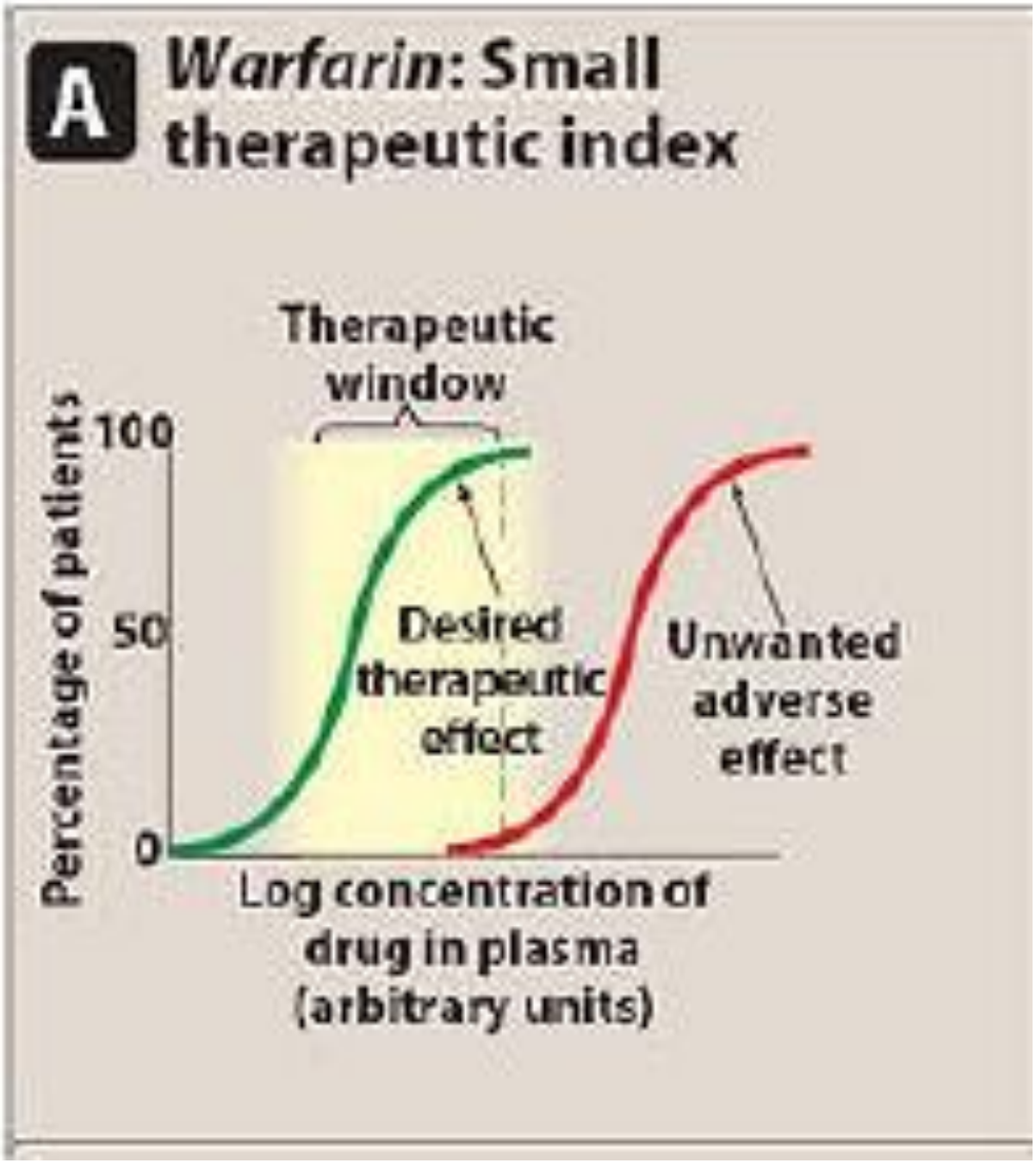


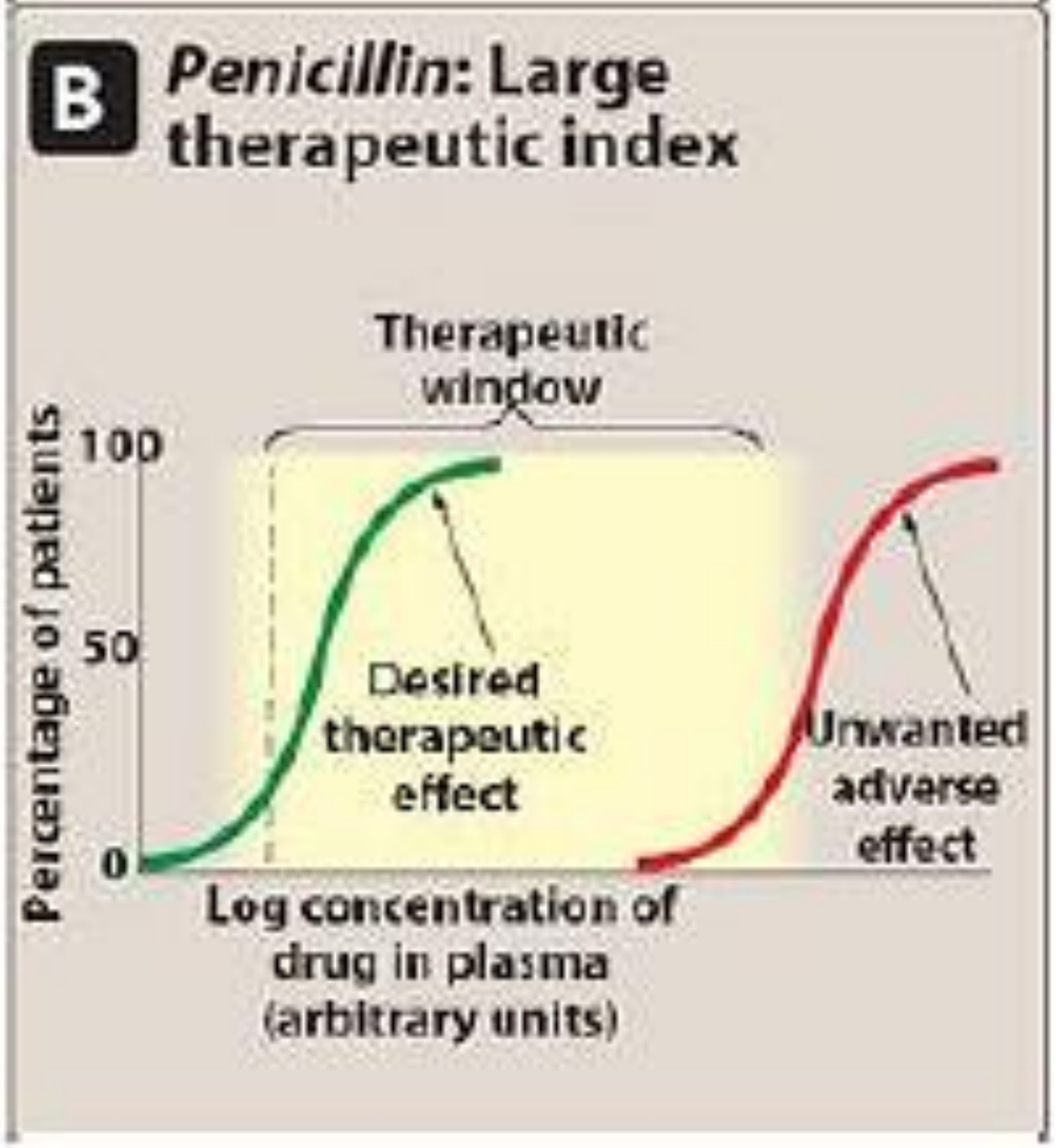
RE 1–1 Potential mechanisms of drug interaction with a receptor. Possible effects resulting f
e-response curves at the right. The traditional agonist (d
e." B is a pha

activation by saturating endogenous ligand

constitutive activty of receptor in absence of ligand




A
Warfarin: Small therapeutic index
Therapeutic window
Percentage of patients
100
50
0
Desired therapeutic effect
Unwanted adverse effect
Log concentration of drug in plasma (arbitrary units)


B
Penicillin: Large therapeutic index
Therapeutic window
Percentage of patients
100
50
0
Desired therapeutic effect
Unwanted adverse effect
Log concentration of drug in plasma (arbitrary units)