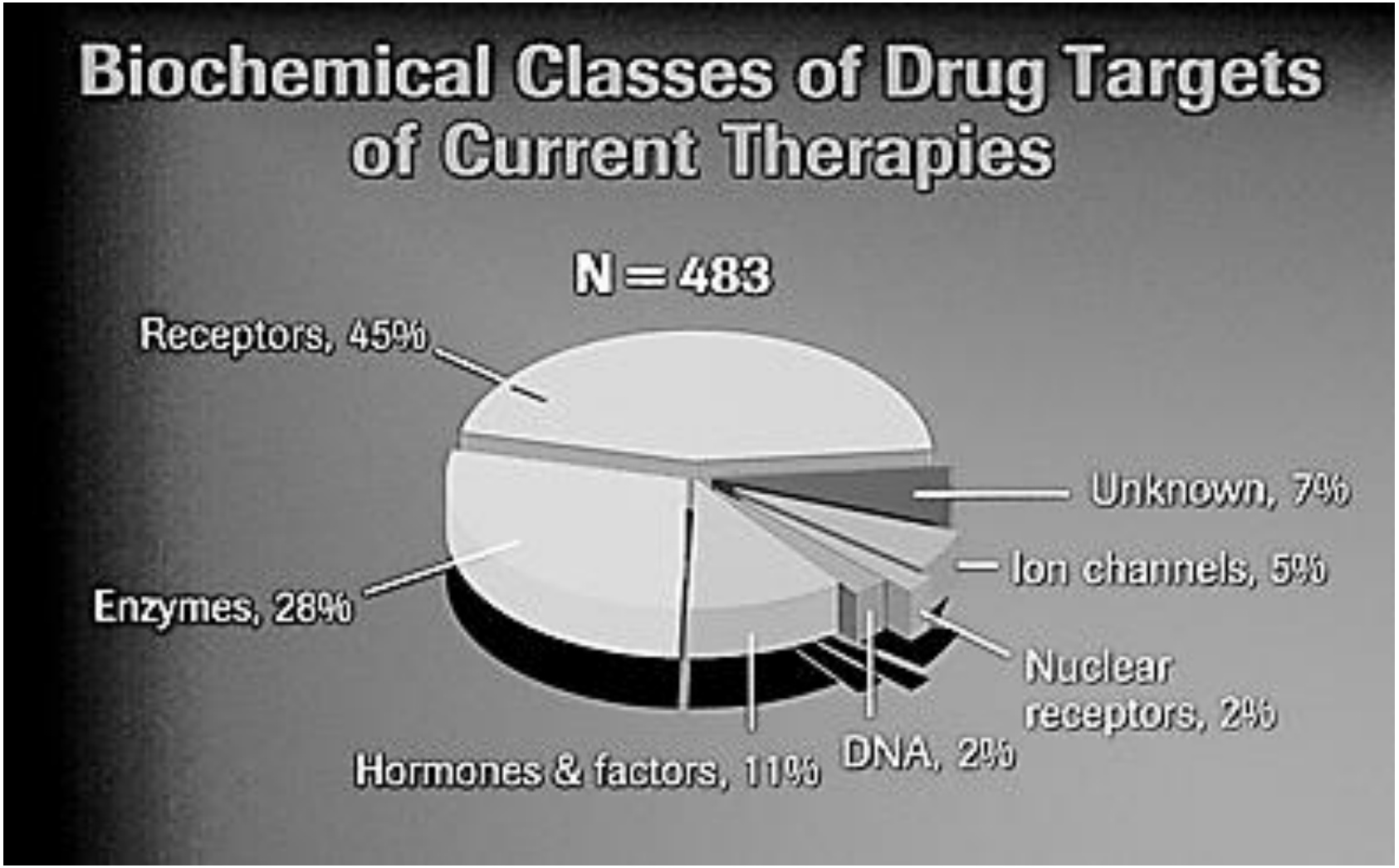
Areas of Pharmacology

- The main areas of pharmacology are:

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

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


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%

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.

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.

Most receptors are proteins that have undergone various post-translational modifications such as covalent attachments of carbohydrate, lipid and phosphate.

Definition of *CELL SURFACE RECEPTOR*:

A receptor that is embedded in the cell membrane and functions to receive chemical information from the extracellular compartment and to transmit that information to the intracellular compartment.

Major receptor families

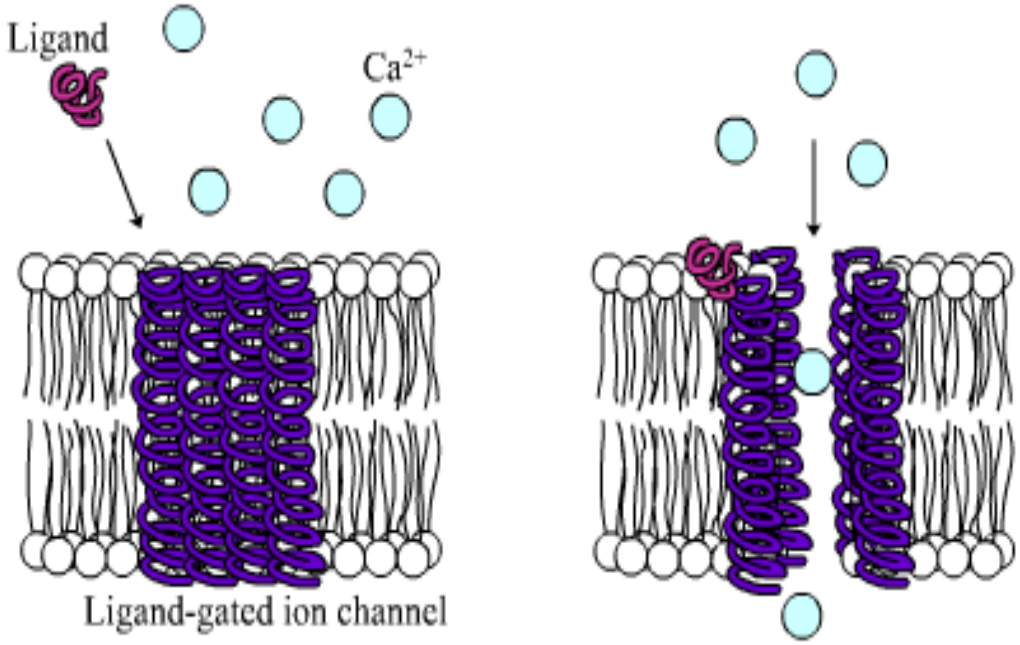
- **Ligand-gated ion channels**
- **G protein-coupled receptors**
- **Enzyme-linked receptors**
- **Intracellular receptors**

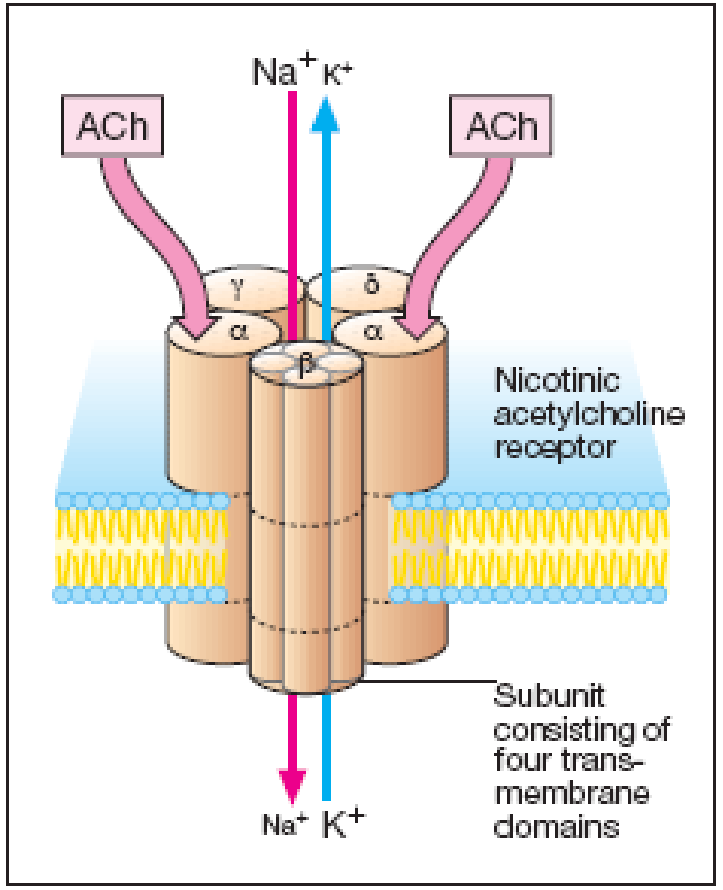
Ligand-gated ion channels

- 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



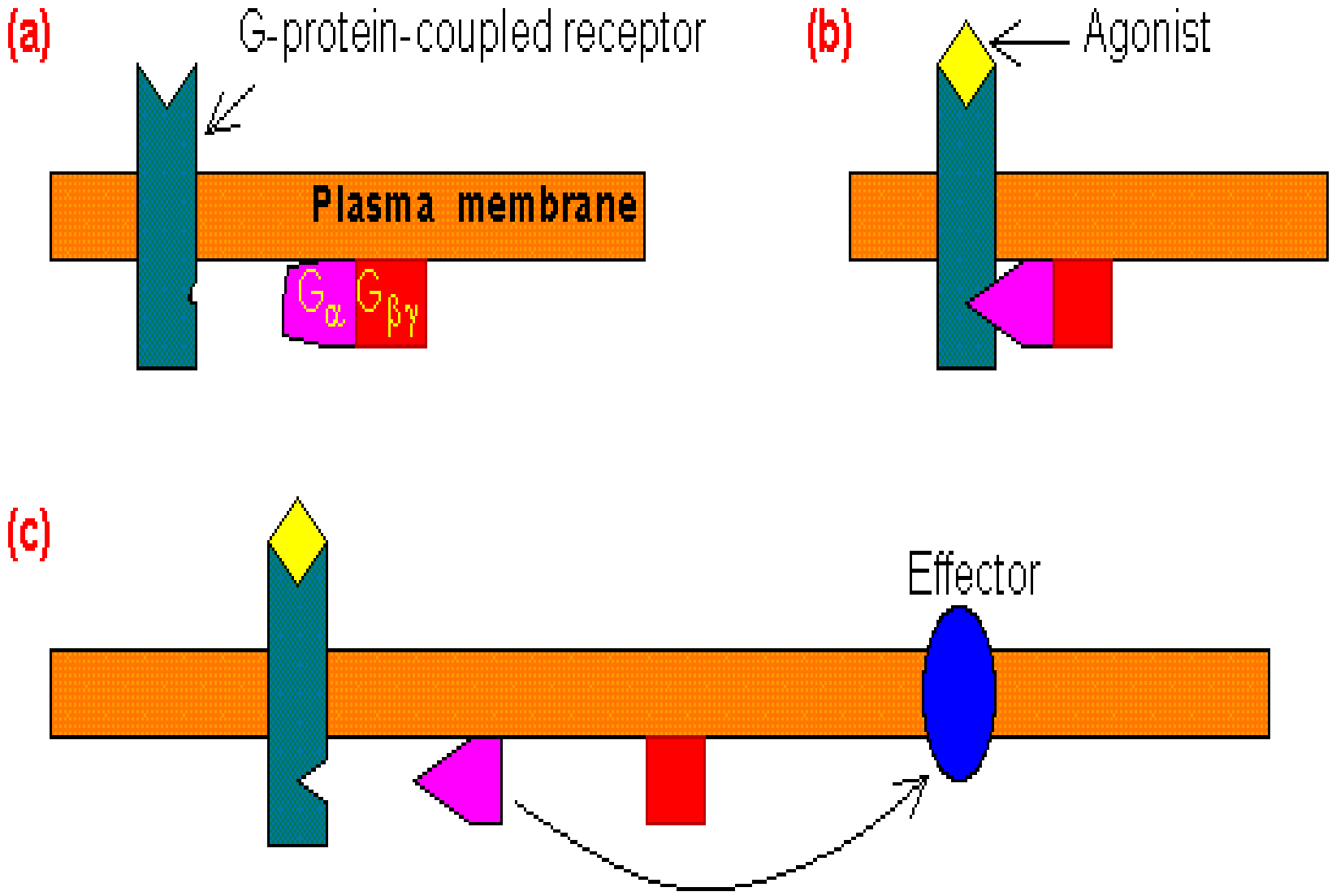


B. Ligand-gated ion channel

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 moscarinic receptors depend n the G proteins) mediate their action on cells.

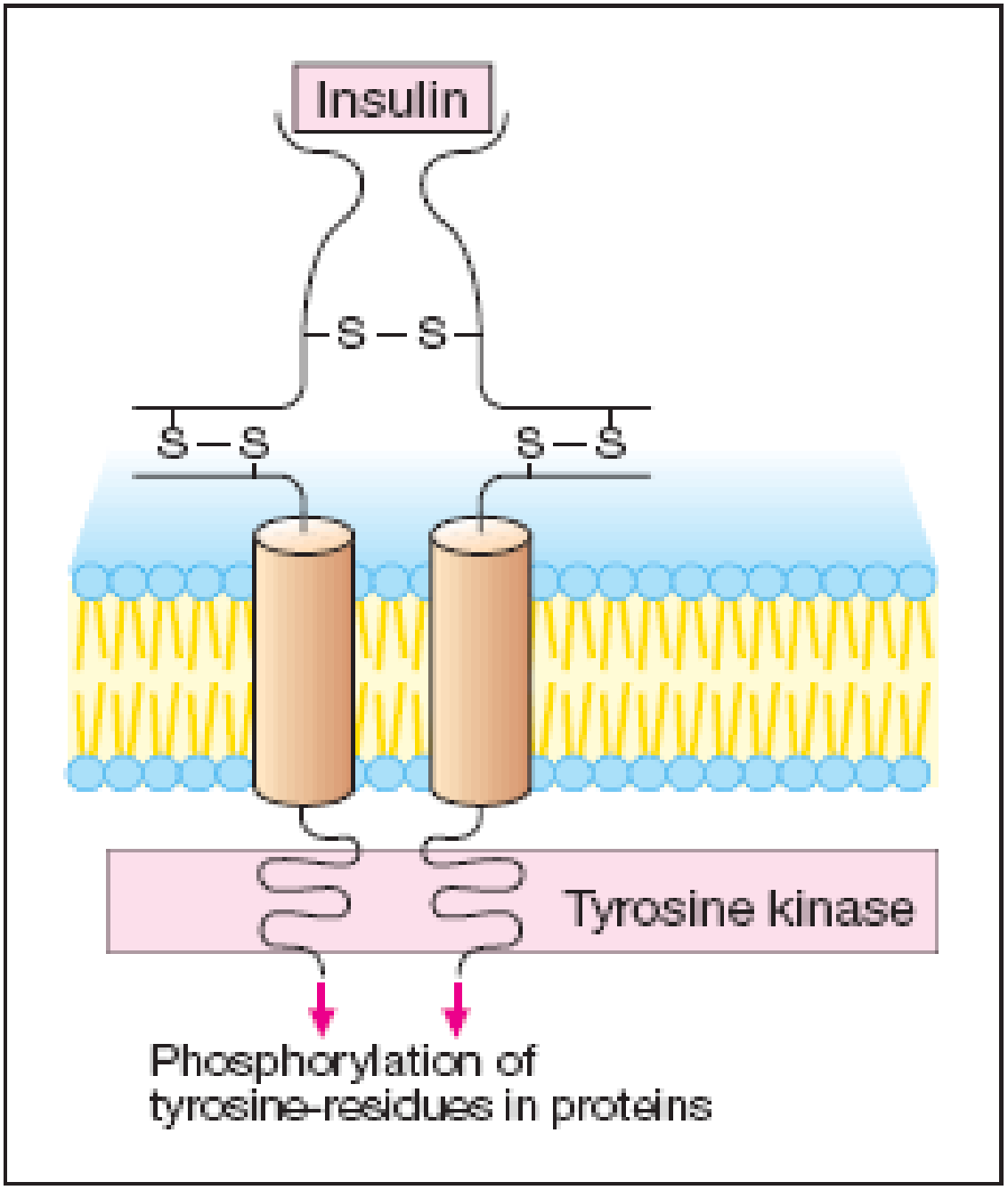

(a)
G-protein-coupled receptor
Plasma membrane
G_α $G_{\beta\gamma}$
(b)
Agonist
(c)
Effector

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.



C. Ligand-regulated enzyme

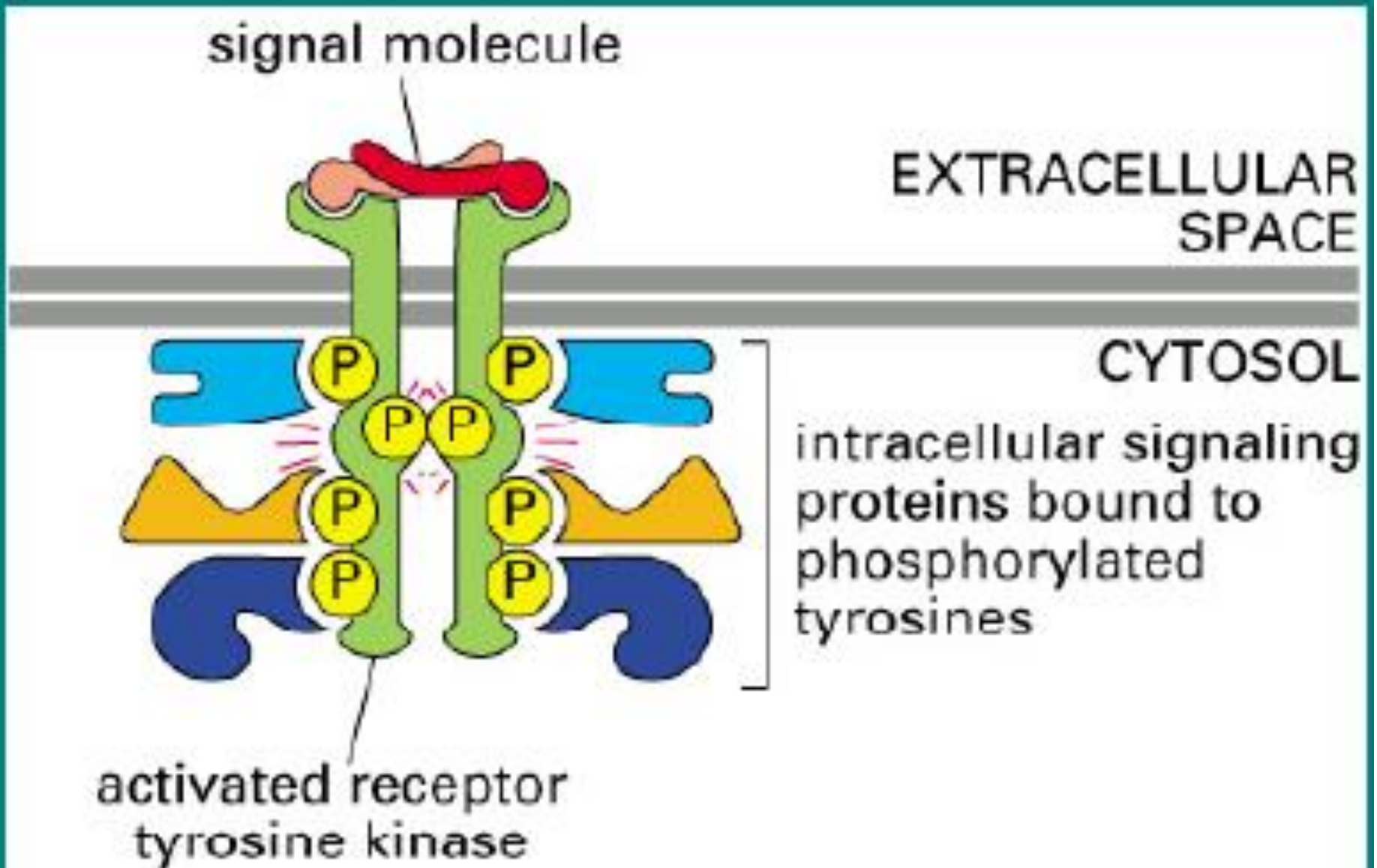
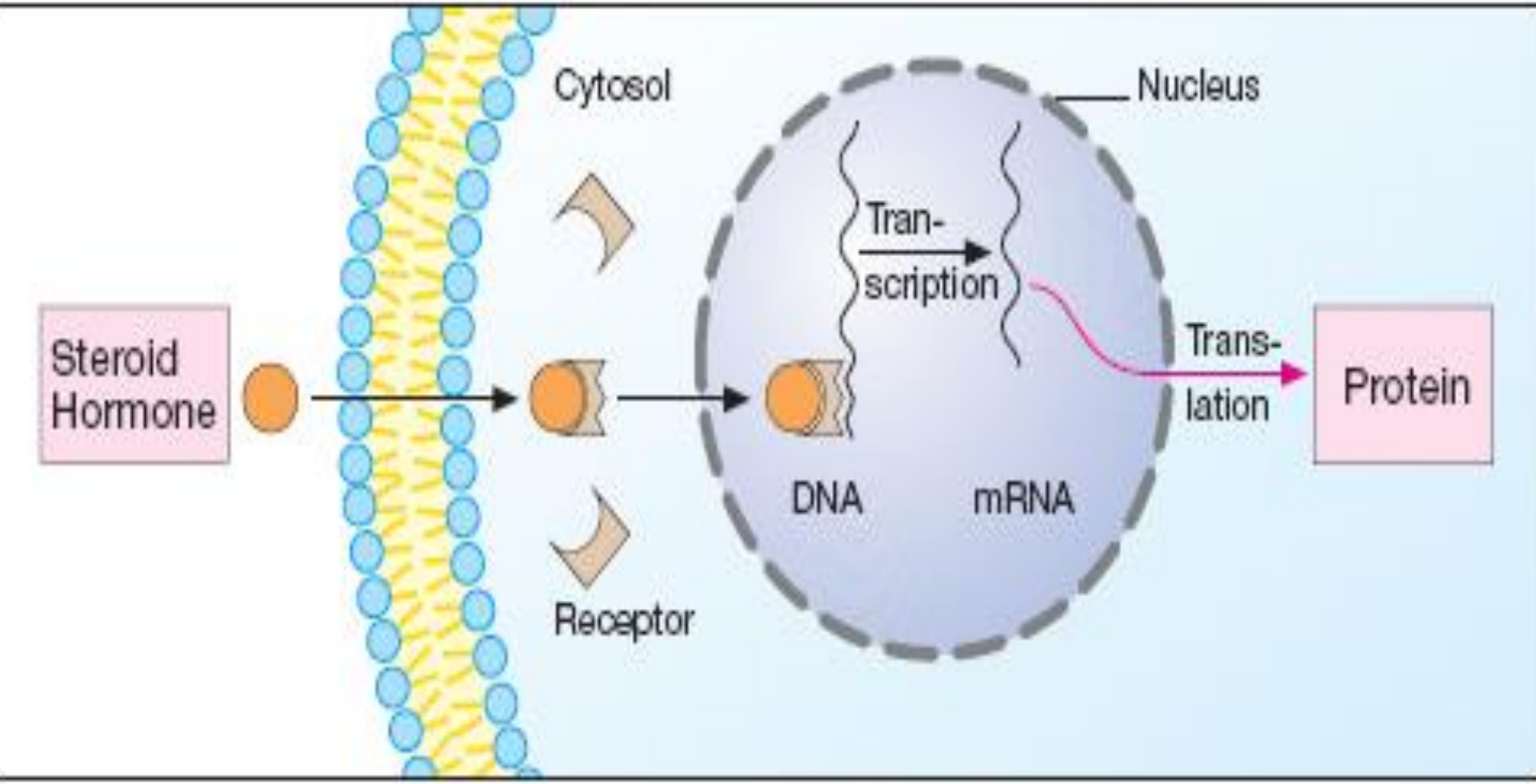


Figure 15–52. Molecular Biology of the Cell, 4th Edition.

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

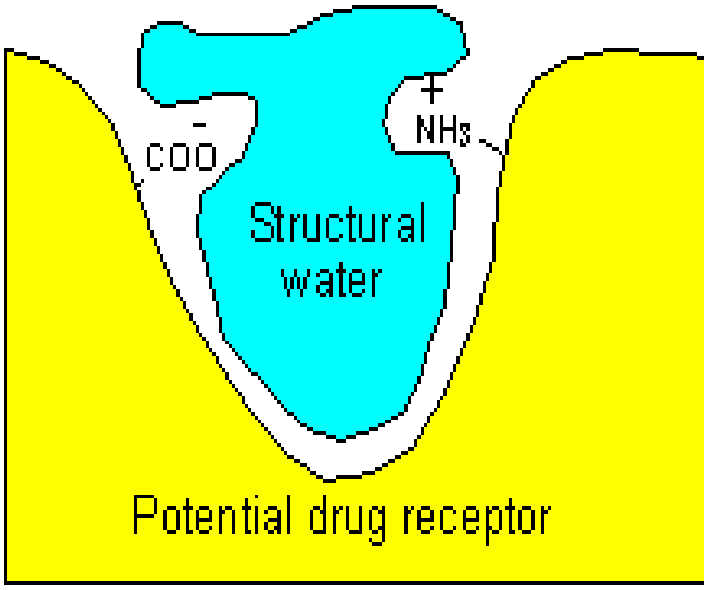
Receptors

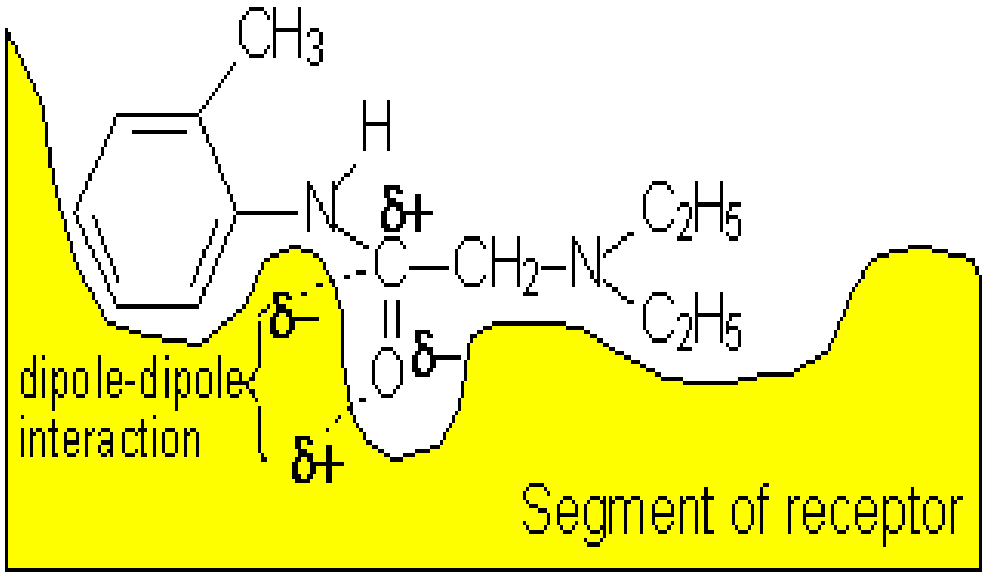
- determine specificity of drug action
- *most* are proteins
- Most drugs bind reversibly (noncovalent)
- not all “drugs” use receptors

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

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

HOW DO DRUGS WORK on RECE

- Some *antagonize receptors*
- Some *activate receptors (Agonists)*

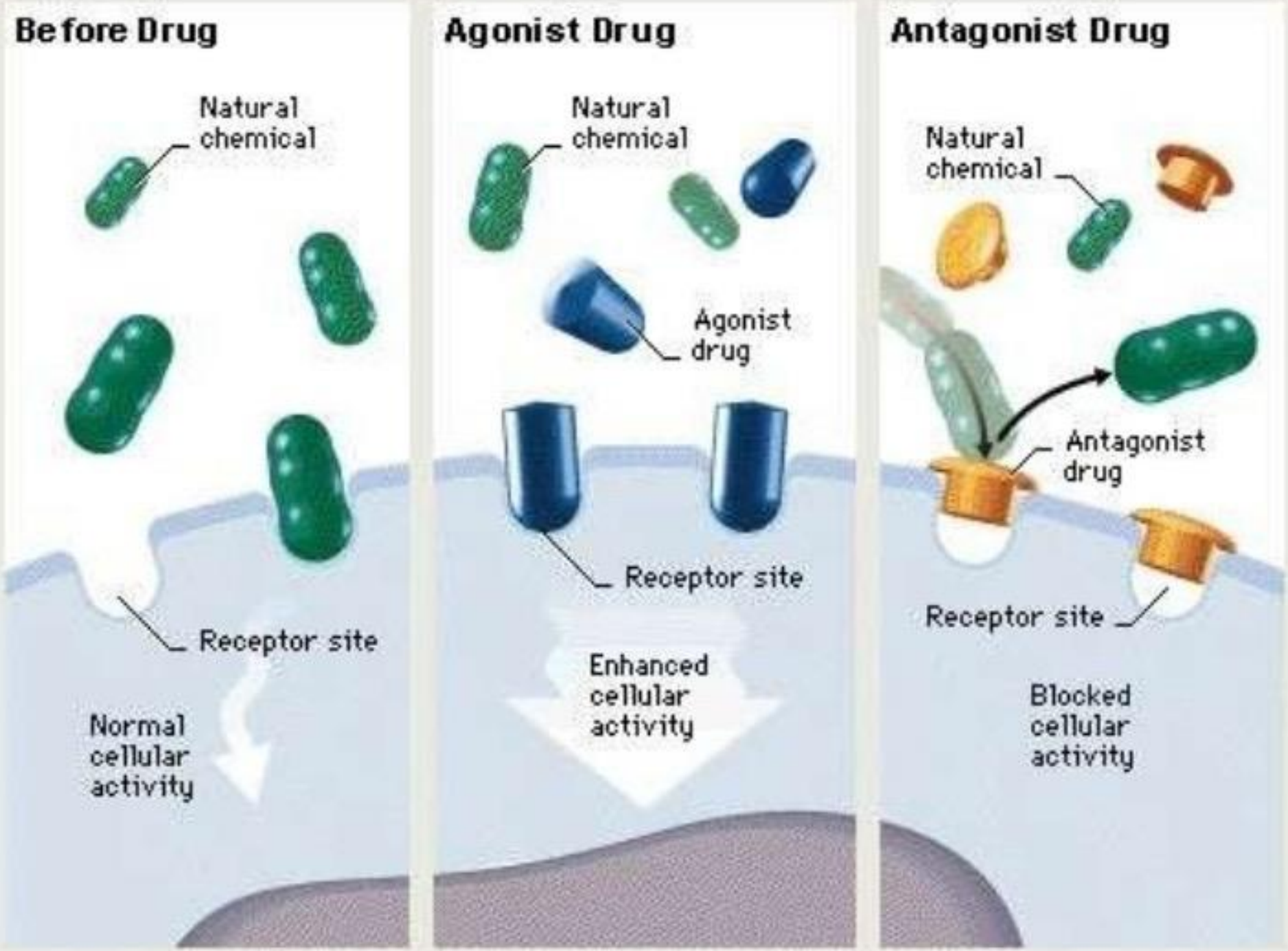
HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS? KEY CONCEPTS:

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

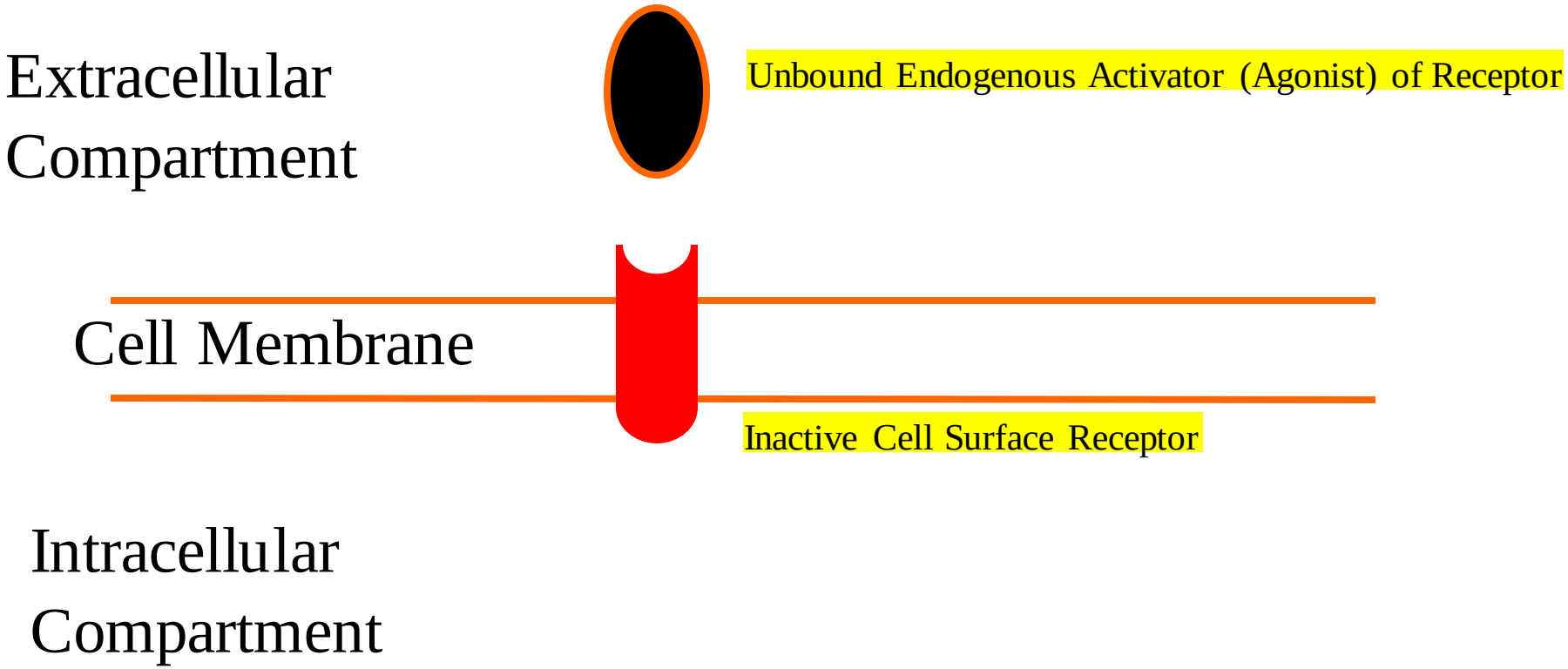
- **Some compounds bind to cell surface receptors, yet do not activate the receptors to trigger a response.**

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

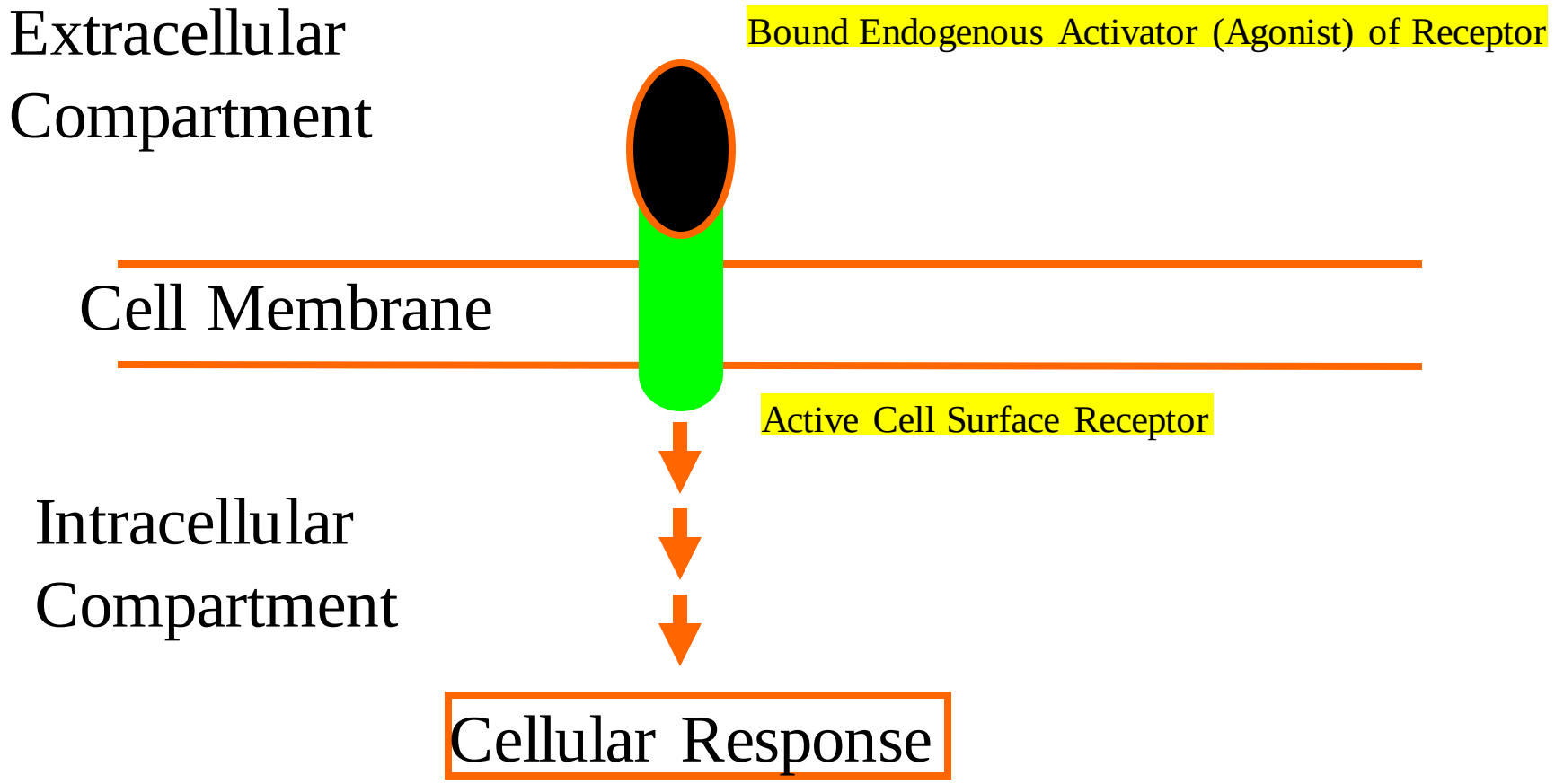
- **The compound is said to “antagonize” or “block” the receptor and is referred to as a receptor antagonist.**


Before Drug
Natural chemical
Receptor site
Normal cellular activity
Agonist Drug
Natural chemical
Agonist drug
Receptor site
Enhanced cellular activity
Antagonist Drug
Natural chemical
Antagonist drug
Receptor site
Blocked cellular activity

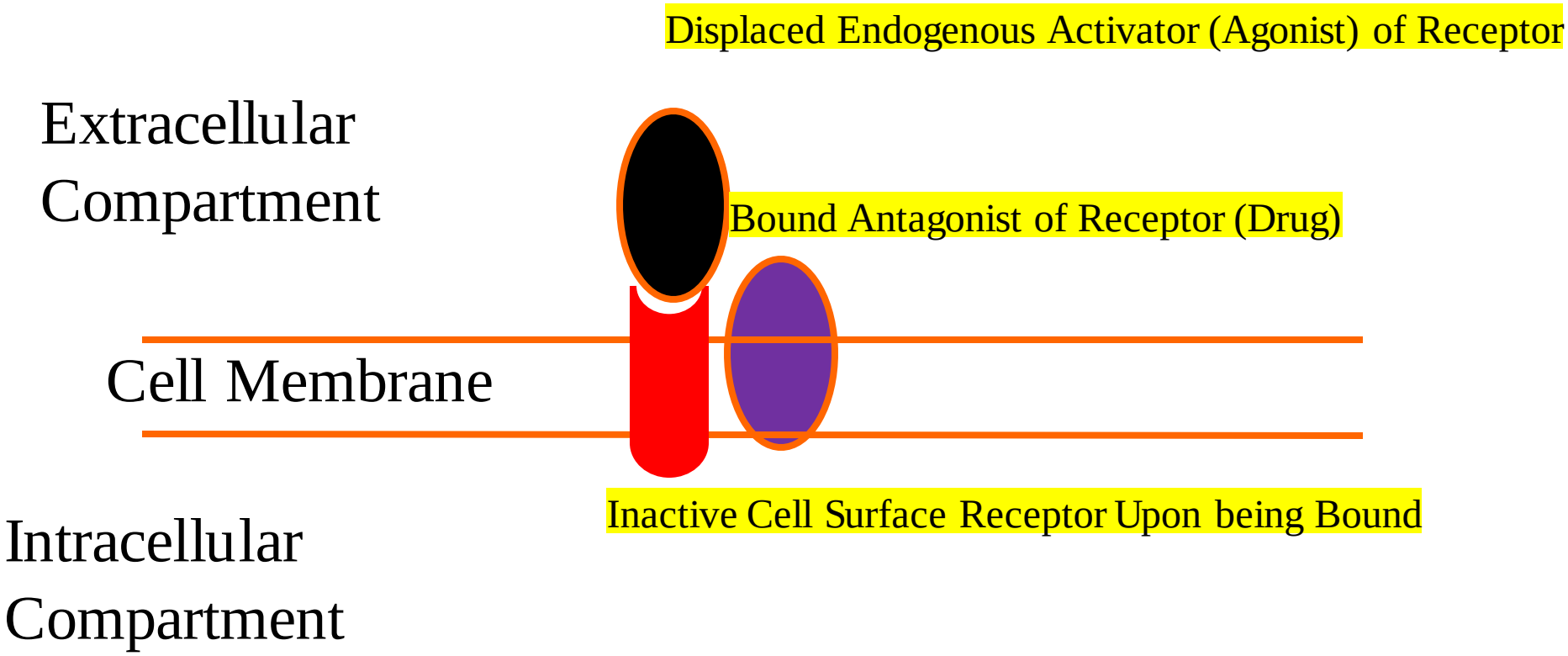
HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS?



HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS?



HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS?



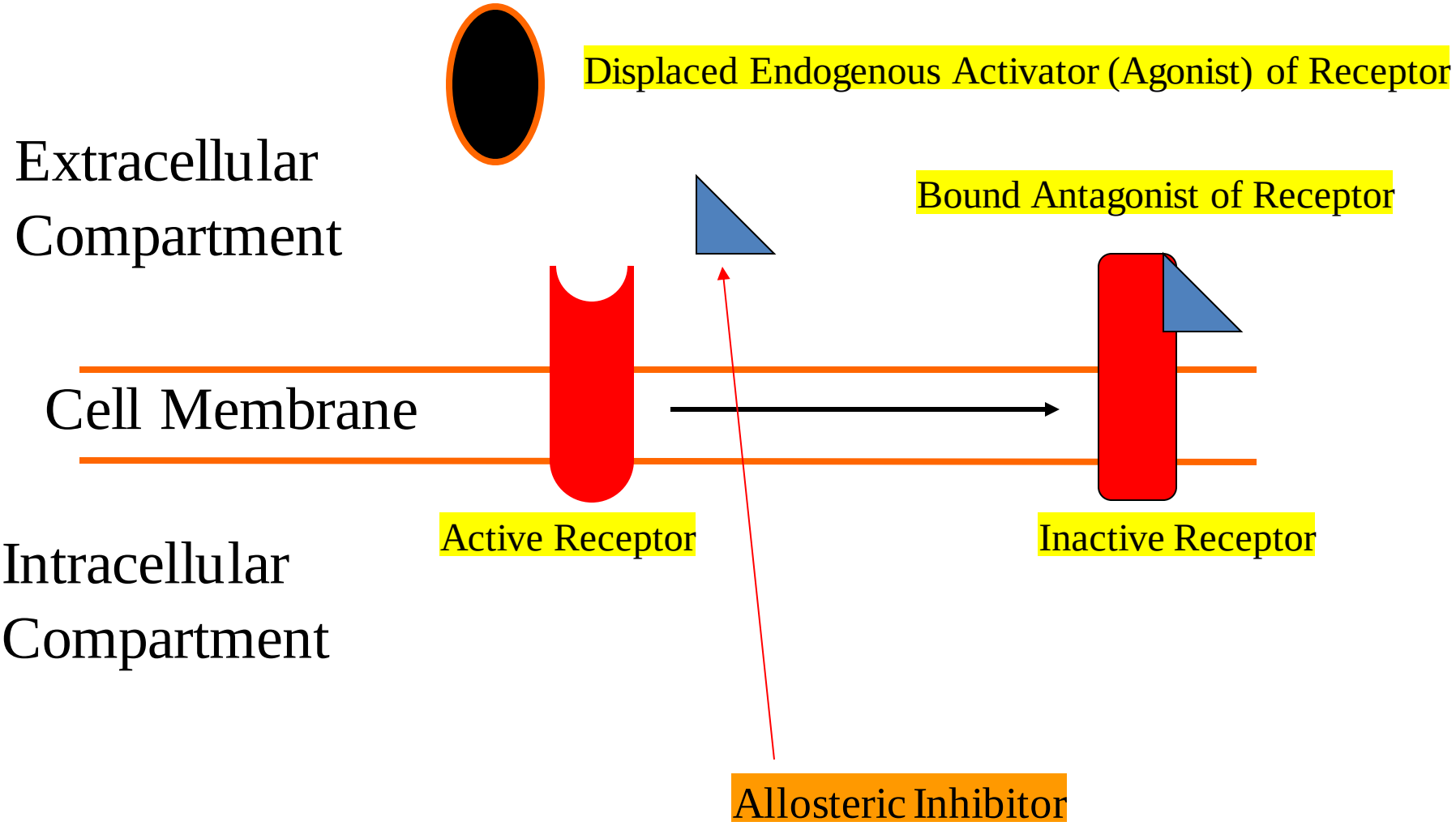
HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS?

Footnote:

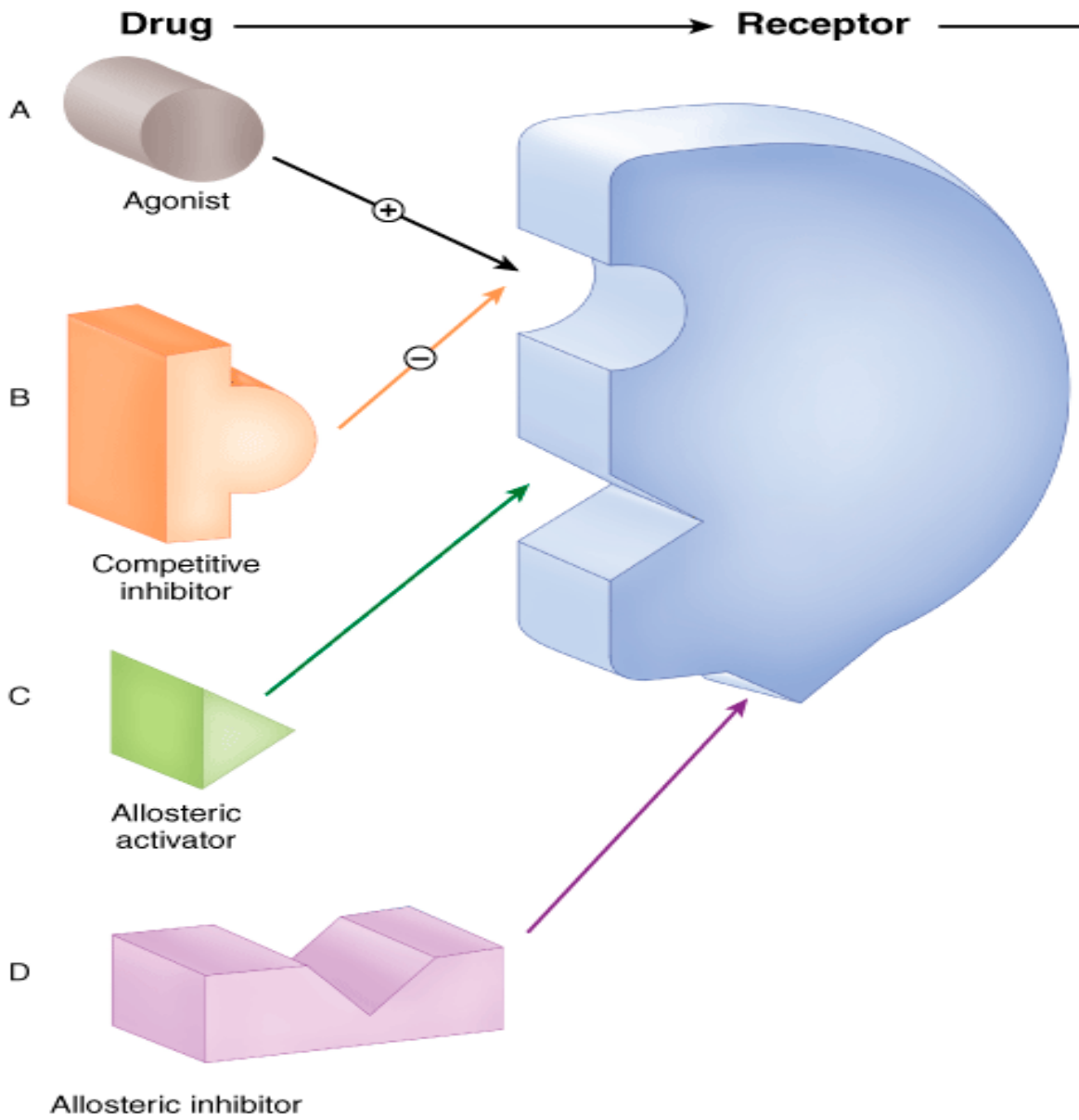
Most antagonists attach to binding site on receptor for endogenous agonist and sterically prevent endogenous agonist from binding.
If binding is reversible - Competitive antagonists
If binding is irreversible - Noncompetitive antagonists

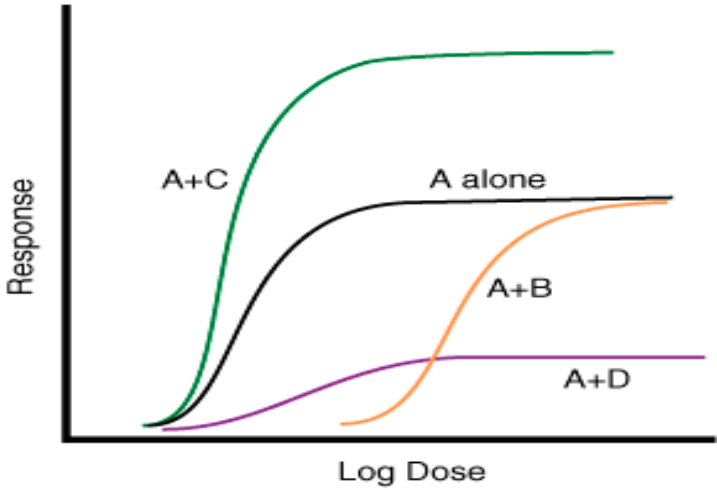
However, antagonists may bind to remote site on receptor and cause allosteric effects that displace endogenous agonist or prevent endogenous agonist from activating receptor. (Noncompetitive antagonists)

HOW DO DRUGS WORK BY ANTAGONIZING CELL SURFACE RECEPTORS?



Drug Receptor Interactions





Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*,

Other Drug Targets

- 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 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

Receptor Occupancy Theory

The "Law" of Mass Action

- **Activation of membrane receptors and target cell responses is *proportional to the degree of receptor occupancy.***
- Assumptions:
  - Association is limited by collision, orientation and energy
  - All receptors are equally accessible
  - All receptors are either free or bound, there is no "partial" binding
  - Neither drug or receptor are altered by binding
  - Binding is reversible

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®])

Drug-receptor binding

$$D + R \xrightarrow{k} DR$$

$$DR \xrightarrow{k^{-1}} D + R$$

$$\frac{k^{-1}}{k} = K_D$$

$$\frac{\text{sec}^{-1}}{M^{-1}\,\text{sec}^{-1}} = M$$

- **This ratio is the equilibrium dissociation constant or KD**

- **This dissociation constant, Kd, indicates the strength of binding between R and D in terms of how easy it is to separate the complex DR**

Hill-Langmuir equation

$$B/B_{max} = \frac{[D]}{[D] + K_D}$$

Drug Receptors & Pharmacodynamics

Receptors largely determine the quantitative relations between dose (or concentration) of the drug and pharmacologic effects.

- **The receptor's affinity for binding a drug determines the concentration of drug required to form a significant number of drug-receptor complexes,**
- **The total number of receptors limits the maximal effect a drug can produce.**

efficacy

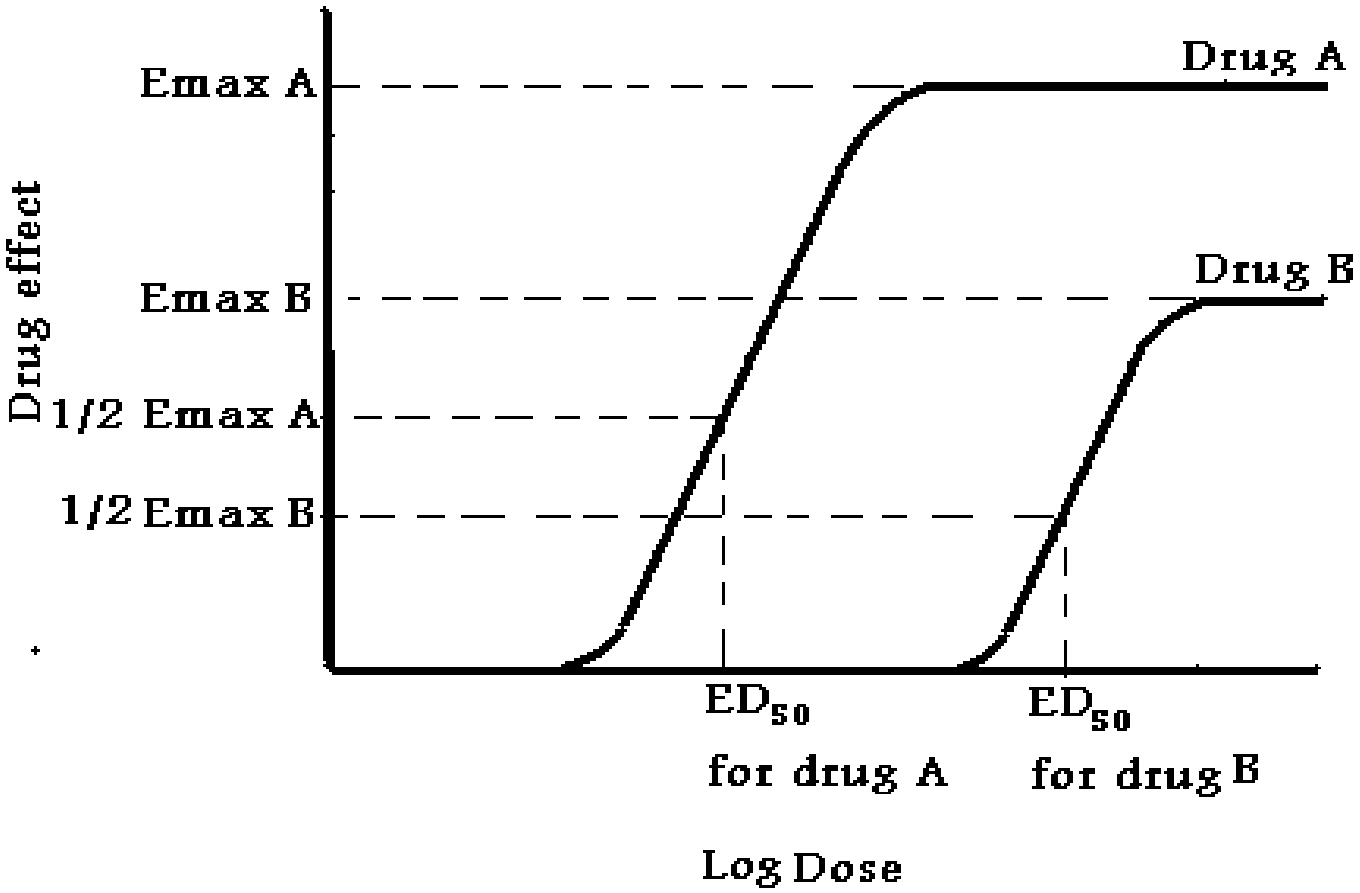
- Efficacy is the maximum effect of a drug, Emax, and does depend on the number of drug-receptor complexes formed, and also on the efficiency of the of coupling of receptor activation to cellular responses.

- Aspirin and morphine produce the same pharmacologic effect (analgesia) but have very different levels of efficacy.

efficacy

- If drug can stimulate a receptor to produce a biological response it is said to have efficacy or intrinsic activity.
- Efficacy refers to the capacity of a drug to produce an effect or the overall magnitude of the maximum response, synonymous with intrinsic activity
- If a drug stimulates a full response, it might to said to be a full agonist and to be very efficacious.

Log dose response curve



- The smaller the EC50, the greater the potency.
- Efficacy is indicated by the height of the log dose response

Antagonism between drugs

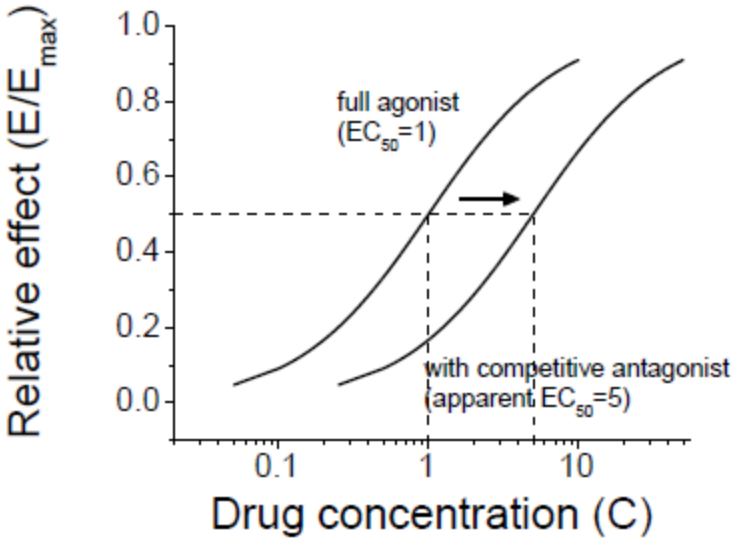
A. Pharmacologic antagonism: occurs when an antagonist prevent an agonist from interacting with its receptors to produce an effect, and it can be either competitive or noncompetitive.

Competitive antagonist compete with agonist in a reversible fashion in the receptors. The log dose-response curve is shifted to the right, indicating that a higher concentration of agonist is necessary to achieve the response.

Noncompetitive antagonist binds irreversibly to the receptors site or to another side that inhibit the response to the agonist. And no matter how much agonist is given, the action of the antagonist can not overcome. The shift in the log response curve in this case is a nonparallel shift.

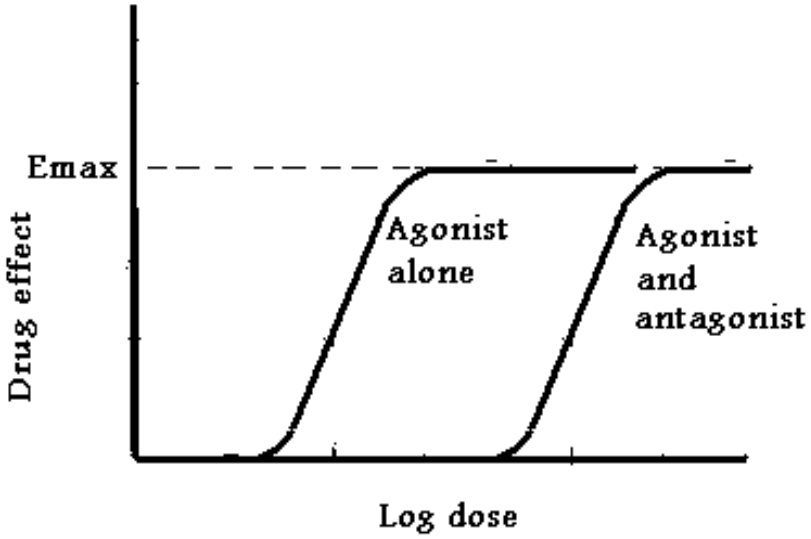
Competitive antagonists

- Bind agonist site
- Do not shift equilibrium towards active or inactive conformation
- “Neutral” antagonists

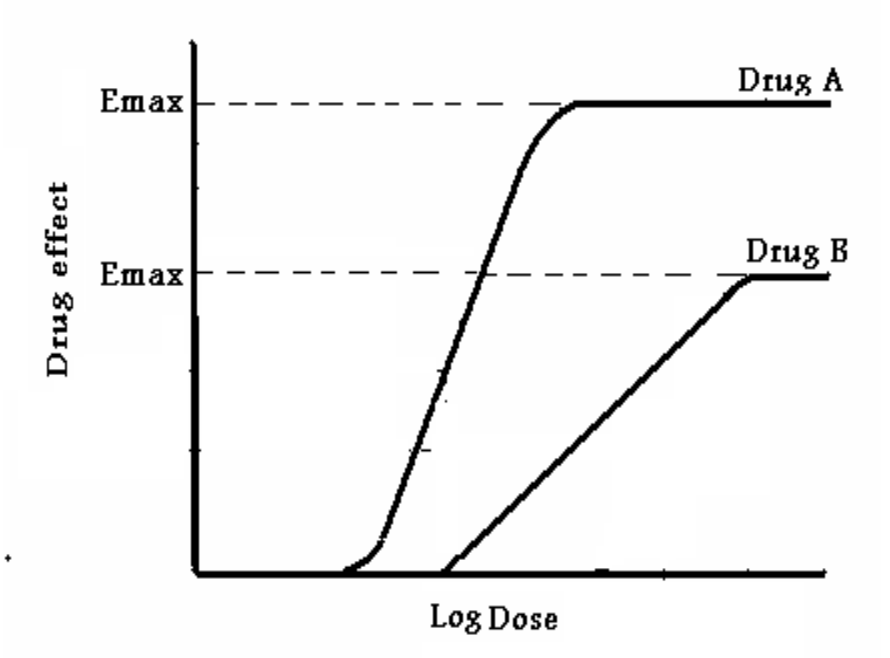


Shift in the log-dose response

Competitive antagonist

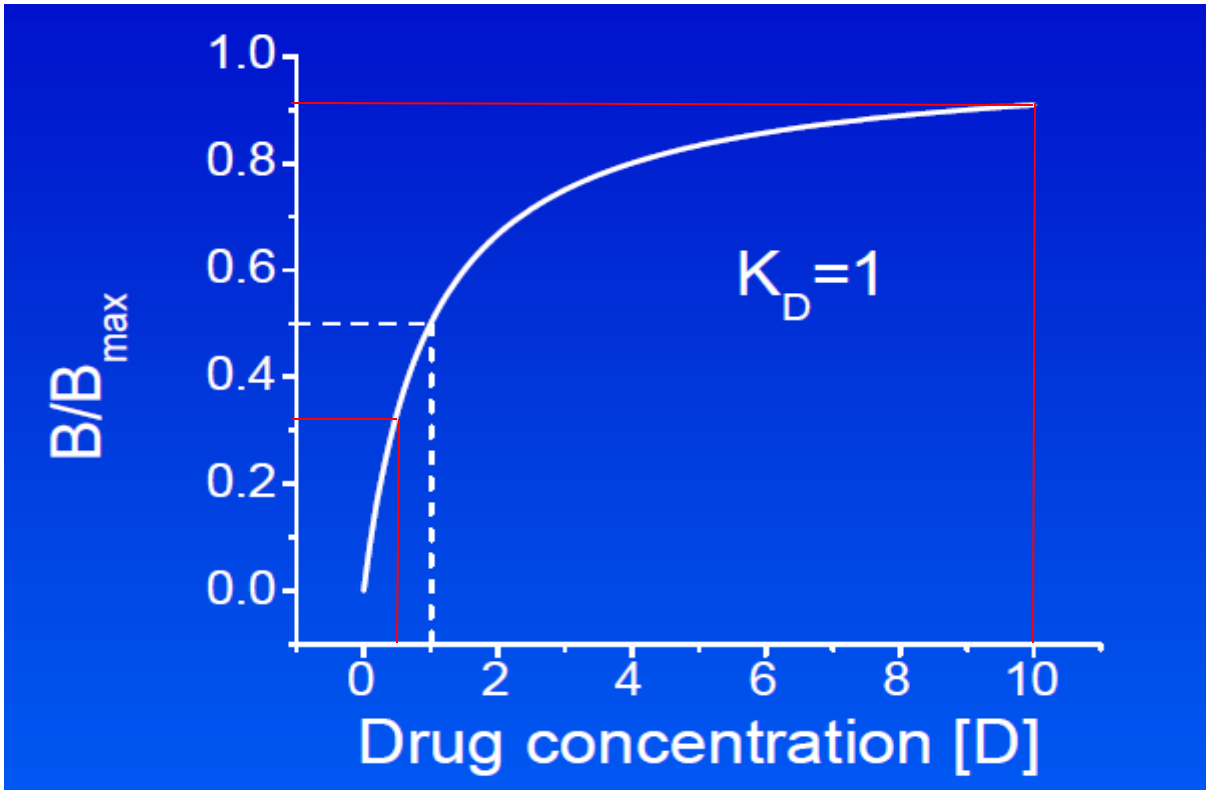


Noncompetitive antagonist



Agonist-Antagonist Relationships

- **Competitive antagonist, higher concentrations of agonist are required to produce a given effect. High agonist concentrations can overcome inhibition by a competitive antagonist.**
- **Irreversible (or noncompetitive) antagonist, reduces the maximal effect the agonist can achieve, although it may not change its EC50.**



KD: concentration at which binding site is 50% occupied.

Affinity 1/Kd

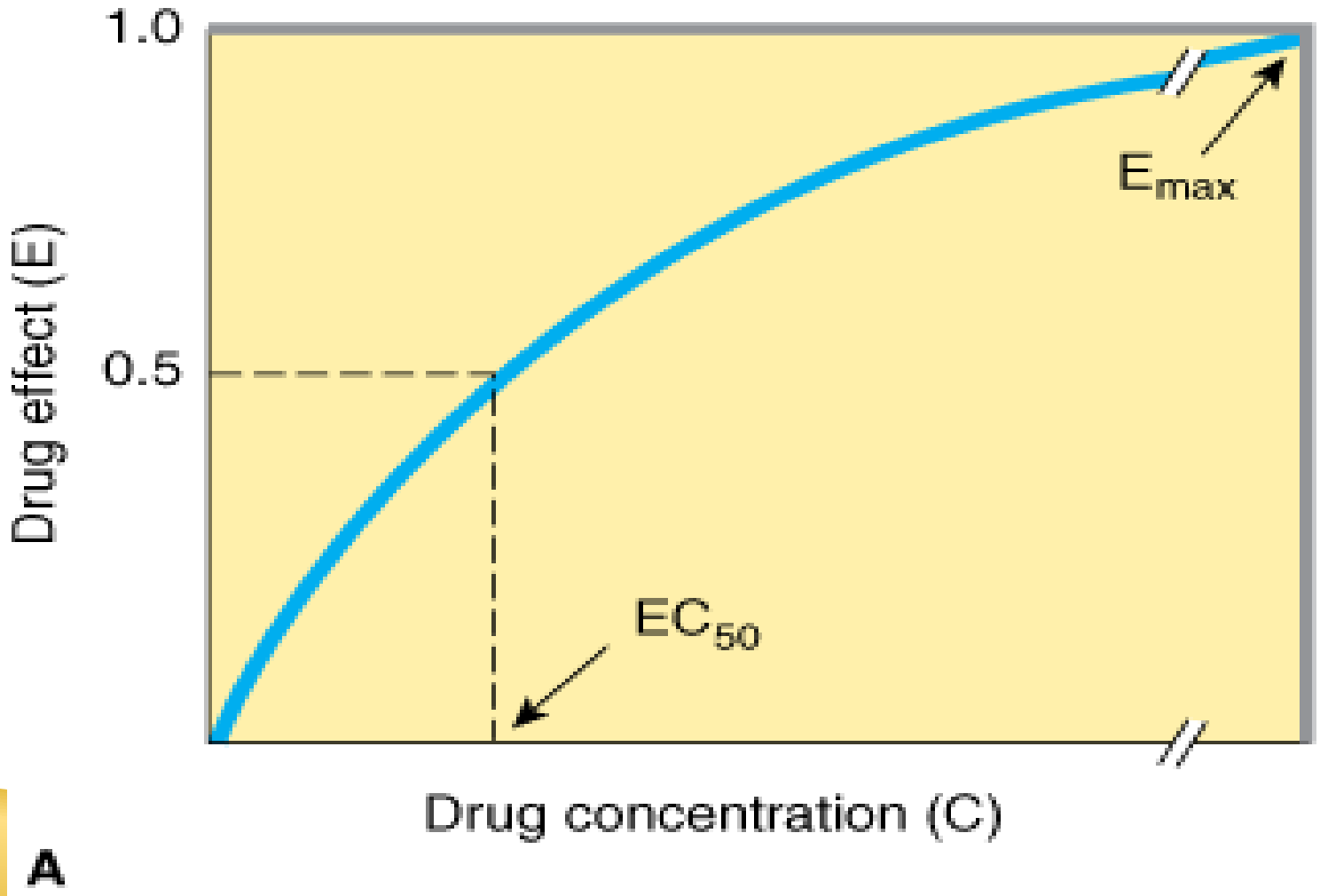
Dose response relationships

- Graduate dose-response relations

As the dose administrated to single subject or isolated tissue is increased , the pharmacologic effect will also increase.

At a certain dose, the effect will reach a maximum level, which is called the ceiling effect or Emax.

Relations between drug concentration and drug effect

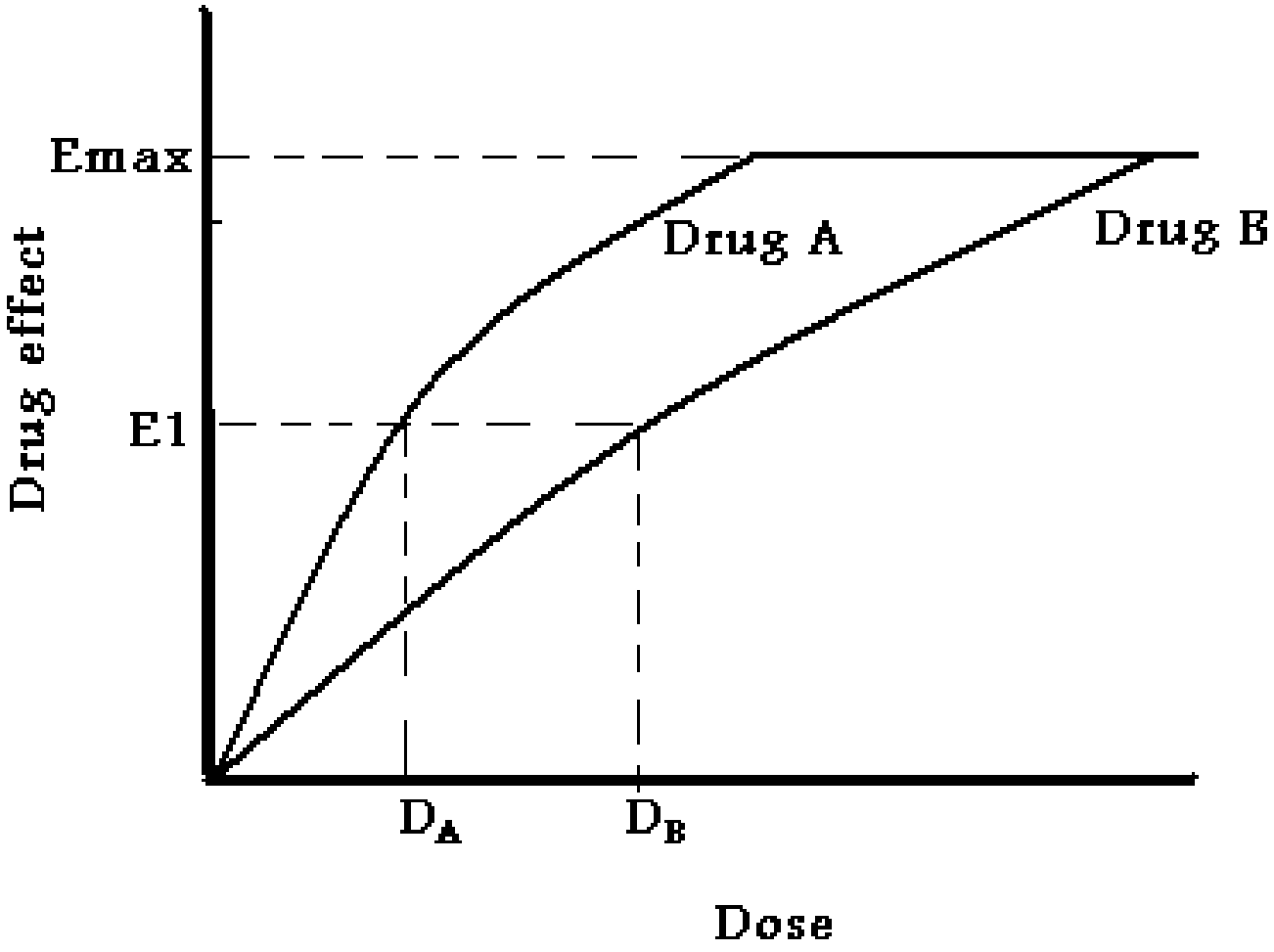


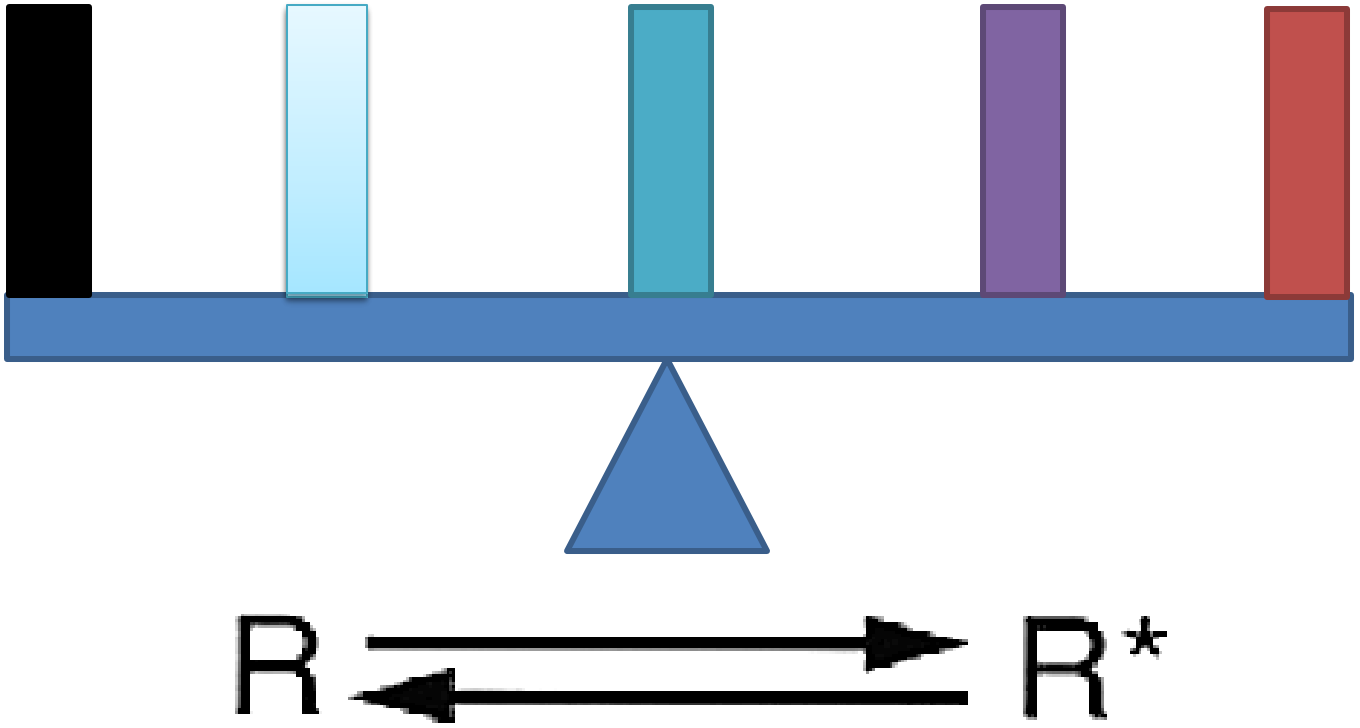
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

Potency

- Potency refers to the affinity of a drug for its receptor or the concentration of drug required to produce a given effect. Low KD, high potency
- • Potency refers to the amount or concentration of drug required to produce a response.
- • On dose-response curves potency is measured on the X-axis.
- • ED50, EC50, and Kd are measures of potency.

Graduate dose-response curve





- Full agonist
- Partial agonist
- Antagonist

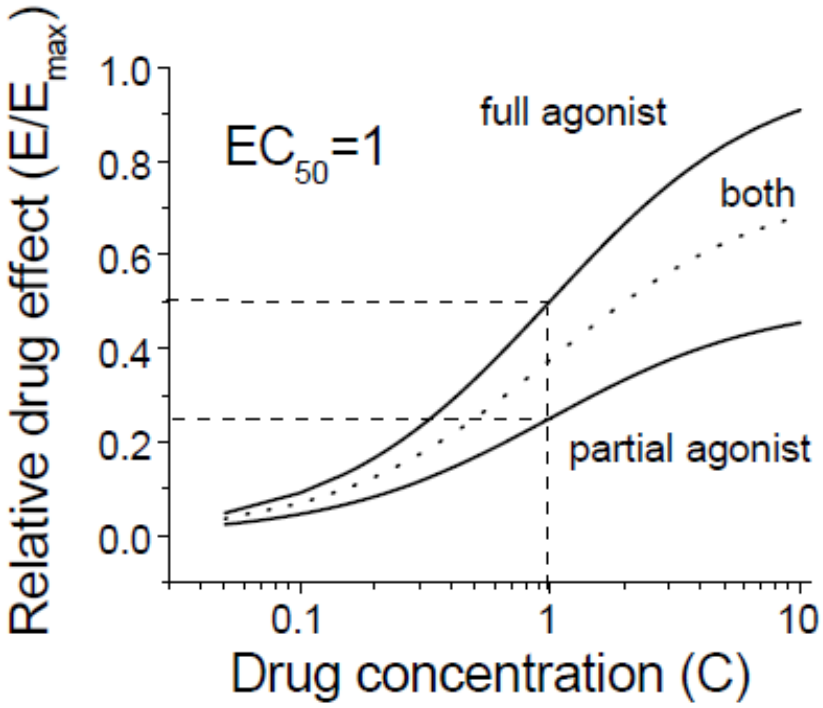
- Partial inverse agonist
- Full inverse agonist

Inverse agonists

- Inverse agonists shift equilibrium towards the inactive conformation
- Effect obvious *if* much constitutive activity

Two-state model of drug-receptor interaction

- Full agonists shift equilibrium “fully” towards the active conformation
- Partial agonists shift equilibrium “partially” towards the active conformation
- Sub-maximal effect with receptors completely occupied


Relative drug effect (E/E$_{max}$)
1.0
0.8
0.6
0.4
0.2
0.0
EC$_{50}$=1
full agonist
both
partial agonist
0.1
1
10
Drug concentration (C)

Antagonism between drugs

B. Physiologic Antagonist: here the drugs act independently on two different receptors, and exemplified by one drug acting on the sympathetic nervous system causing the heart rate to increase and causing vasoconstruction; while another drug acting on the parasympathetic nervous system decrease the heart rate and causes vasodilation.

C. Chemical antagonist (Antagonism by neutralization):

Occurs when two drugs combine with one another to form an inactive compound, and the best example being the drugs containing sulfhydryl (SH) groups, when combine with mercury or arsenic.

Enhancement of drug effects

A. Additive drug effect occurs if two drugs with the same effect , when given together produce an effect that is equal in magnitude to the sum of the effect.

$$E_{AB} = E_A + E_B \qquad 1 + 1 = 2$$

B. Synyrgic drug effect occurs if two drugs with the same effect, when given together, produce an effect that is greater in magnitude than the sum of effects when the drugs are given individually.

$$E_{AB} > E_A + E_B \qquad 1 + 1 > 2$$

C. Potentiation drug effect occurs if a drug lacking an effect of its own increase the effect of a second active drug.

$$E_{AB} > E_A + E_B \qquad 0 + 1 > 2$$

Therapeutic index and margin of safety

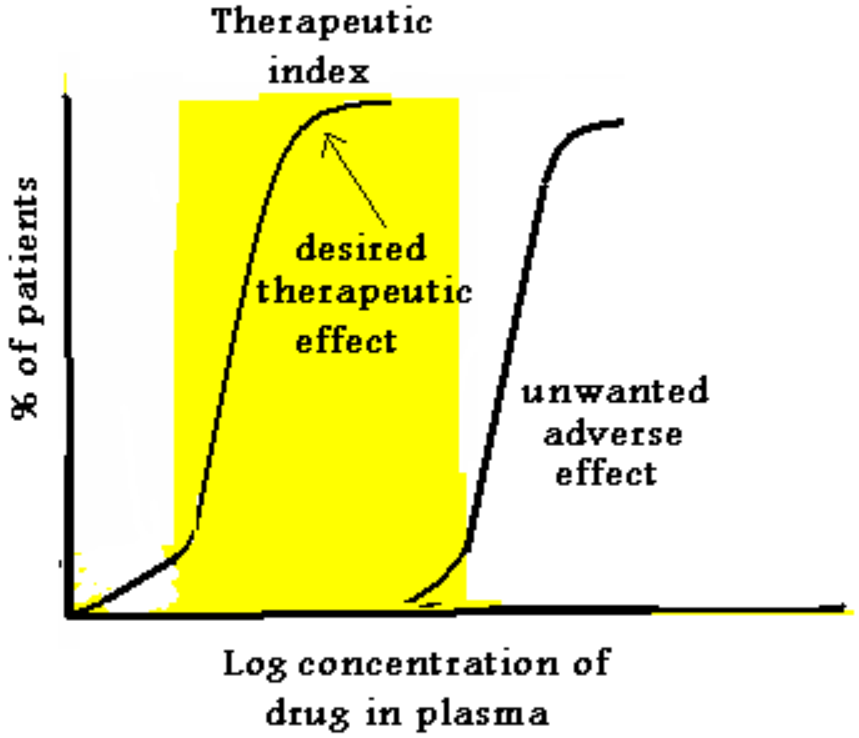
Therapeutic index of a drug is a ratio of the dose that produces toxicity to the dose that produces a clinically desired or effective response in a population individuals:

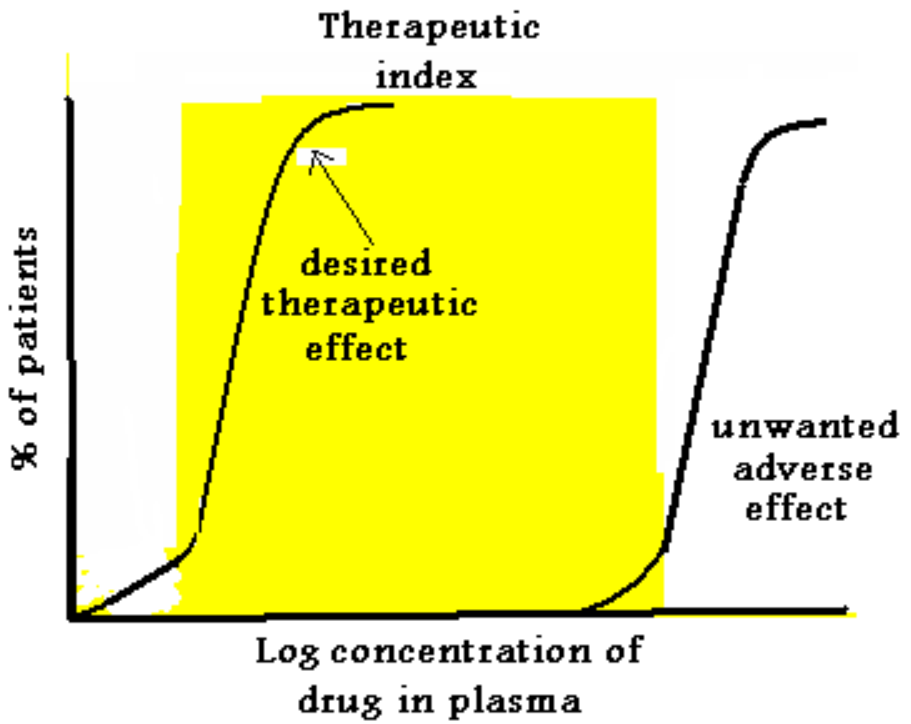
$$TI = \frac{TD_{50}}{ED_{50}}$$

Where TD_{50} is the minimum dose that is lethal or toxic for 50% of the population, and ED_{50} is the minimum dose that is effective for 50% of the population.

Ideally the TD_{50} Should be a much higher dose than the ED_{50} so that the therapeutic index would be large.

Therapeutic index and margin of safety





Properties of an Ideal Drug

- Effective
- Safety
- Selective
- Reversible Action
- Predictable
- Freedom from drug interactions
- Low cost
- Chemically stable