Pharmacodynamics

Dr. Alia Shatanawi

Learning Objectives

- Define pharmacodynamics and its scope in pharmacology.
- Differentiate pharmacodynamics from pharmacokinetics.
- Describe how drugs act on biological targets to produce effects.
- Identify major drug targets: receptors, enzymes, ion channels, and transporters.

Introduction

- Pharmacology is the study of the biochemical and physiological aspects of the drug effects including absorption, distribution, metabolism, elimination, toxicity and specific mechanism of action.

- The main areas of pharmacology are :

  - **Pharmacokinetics**: the way the body handle drug absorption, distribution, biotransformation, and excretion.

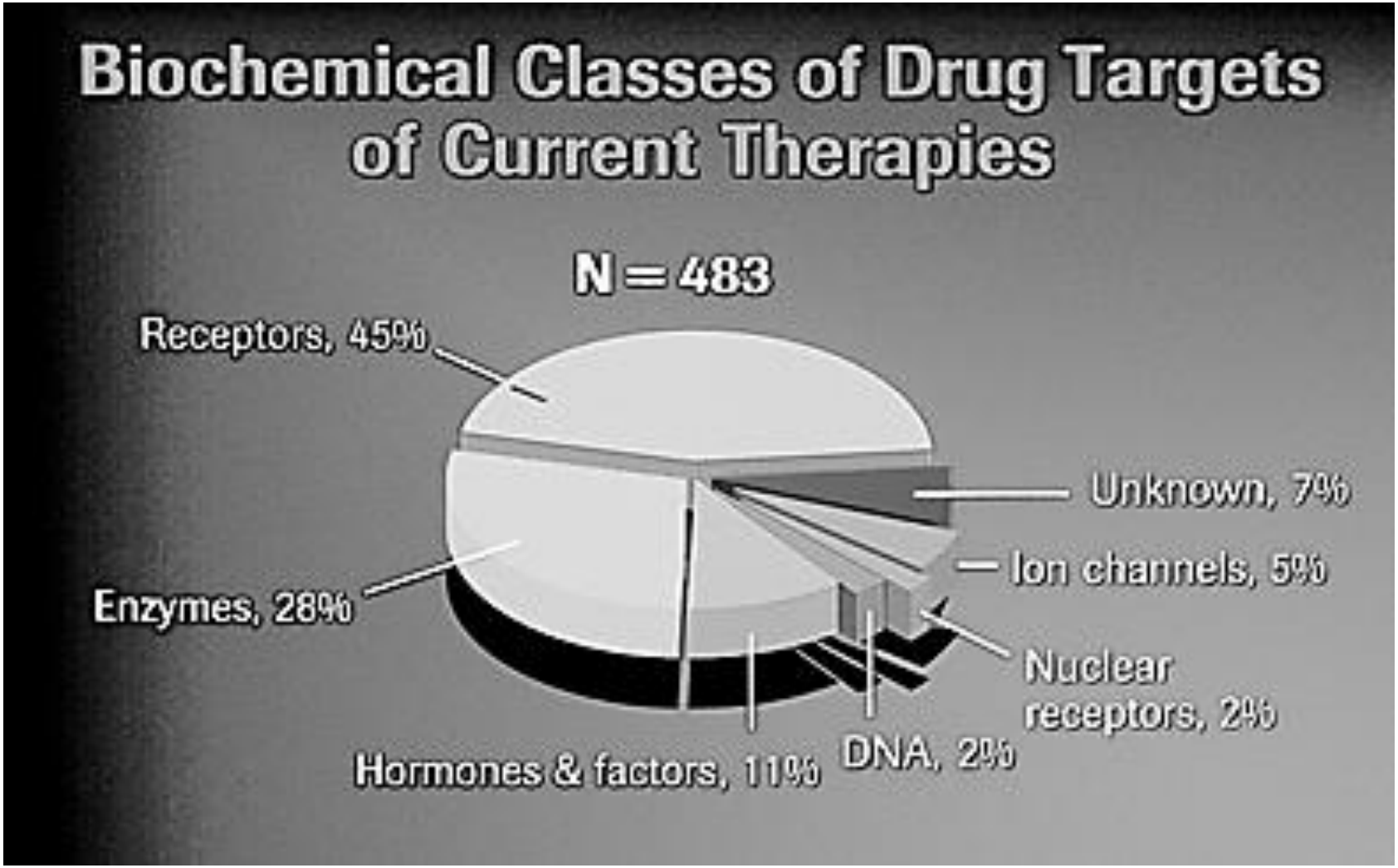
  - **Pharmacodynamics**: the study of the biochemical and physiological effect of the drugs and their mechanism of action.

Definitions

Drug: It is any chemical that affect living processes. It modifies an already existing function, and does not create a new function.

Pharmacodynamics

- Drug targets are usually receptors or enzymes. The drug needs to bind a sufficient number of target protein at a reasonable dose, so the drug should be potent .
- The study of the biochemical and physiological effect of the drugs and their mechanism of action.
- The study of the relationship of drug concentration to drug effects .


Biochemical Classes of Drug Targets of Current Therapies
N = 483
Receptors, 45%
Unknown, 7%
Ion channels, 5%
Enzymes, 28%
Nuclear receptors, 2%
Hormones & factors, 11%
DNA, 2%

Mechanism of drug action

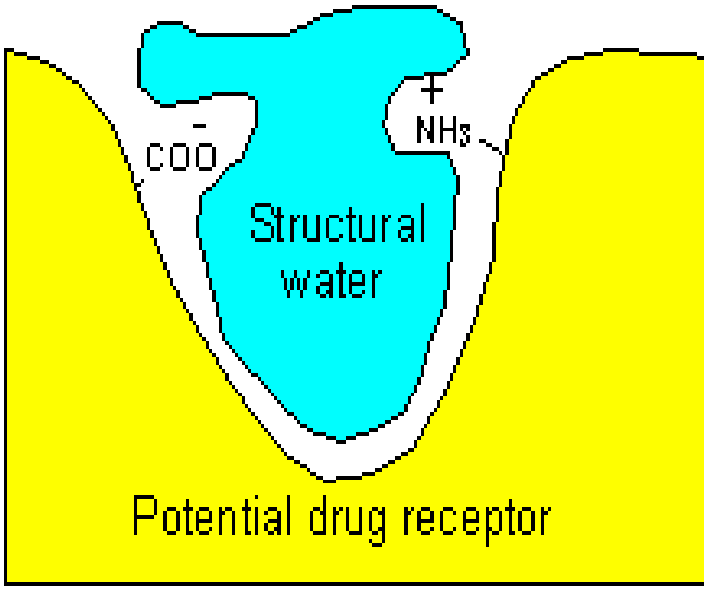
- Most drugs exert their effect by interacting with a specialized target macromolecules, called receptors, present on the cell surface or intracellularly.
-
- The receptors will transduce the binding into a response by causing a conformational changes or biochemical effect.

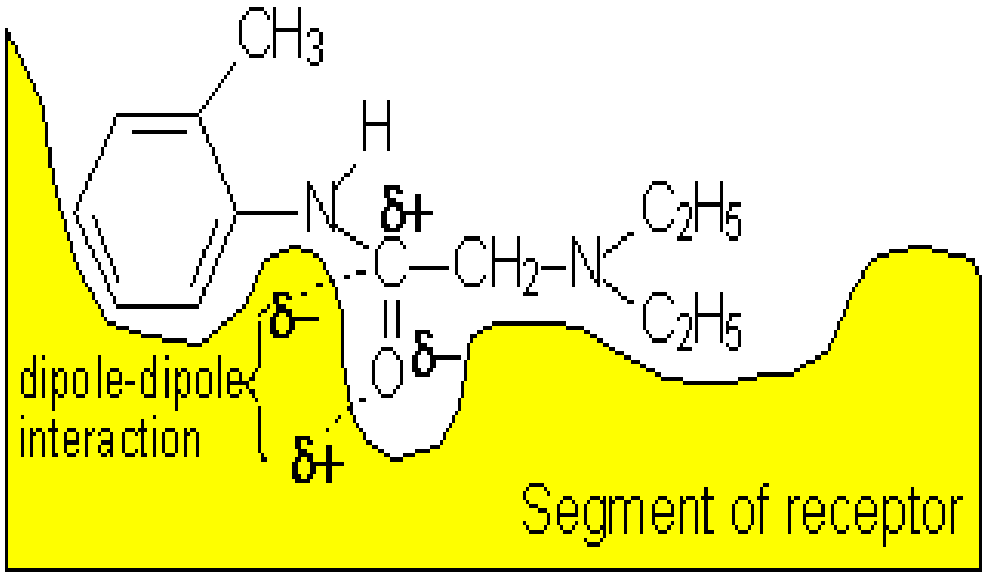
Mechanism of drug action

- **Receptors** are large macromolecules with a well-defined 3D shape .

- The two fundamental properties underlying specificity in drug-receptor interactions are complementarity of shape between drug and receptor, and complementarity between the electrostatic, hydrophobic, and hydrogen bonding surfaces of each component .

Lock and key


COO
NH3
Structural water
Potential drug receptor


CH3
H
N
δ+
C
CH2
N
C2H5
C2H5
O
δ−
δ−
δ+
dipole-dipole interaction
Segment of receptor

Receptors

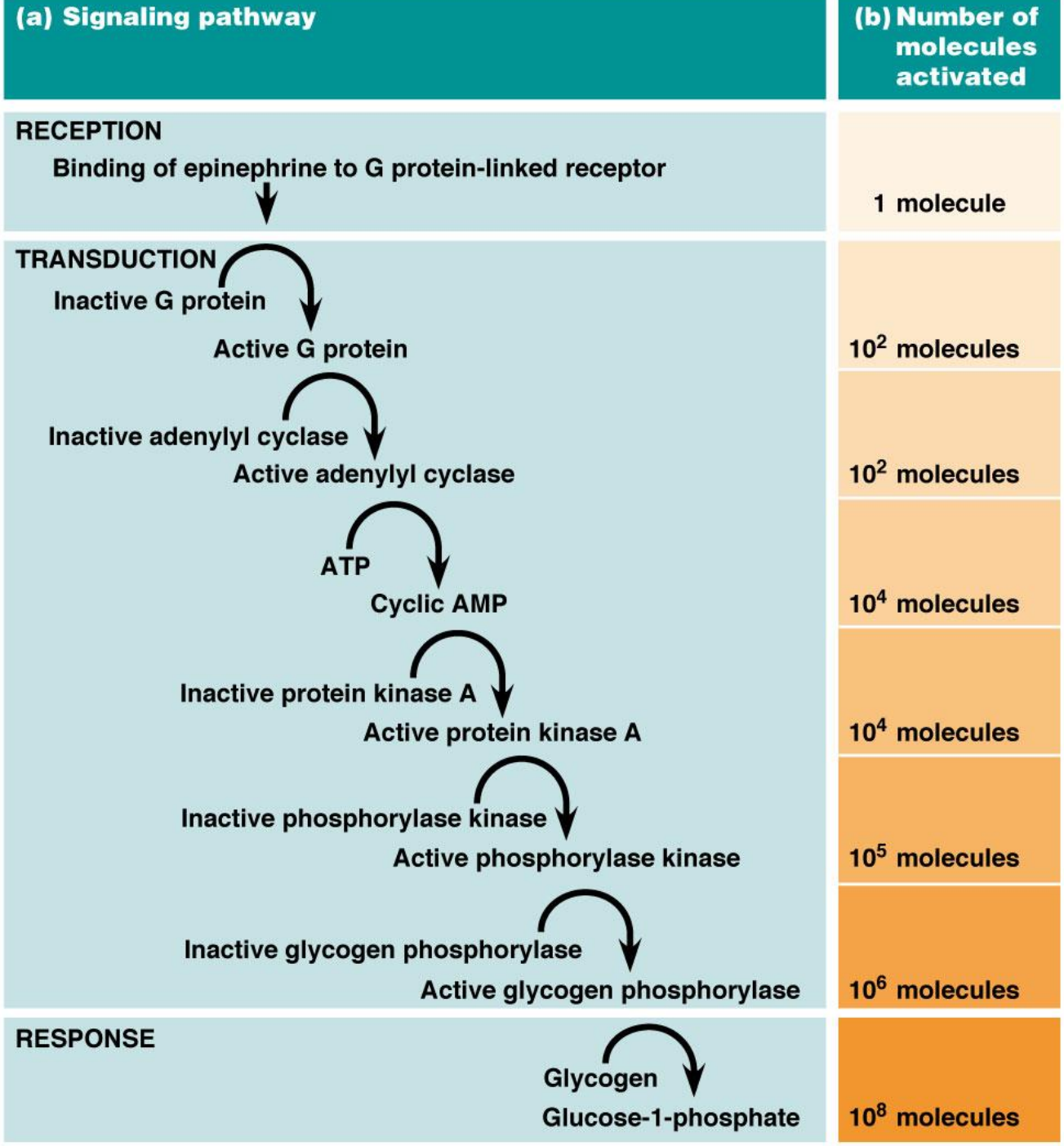
- determine specificity of drug action
- *most* are proteins
- Most drugs bind reversibly (noncovalent(
- not all “drugs” use receptors

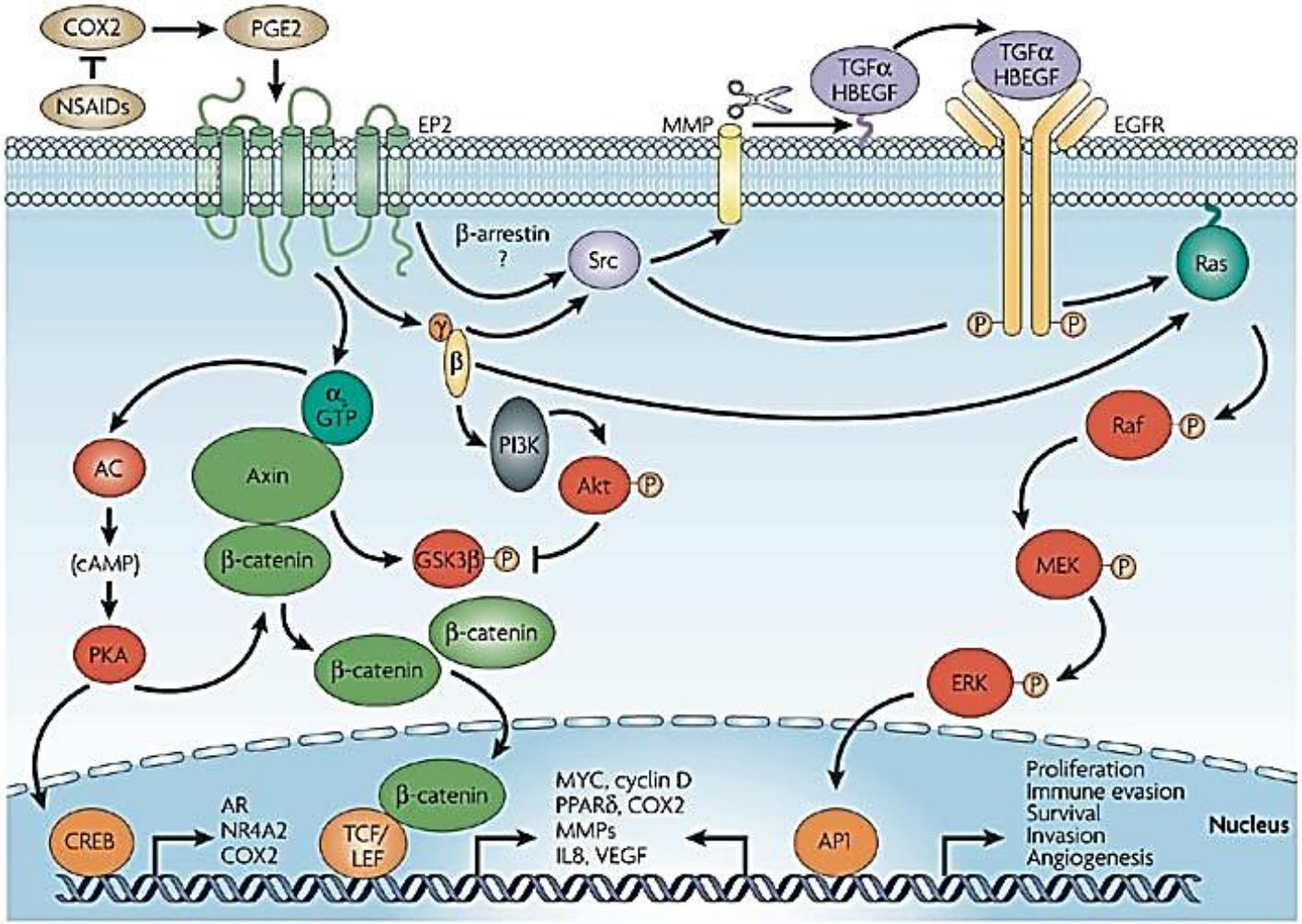
Characteristics of Drug-Receptor Interactions

- Chemical Bond: ionic, hydrogen, hydrophobic, Van der Waals, and covalent.
- Saturable
- Competitive
- Specific and Selective
- Structure-activity relationships
- Transduction mechanisms

Receptors are an Excellent Drug Target

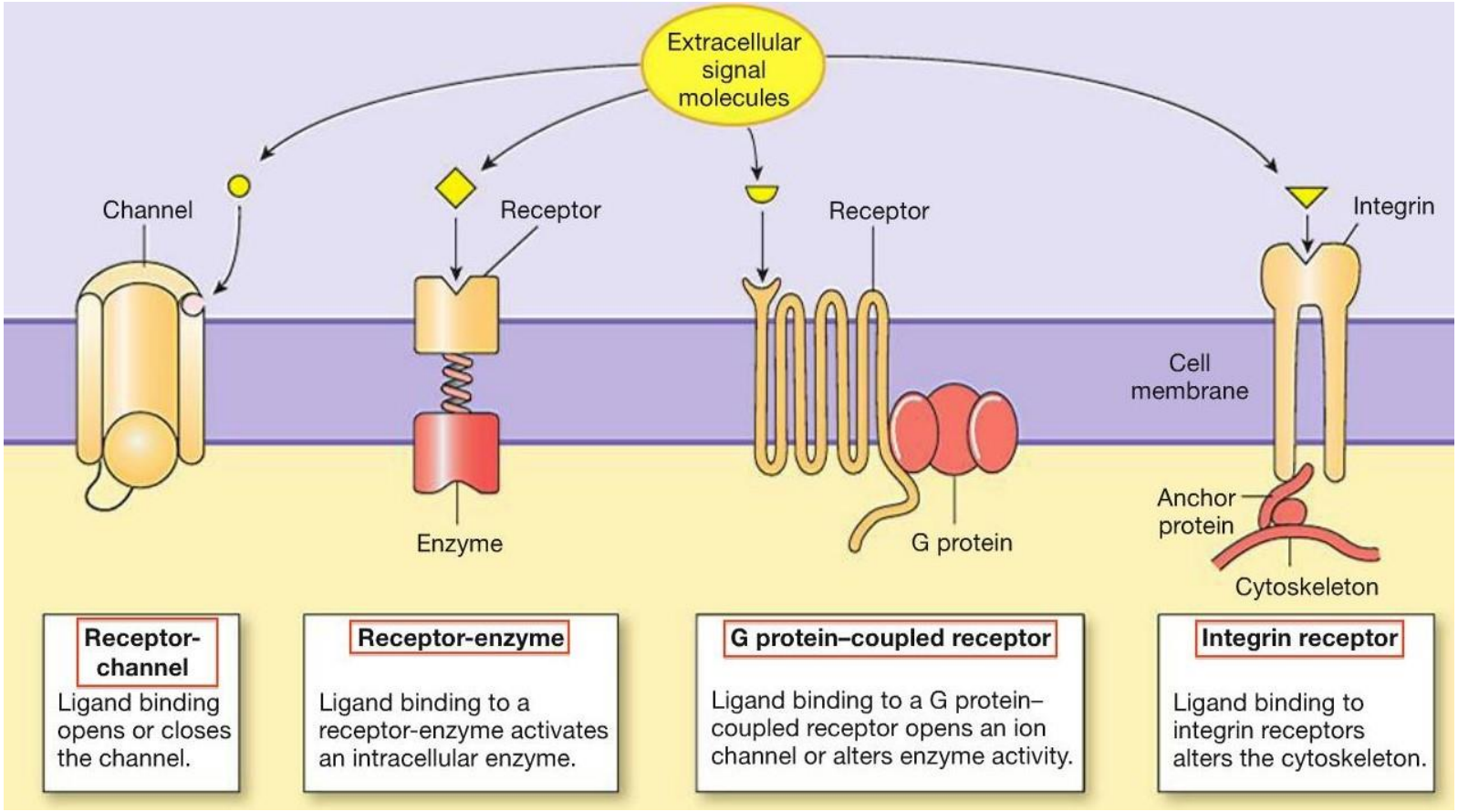
- Activated receptors directly, or indirectly, regulate cellular biochemical processes within and between cells to change cell function.
- Recognition sites are precise molecular regions of receptor macromolecules to which the ligand binds providing:
- Specificity
- Selectivity
- Sensitivity





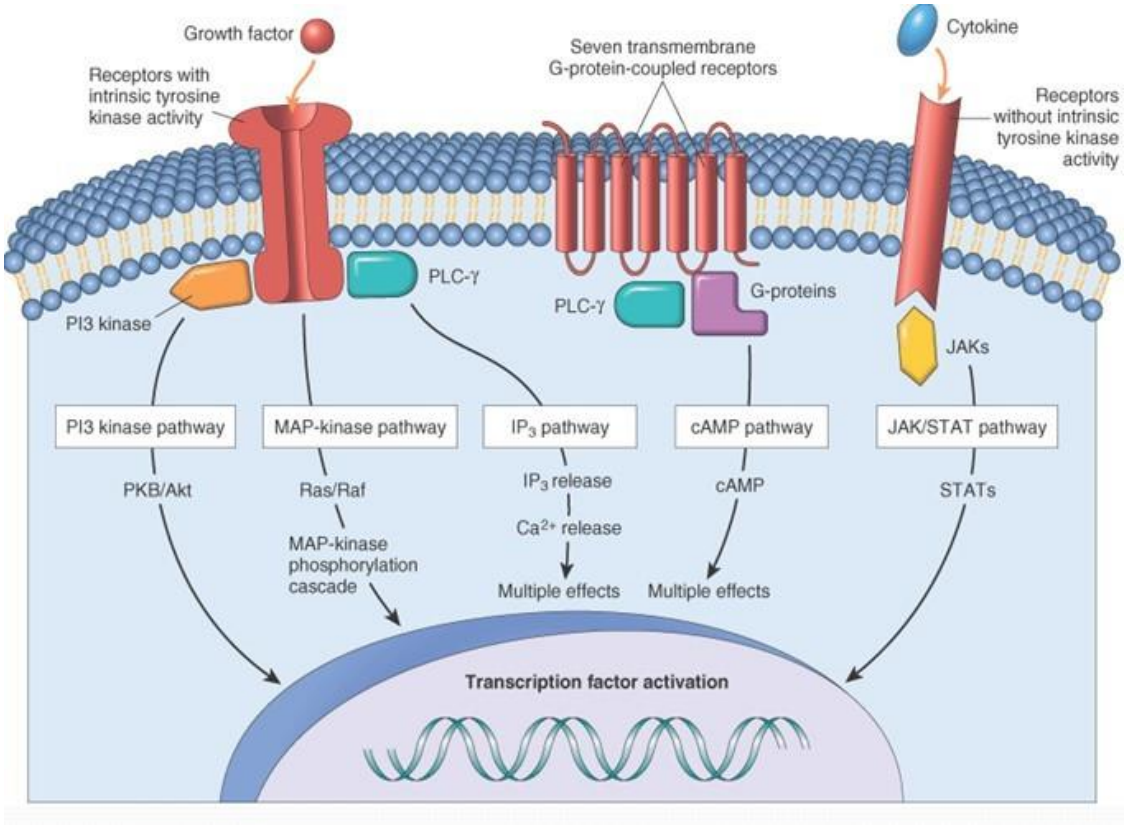
Nature Reviews | Cancer

CELL SURFACE (MEMBRANE) RECEPTORS



Cell-surface (or transmembrane) **receptors** are **membrane**-anchored, or integral proteins that bind to **external ligand molecules**. This type of **receptor** spans the plasma **membrane** and performs signal transduction, converting an extracellular signal into an intracellular signal.

CELL SURFACE (MEMBRANE) RECEPTORS



This large group of membrane-bound receptors comprises the 7TM or 1TM receptor families. All recruit multiple intracellular signaling cascades known as “second messengers.”

Major receptor families

Ligand-gated ion channels

G protein-coupled receptors

Enzyme-linked receptors

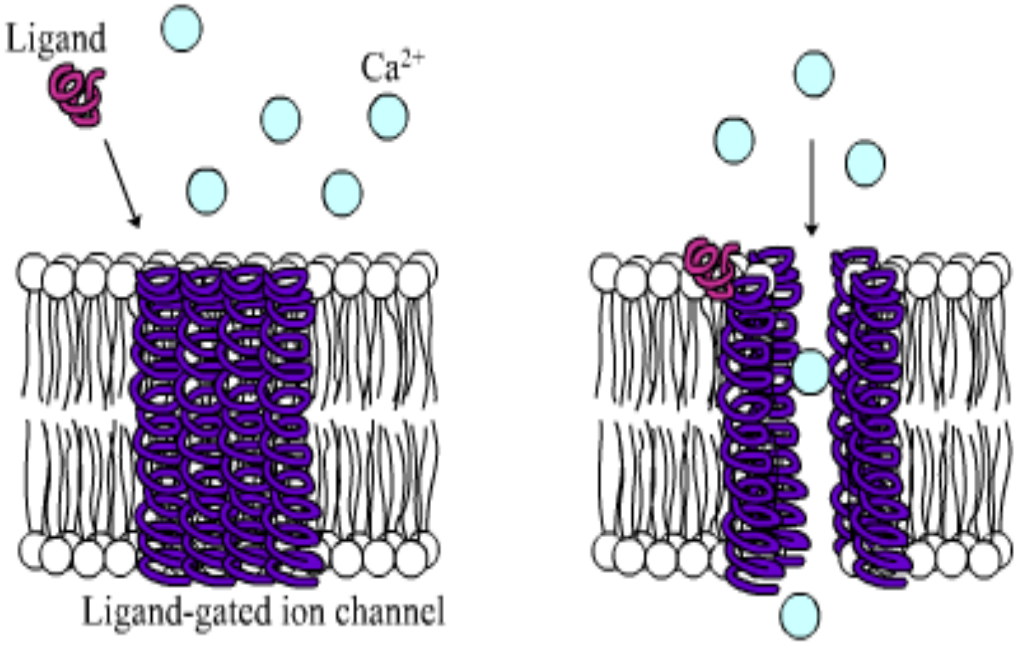
Intercellular receptors

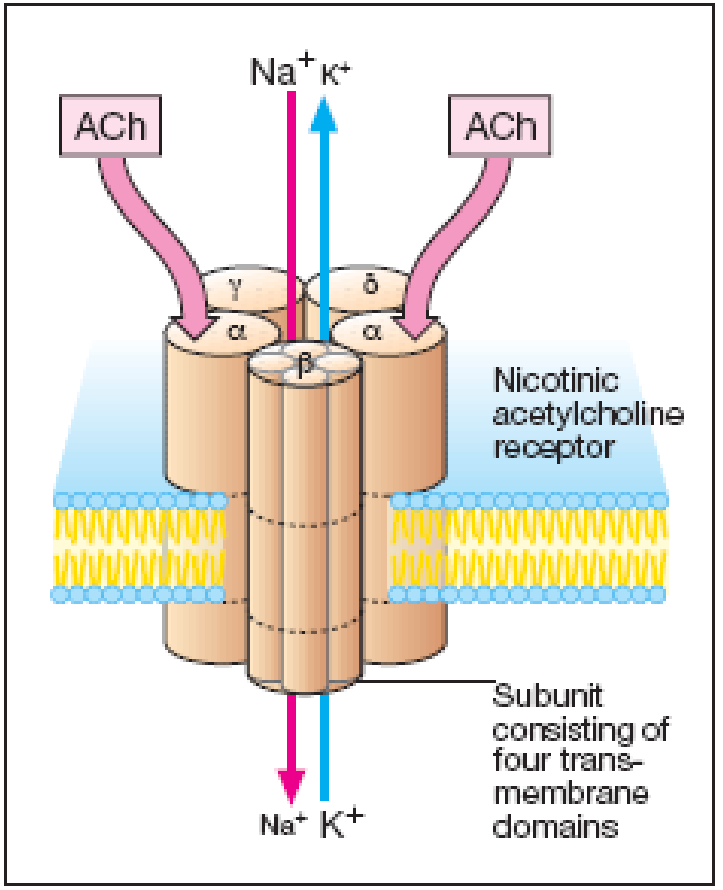
Ligand-gated ion channels

Responsible for regulation of the flow of ions channels across cell membranes.

Regulated by binding of a ligand to the channels.

The best example being the nicotinic receptor, in which the binding of the acetylcholine results in sodium influx and the activation of contraction in skeletal muscle

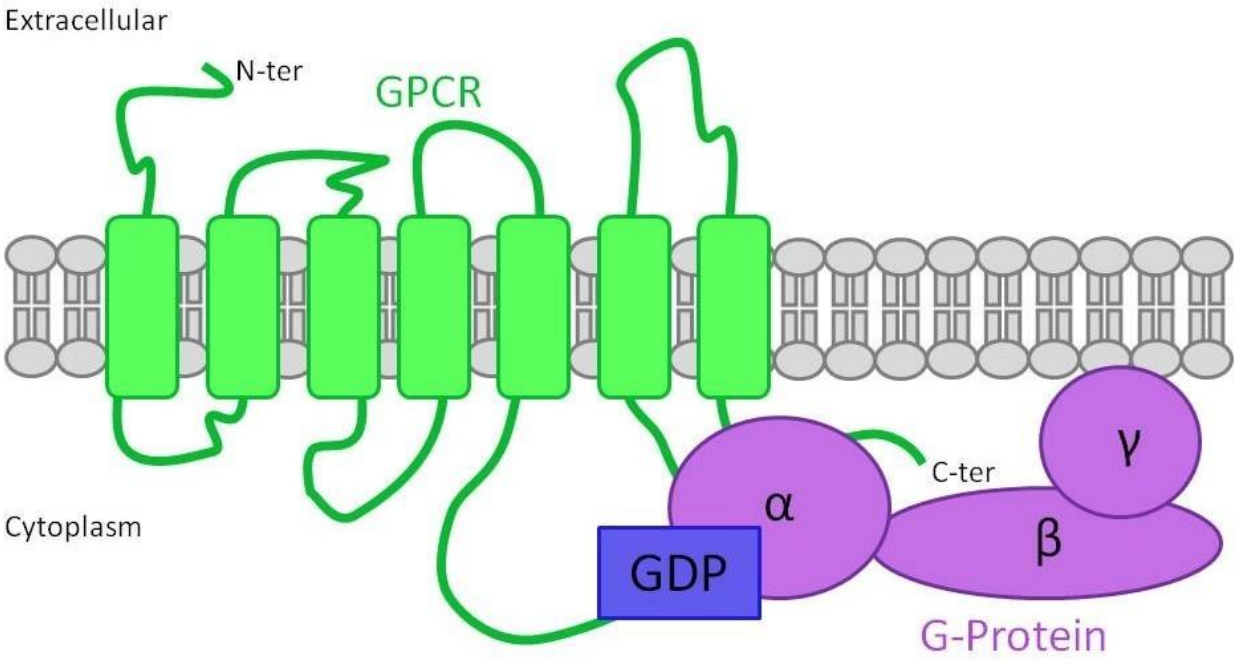




B. Ligand-gated ion channel

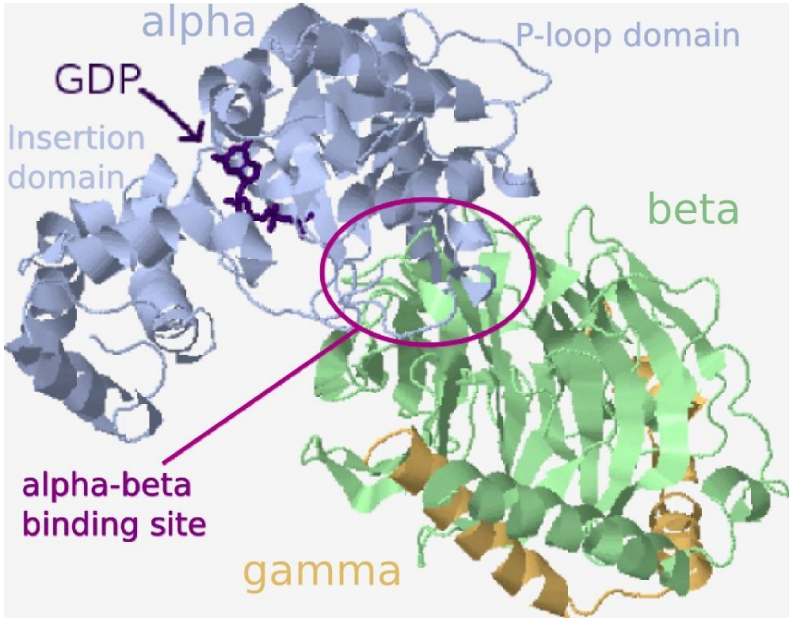
GPCR and G PROTEINs

- **GPCR are so called because they are bound to an intracellular G protein**
- **Guanine nucleotide-binding proteins (G proteins)** act as molecular switches inside cells, and are involved in transmitting signals from a variety of stimuli.



G PROTEIN

There are two classes of G proteins: the **monomeric small GTPases**, and the **heterotrimeric G protein complexes**.

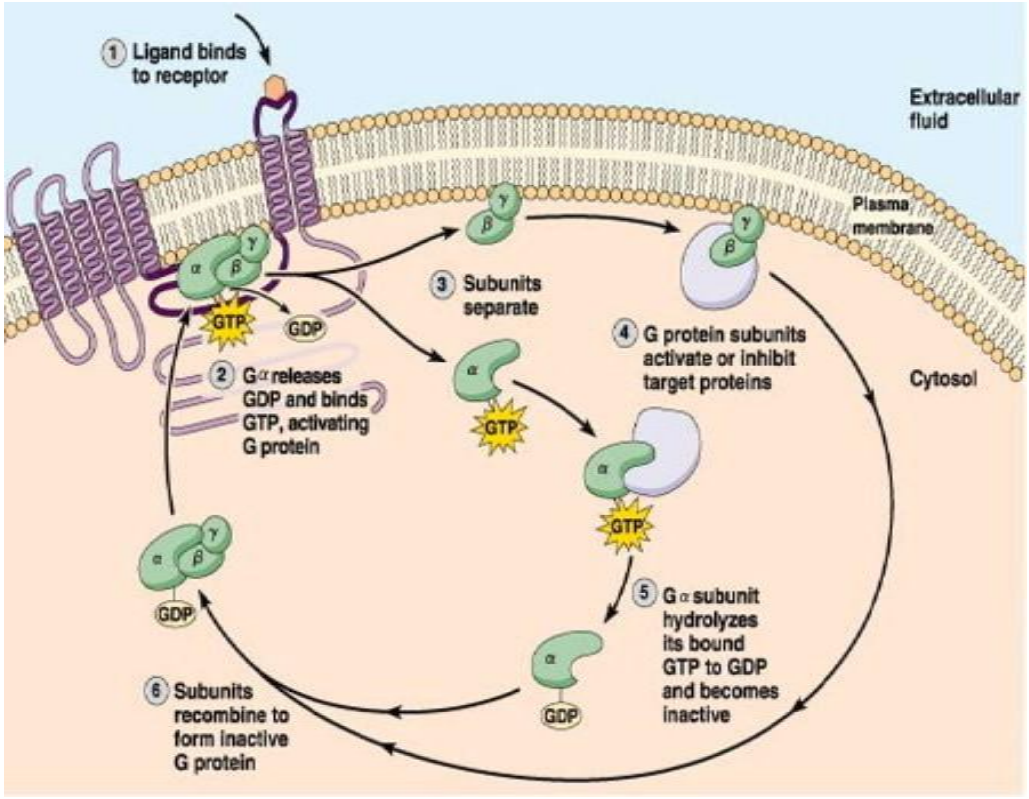


- The heterotrimeric G protein is made up of ***alpha*** (α), ***beta*** (β) and ***gamma*** (γ) subunits.
- The ***alpha*** (α) subunit holds the catalytic GTPase activity.
- The ***beta*** (β) and ***gamma*** (γ) subunits can form a stable dimeric complex referred to as the beta-gamma complex with regulatory activity.

Their activity is regulated by factors that control their ability to bind to and hydrolyze guanosine triphosphate (GTP) to guanosine diphosphate (GDP.(

ACTIVATION/INACTIVATION CYCLE OF GPCR

ACTIVATION: ligand binding results in G-protein exchange of GTP for GDP. The activated G-protein then dissociates into an **alpha (G-alpha)** and a **beta-gamma** complex.



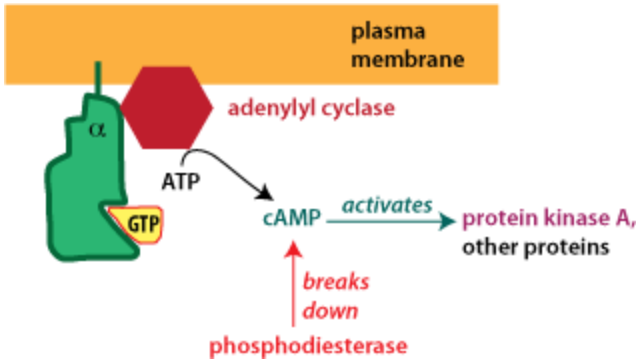
- G-alpha bound to GTP is active, and diffuses along the membrane surface to activate target proteins, (often enzymes that generate **second messengers.(**

- The beta-gamma complex is also able to diffuse and activate proteins, typically affecting ion channels

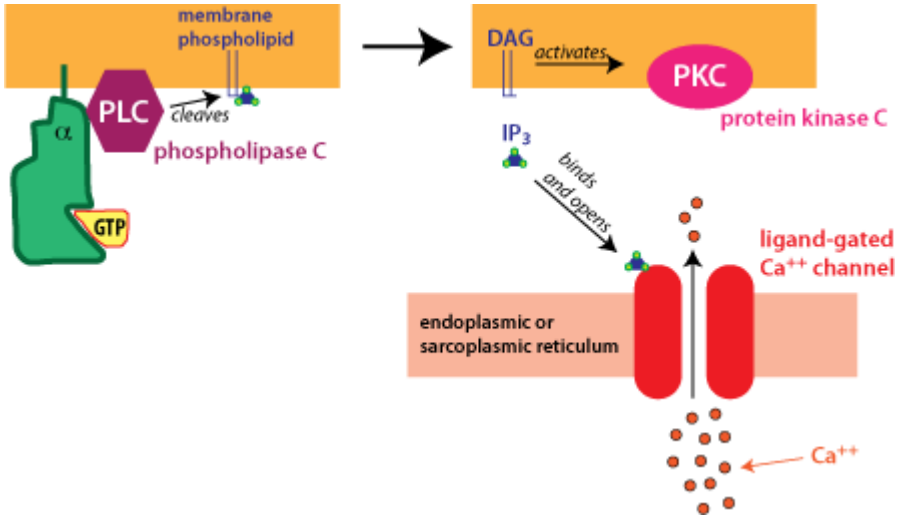
INACTIVATION: it occurs because G-alpha has intrinsic **GTPase activity**. After GTP hydrolysis, G-alpha bound to GDP will reassociate with a beta-gamma complex to form an inactive G-protein that can again associate with a receptor

DISTINCT Gα subunits

The many classes of G_α subunits behave differently in the recognition of the effector molecule, but share similar activation mechanisms.



- **G_i/G_o inhibit adenylyl cyclase (AC),** activate K^+ channels or inhibit Ca^{2+} channels
- **Gs activates adenylyl cyclase (AC),** and increase intracellular cAMP levels. cAMP major effect is to bind to and activate **cAMP-dependent kinase (PKA(**



- **G_q activates phospholipase C (PLC),** which transforms PIP_2 into $InsP_3$ and DAG.

In turn, DAG activates protein C kinase (PKC) while InsP3 increases intracellular [Ca.[$^{+2}$

G protein-coupled receptors

- Receptors on the inner face of the plasma membrane regulate or facilitate effector proteins through a group of guanosine triphosphate (GTP) proteins known as G proteins.

- Some hormones peptide receptors and neurotransmitter receptors (e.g., adrenergic and muscarinic receptors depend n the G proteins) mediate their action on cells.

Enzyme-linked receptors

- Binding of the ligand to the extra cellular domain activates or inhibits the related cytosolic enzyme .

- The most common are the receptors that have a tyrosine kinase activity as part of their structure, in which the binding results in the phosphorylation of tyrosine residues of specific protein .

- The addition of phosphate group can modify the three-dimensional structure of the target protein, and so resulting in molecular switch .

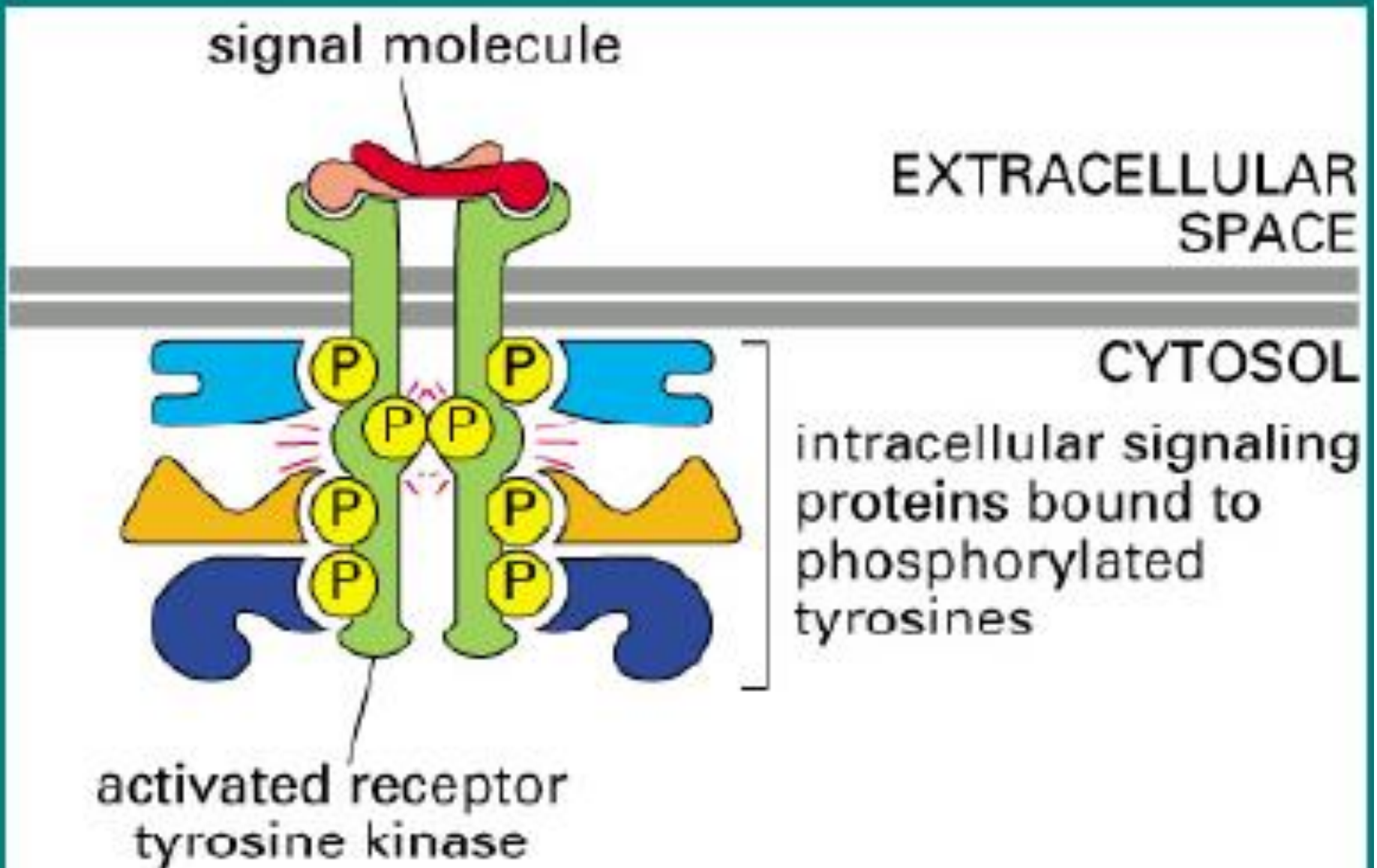
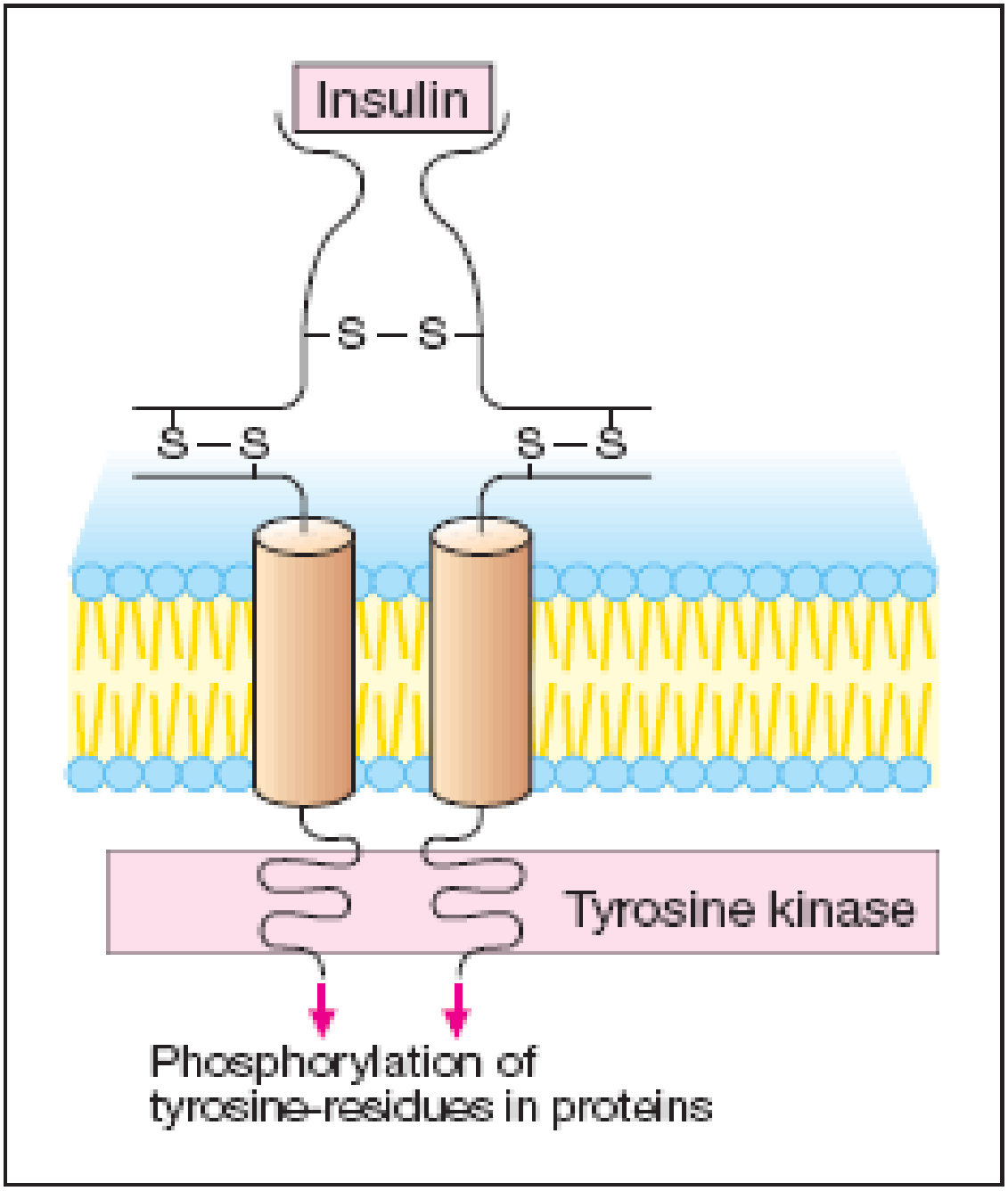


Figure 15–52. Molecular Biology of the Cell, 4th Edition.



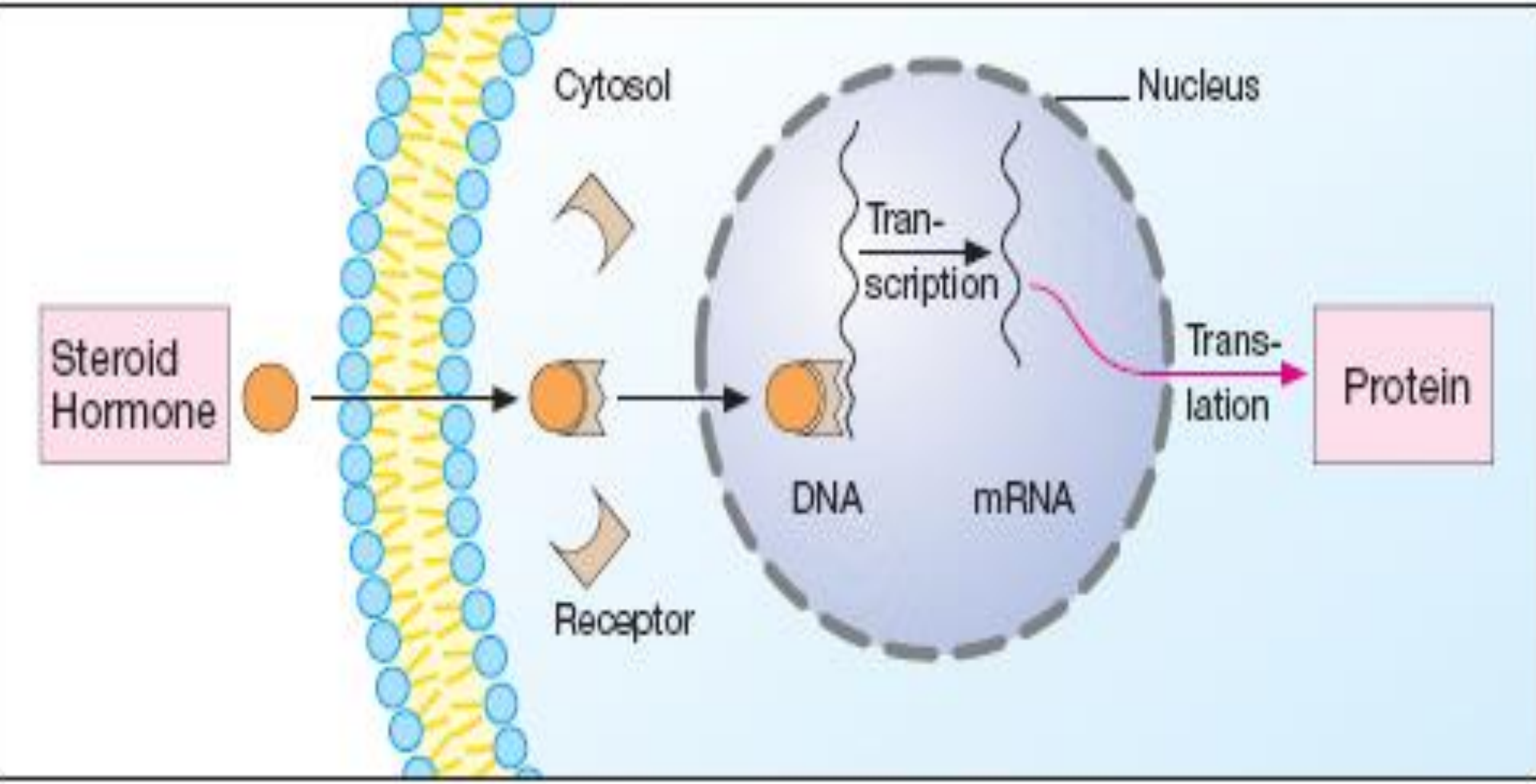
C. Ligand-regulated enzyme

Intracellular receptors

- In this family the ligand must diffuse into the cell to interact with the receptors .

- Therefore the ligand must have sufficient lipid solubilities to be able to move across the target cell membranes .

- The best example being the steroids hormones. In which the activated ligand-receptor complex migrate to the nucleus, where it bind to a specific DNA sequences, resulting in regulation of the gene expression .



D. Protein synthesis-regulating receptor

HOW DO DRUGS WORK?

Most work by interacting with endogenous proteins:

- Some *antagonize, block or inhibit endogenous proteins*
- Some *activate endogenous proteins*
- A few have *unconventional mechanisms of action*

HOW DO DRUGS ANTAGONIZE, BLOCK OR INHIBIT ENDOGENOUS PROTEINS?

- Antagonists of Cell Surface Receptors
- Antagonists of Nuclear Receptors
- Enzyme Inhibitors
- Ion Channel Blockers
- Transport Inhibitors
- Inhibitors of Signal Transduction Proteins

HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS ?

KEY CONCEPTS:

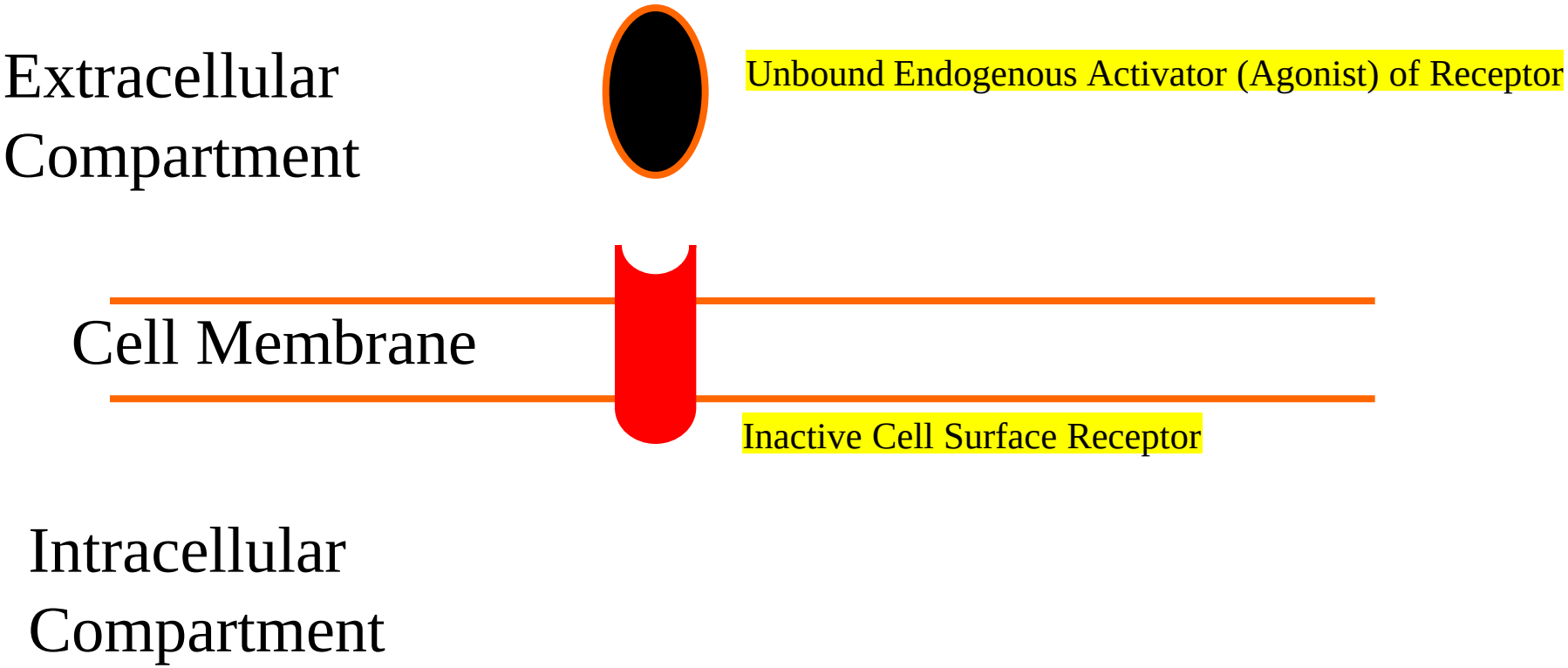
- **Cell surface receptors exist to transmit chemical signals from the outside to the inside of the cell.**

- **Some compounds bind to cell surface receptors, yet do not activate the receptors to trigger a response.**

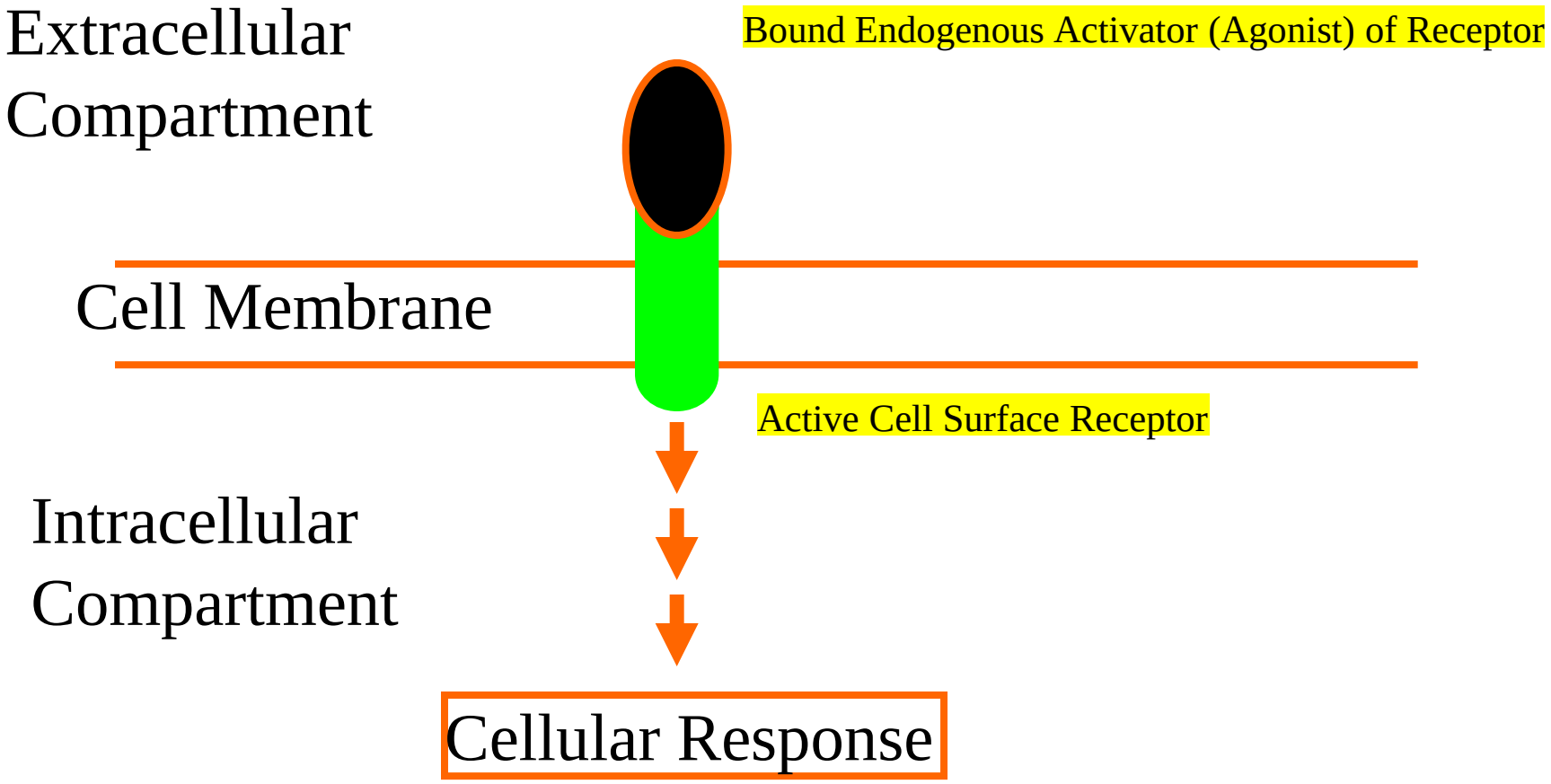
- **When cell surface receptors bind the molecule, the endogenous chemical cannot bind to the receptor and cannot trigger a response.**

- **The compound is said to “antagonize” or “block” the receptor and is referred to as a receptor antagonist.**

HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS?



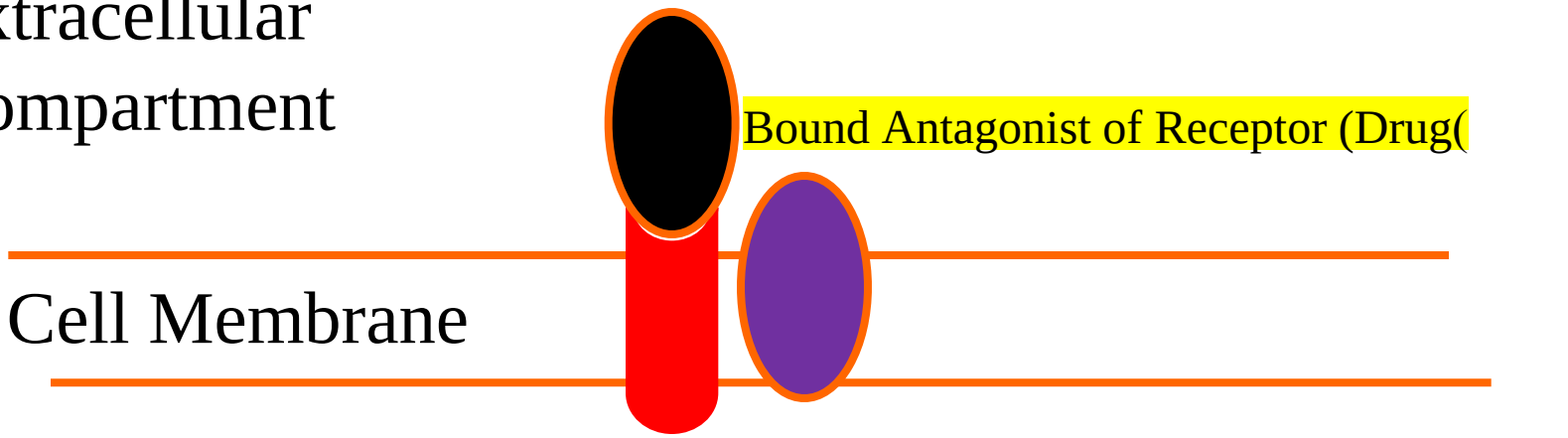
HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS?



HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS?

Displaced Endogenous Activator (Agonist) of Receptor

Extracellular Compartment



Bound Antagonist of Receptor (Drug(

Cell Membrane

Inactive Cell Surface Receptor Upon being Bound

Intracellular Compartment

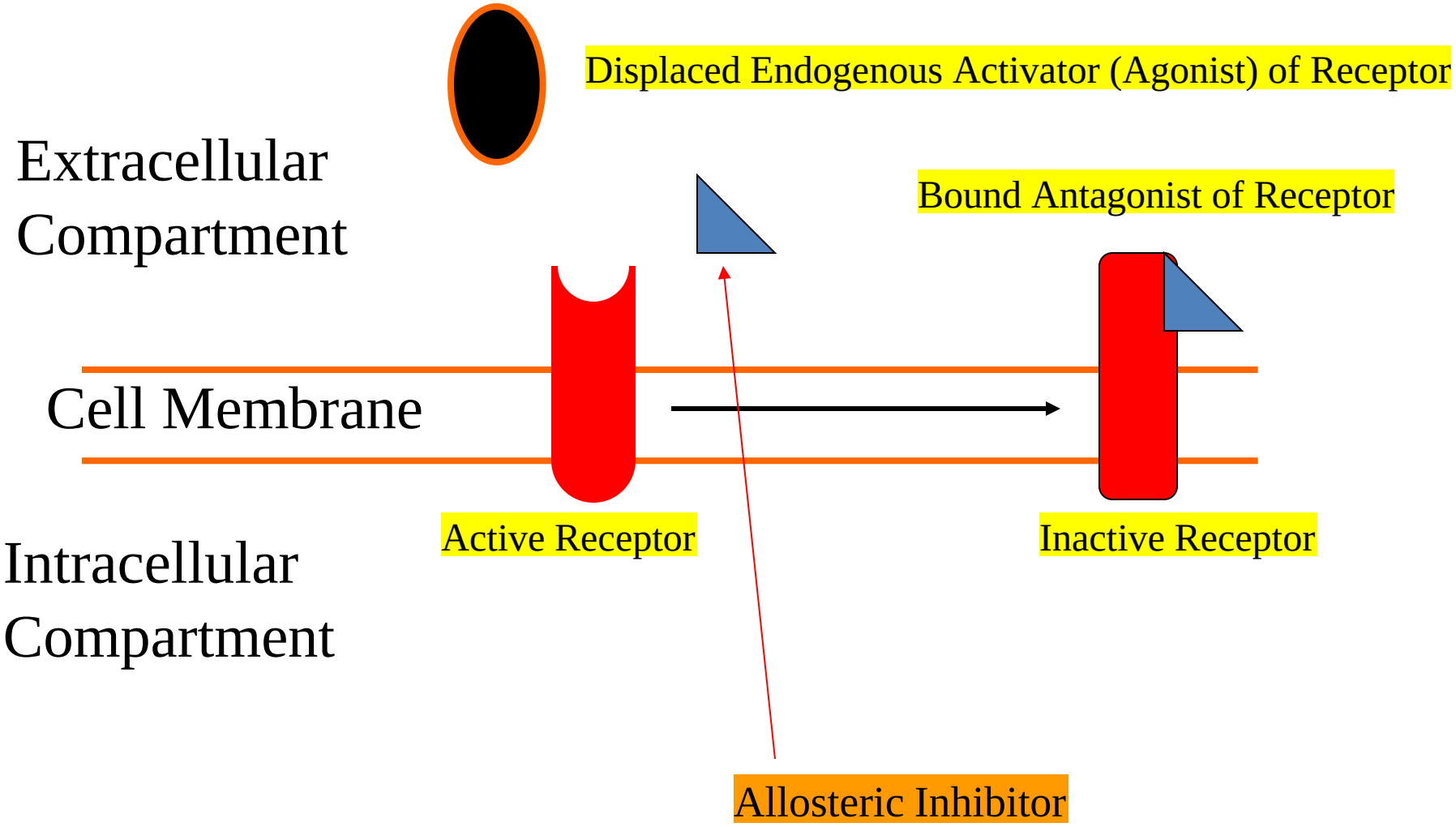
HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS?

Footnote :

Most antagonists attach to binding site on receptor for endogenous agonist and sterically prevent endogenous agonist from binding .
If binding is reversible - Competitive antagonists
If binding is irreversible - Noncompetitive antagonists

However, antagonists may bind to remote site on receptor and cause allosteric effects that displace endogenous agonist or prevent endogenous agonist from activating receptor. (Noncompetitive antagonists(

HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS?



ARE DRUGS THAT ANTAGONIZE CELL SURFACE RECEPTORS CLINICALLY USEFUL?

Some important examples:

Angiotensin Receptor Blockers (ARBs) for high blood pressure , heart failure, chronic renal insufficiency
)losartan [Cozaar®]; valsartan [Diovan([®

Beta-Adrenoceptor Blockers for angina, myocardial infarction , heart failure, high blood pressure, performance anxiety
)propranolol [Inderal®]; atenolol [Tenormin([®

HOW DO DRUGS ANTAGONIZE, BLOCK OR INHIBIT ENDOGENOUS PROTEINS?

Antagonists of Cell Surface Receptors

- Antagonists of Nuclear Receptors
- Enzyme Inhibitors
- Ion Channel Blockers
- Transport Inhibitors
- Inhibitors of Signal Transduction Proteins

ARE DRUGS THAT ANTAGONIZE NUCLEAR RECEPTORS CLINICALLY USEFUL?

Some important examples:

• Mineralocorticoid Receptor Antagonists for edema due to liver cirrhosis and for heart failure
)spironolactone [Aldactone([®

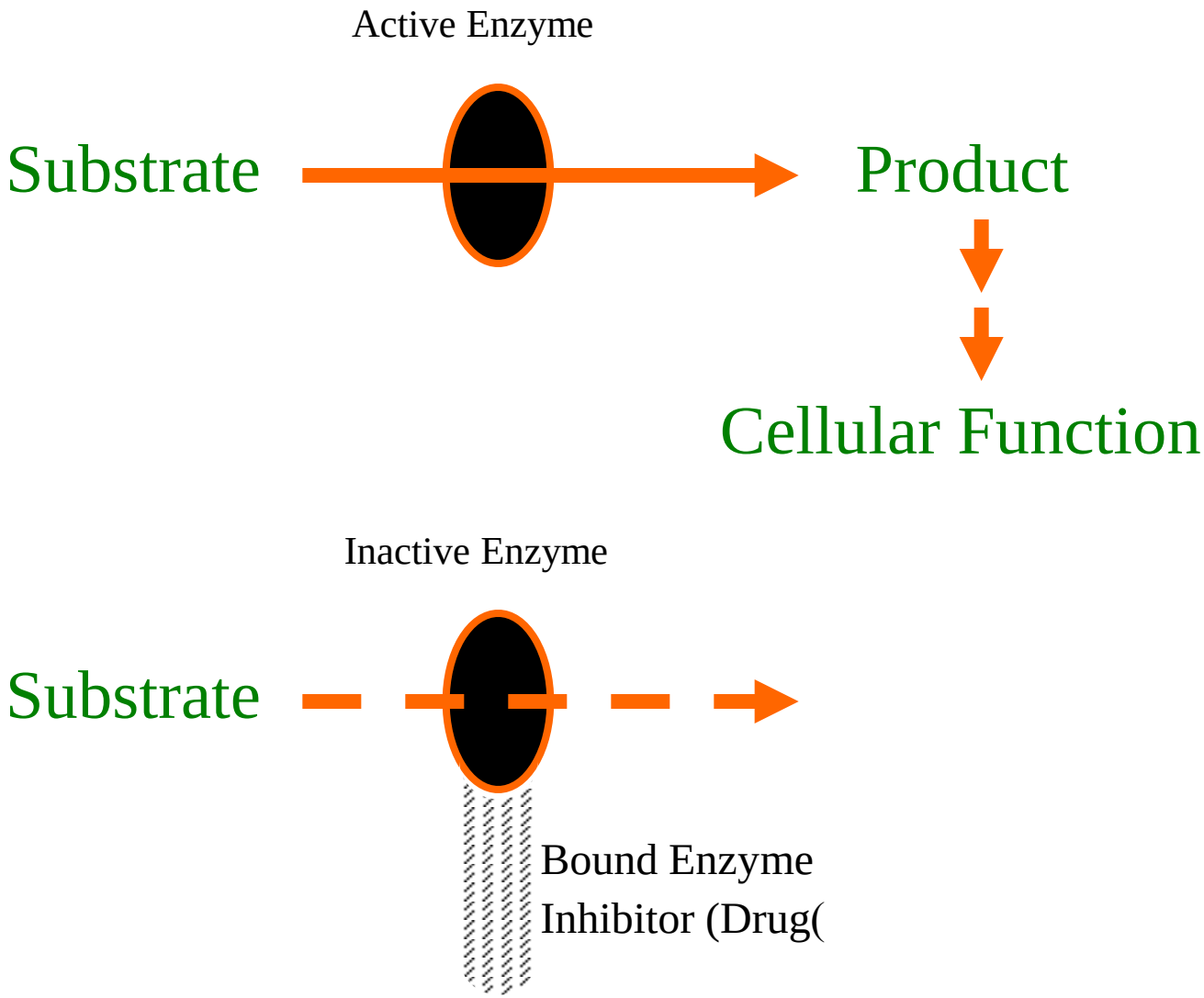
• Estrogen Receptor Antagonists for the prevention and treatment of breast cancer (tamoxifen [Nolvadex([®

HOW DO DRUGS ANTAGONIZE, BLOCK OR INHIBIT ENDOGENOUS PROTEINS?

Antagonists of Cell Surface Receptors

- Antagonists of Nuclear Receptors
- Enzyme Inhibitors
- Ion Channel Blockers
- Transport Inhibitors
- Inhibitors of Signal Transduction Proteins

HOW DO DRUGS WORK BY INHIBITING ENZYMES?



HOW DO DRUGS WORK BY INHIBITING ENZYMES? KEY CONCEPTS:

Enzymes catalyze the biosynthesis of products from substrates.

- Some drugs bind to enzymes and inhibit enzymatic activity.

- Loss of product due to enzyme inhibition mediates the effects of enzyme inhibitors.

ARE DRUGS THAT INHIBIT ENZYMES CLINICALLY USEFUL?

Some important examples:

• Cyclooxygenase Inhibitors for pain relief, particularly due to arthritis (aspirin; ibuprofen [Motrin([®

HMG-CoA Reductase Inhibitors for hypercholesterolemia)atorvastatin [Lipitor®]; pravastatin [Pravachol([®

Angiotensin Converting Enzyme (ACE) Inhibitors for high blood pressure, heart failure, and chronic renal insufficiency
)captopril [Capoten®]; ramipril [Altace([®

HOW DO DRUGS ANTAGONIZE, BLOCK OR INHIBIT ENDOGENOUS PROTEINS?

- Antagonists of Cell Surface Receptors
- Antagonists of Nuclear Receptors
- Enzyme Inhibitors
- Ion Channel Blockers
- Transport Inhibitors
- Inhibitors of Signal Transduction Proteins

ARE DRUGS THAT BLOCK ION CHANNELS CLINICALLY USEFUL?

Some important examples:

Calcium Channel Blockers (CCBs) for angina and high blood pressure

)amlodipine [Norvasc®]; diltiazem [Cardizem([®

- Sodium Channel Blockers to suppress cardiac arrhythmias

)lidocaine [Xylocaine®]; amiodarone [Cordarone([®

HOW DO DRUGS ANTAGONIZE, BLOCK OR INHIBIT ENDOGENOUS PROTEINS?

Antagonists of Cell Surface Receptors

- Antagonists of Nuclear Receptors
- Enzyme Inhibitors
- Ion Channel Blockers
- Transport Inhibitors
- Inhibitors of Signal Transduction Proteins

ARE DRUGS THAT INHIBIT TRANSPORTERS CLINICALLY USEFUL?

Some important examples:

Selective Serotonin Reuptake Inhibitors (SSRIs) for the treatment of depression

)fluoxetine [Prozac®]; fluvoxamine [Luvox([®

Inhibitors of Na-2Cl-K Symporter (Loop Diuretics) in renal epithelial cells to increase urine and sodium output for the treatment of edema

)furosemide [Lasix®]; bumetanide [Bumex([®

HOW DO DRUGS ANTAGONIZE, BLOCK OR INHIBIT ENDOGENOUS PROTEINS?

Antagonists of Cell Surface Receptors

- Antagonists of Nuclear Receptors
- Enzyme Inhibitors
- Ion Channel Blockers
- Transport Inhibitors
- Inhibitors of Signal Transduction Proteins

ARE DRUGS THAT INHIBIT SIGNAL TRANSDUCTION PROTEINS CLINICALLY USEFUL?

Some important examples:

Tyrosine Kinase Inhibitors for chronic myelocytic leukemia)imatinib [Gleevec([®

Type 5 Phosphodiesterase Inhibitors for erectile dysfunction)sildenafil [Viagra([®

- This is a major focus of drug development

HOW DO DRUGS WORK BY ACTIVATING ENDOGENOUS PROTEINS?

Agonists of Cell Surface Receptors

)*e.g.* alpha-agonists, morphine agonists(

- Agonists of Nuclear Receptors

)*e.g.* HRT for menopause, steroids for inflammation(

- Enzyme Activators

)*e.g.* nitroglycerine (guanylyl cyclase), pralidoxime(

- Ion Channel Openers

)*e.g.* minoxidil (K) and alprazolam (Cl((

HOW DO CHEMICALS WORK BY ACTIVATING CELL SURFACE RECEPTORS?
KEY CONCEPTS:

•Cell surface receptors exist to transmit chemical signals from the outside to the inside of the cell.

• Some chemicals bind to cell surface receptors and trigger a response.

• Chemicals in this group are called receptor agonists.

• Some agonists are actually the endogenous chemical signal, whereas other agonists mimic endogenous chemical signals.

HOW DO CHEMICALS WORK BY UNCONVENTIONAL MECHANISMS OF ACTION?

- Disrupting of Structural Proteins

e.g. vinca alkaloids for cancer, colchicine for gout

- Being Enzymes

e.g. streptokinase for thrombolysis

- Covalently Linking to Macromolecules

e.g. cyclophosphamide for cancer

- Reacting Chemically with Small Molecules

e.g. antacids for increased acidity

- Binding Free Molecules or Atoms

e.g. drugs for heavy metal poisoning, infliximab (anti-TNF(

HOW DO DRUGS WORK BY UNCONVENTIONAL MECHANISMS OF ACTION (Continued?(

- Being Nutrients

e.g. vitamins, minerals

- Exerting Actions Due to Physical Properties

e.g. mannitol (osmotic diuretic), laxatives

- Working Via an Antisense Action

e.g. fomivirsen for CMV retininitis in AIDS

- Being Antigens

e.g. vaccines

- Having Unknown Mechanisms of Action

e.g. general anesthetics