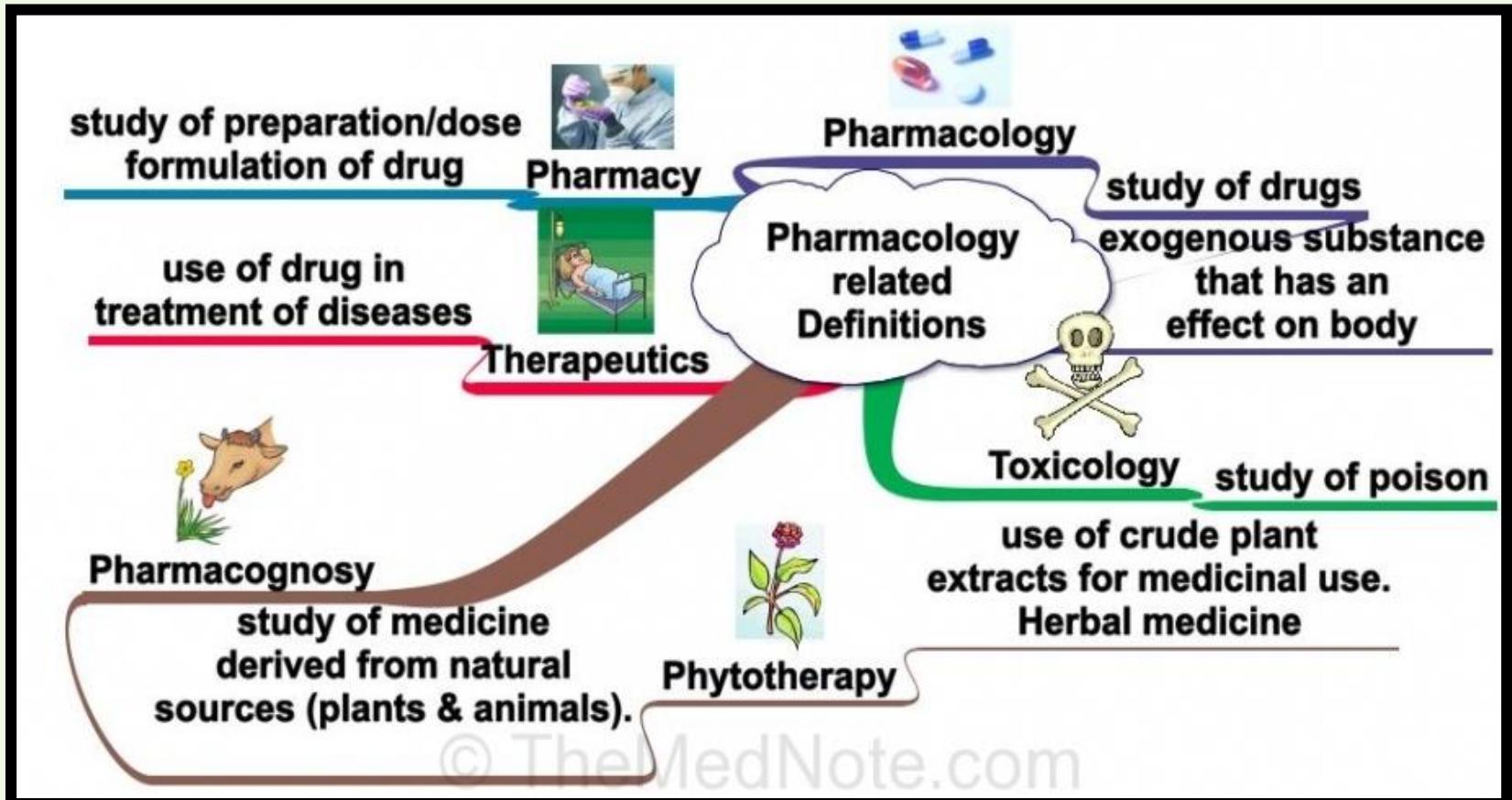


Definition of Pharmacology

「Pharmakon」 & 「Lo-gia」
藥物或毒物 研究



The related areas of pharmacology



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Pharmacology

- In its broadest sense, pharmacology encompasses the study of **all compounds that interact with the body**, and includes **knowledge of the interactions** between these compounds and body constituents at any level of organization.



Terminology

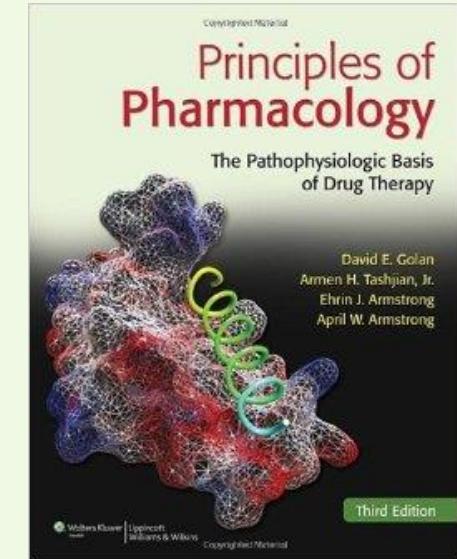
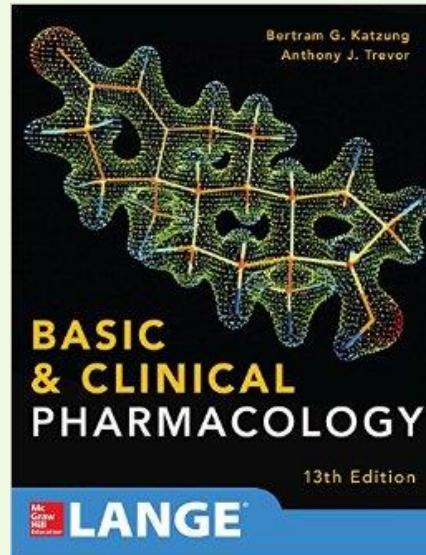
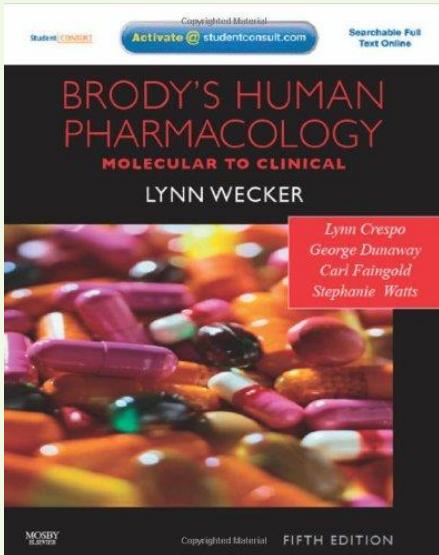
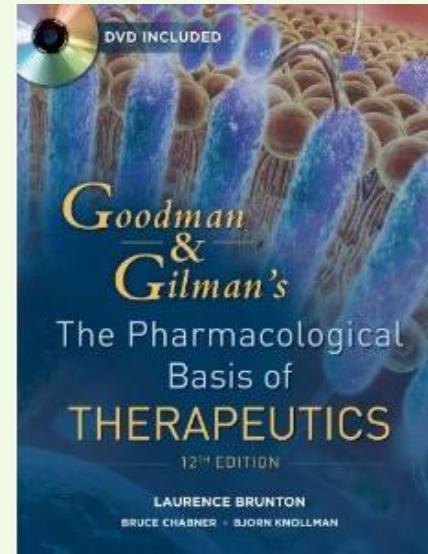
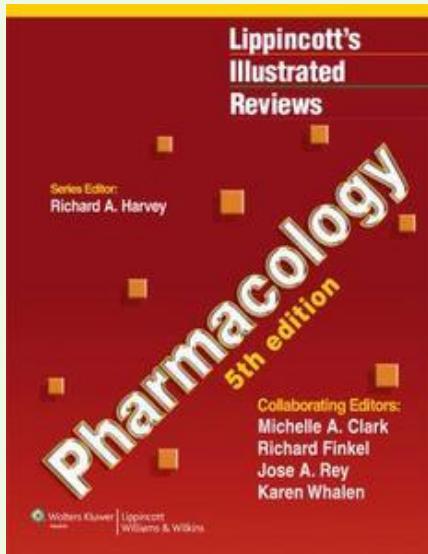
- **Pharmacokinetics:**
Factors that influence the rates of delivery, distribution, and disappearance of drug.
- **Pharmacodynamics:**
Study of fundamental or molecular interactions between drug and effector macromolecule (or receptor).
- **Pharmacogenetics:**
Concerned with unanticipated or unusual responses to drugs.
- **Pharmacogenomics:**
The application of genomic technology to drug characterization and development.



- **Toxicology:**
The science of poisons of drugs.
- **Pharmacovigilance:**
The area of pharmacology concerned with the safety of drugs.
- **Molecular therapies:**
Novel therapeutic approaches includes gene therapy, the use of specific anti-bodies, and strategies for targeted drug delivery.
- **Nutraceutical:**
The term used to describe the dietary and herbal supplements and their potential to impact conventional drug therapy and medical interventions.



Textbooks



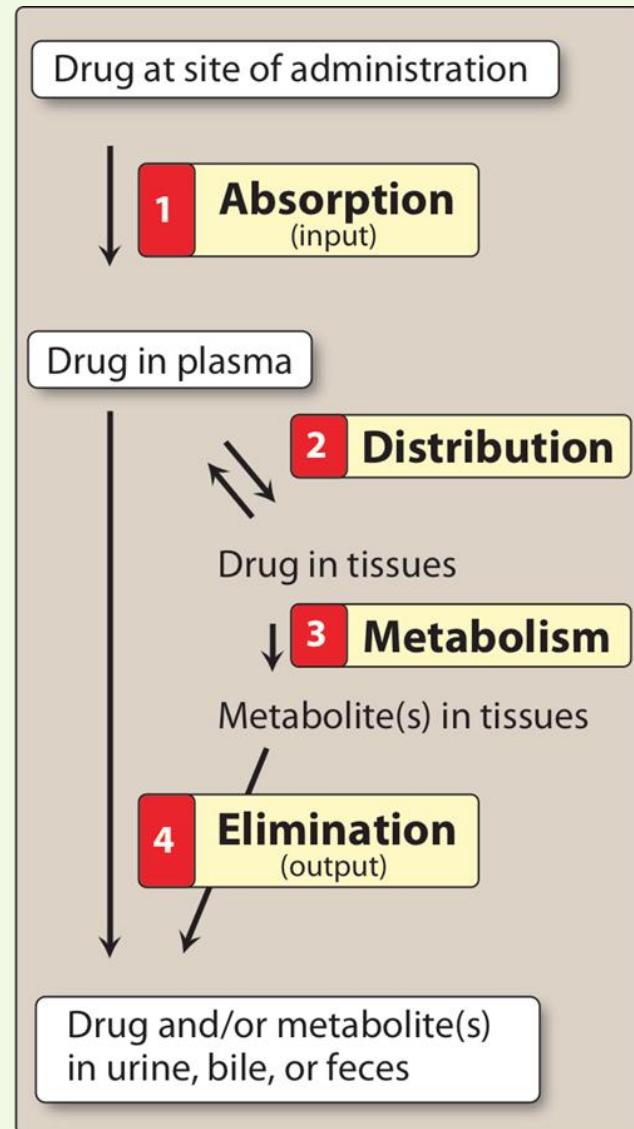


Pharmacokinetics

- 1. Absorption**
- 2. Distribution**
- 3. Metabolism**
- 4. Elimination**



Schematic representation of drug absorption, distribution, metabolism, and elimination





Routes of drug administration

1. Enteral

- a. Oral: The most common route of administration.
- b. Sublingual

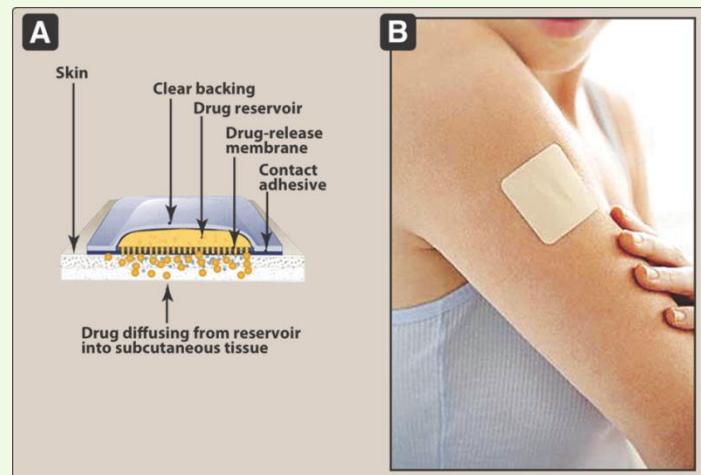
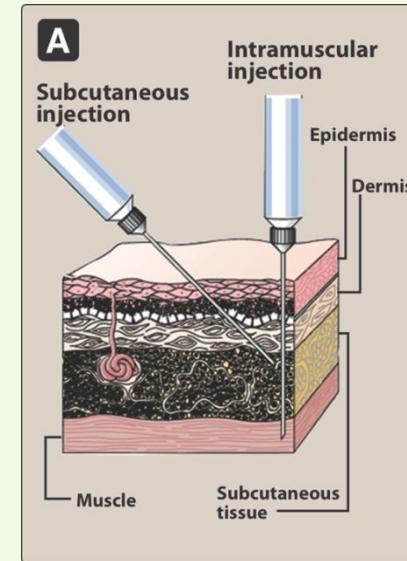
2. Parenteral: Used for drugs that are poorly absorbed from the gastrointestinal (GI) tract.

- a. Intravascular (IV): The most common parenteral route.
- b. Intramuscular (IM)
- c. Subcutaneous (SC)

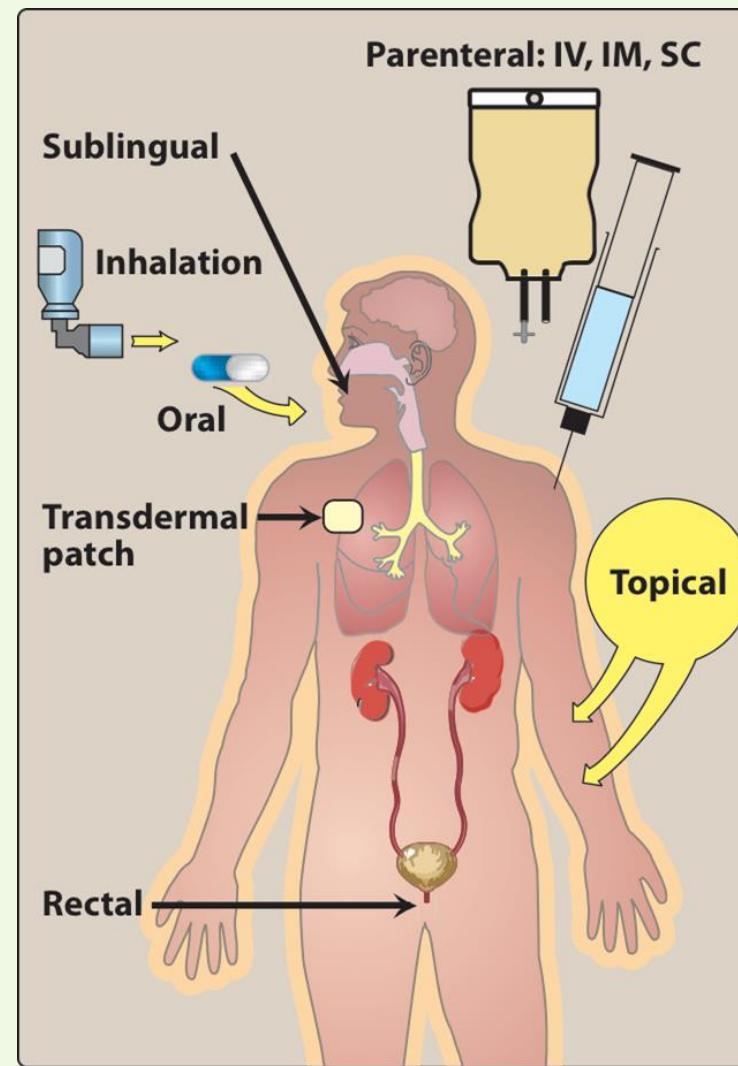


3. Other

- a. Inhalation
- b. Intranasal
- c. Intrathecal/ Intraventricular
- d. Topical
- e. Transdermal
- f. Rectal



Commonly used routes of drug administration



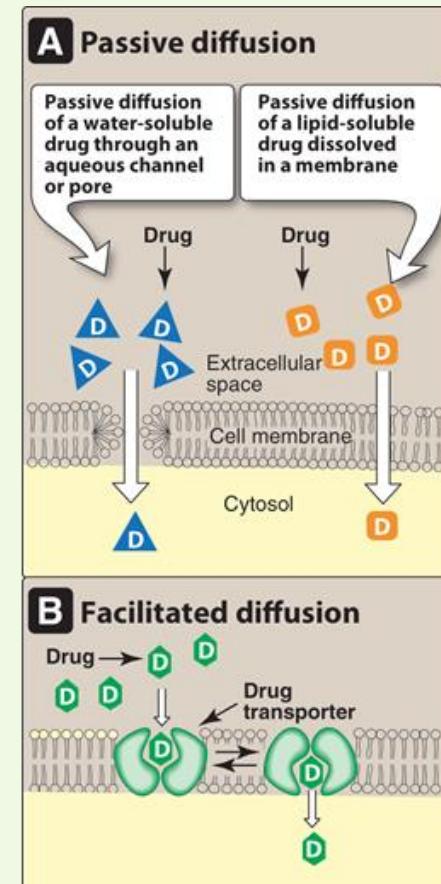


Drug absorption

A drug from its **site of administration** to the **blood stream**.

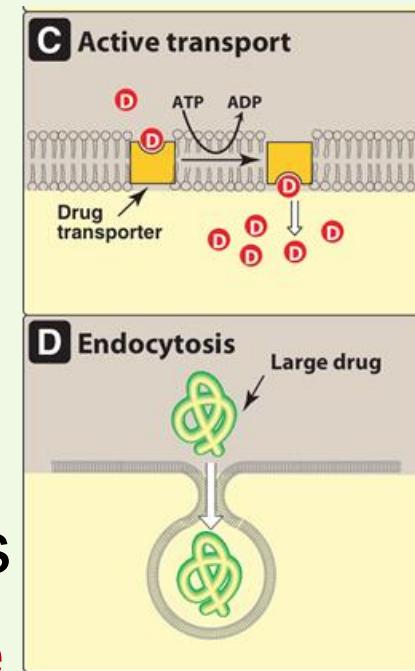
Transport of drug from the GI tract

- Passive diffusion:** The drug moves from **higher** to **lower** concentration.
- Facilitated diffusion:** Agents can enter the cell through specialized transmembrane carrier proteins, this process **does not require energy**.





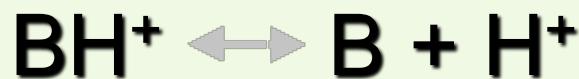
- c. **Active transport:** This mode of drug entry involves **specific carrier proteins** that span the membrane; energy-dependent and **against concentration gradient**.
- d. **Endocytosis and exocytosis:** These types of drug delivery systems transport drugs of **exceptionally large size** across the cell membrane.





Factors influencing absorption

1. Effect of pH on drug absorption



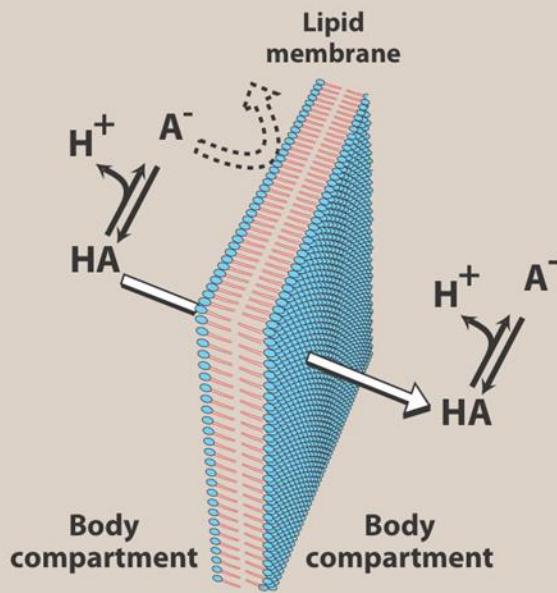
- a. Passive diffusion of an uncharged drug through a membrane.
- b. Determination of how much drug will be found on either side of a membrane:

For acids: $pH = pK_a + \log [A^-]/[HA]$

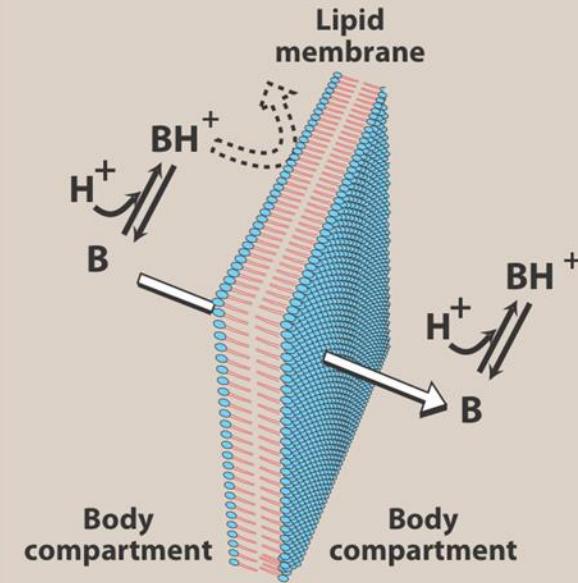
For bases: $pH = pK_a + \log [B]/[BH^+]$



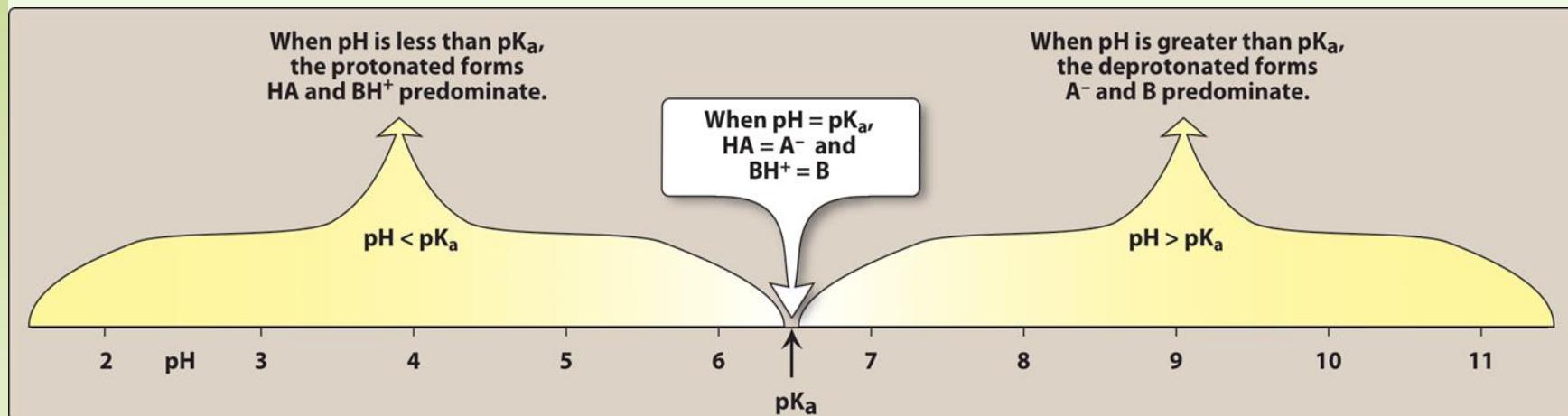
A Weak acid



B Weak base



A. Diffusion of the non-ionized form of a weak acid through a lipid membrane. B. Diffusion of the non-ionized form of a weak base through a lipid membrane.



The distribution of a drug between its ionized and non-ionized forms depends on the ambient pH and pK_a of the drug. For illustrative purposes, the drug has been assigned a pK_a of 6.5.

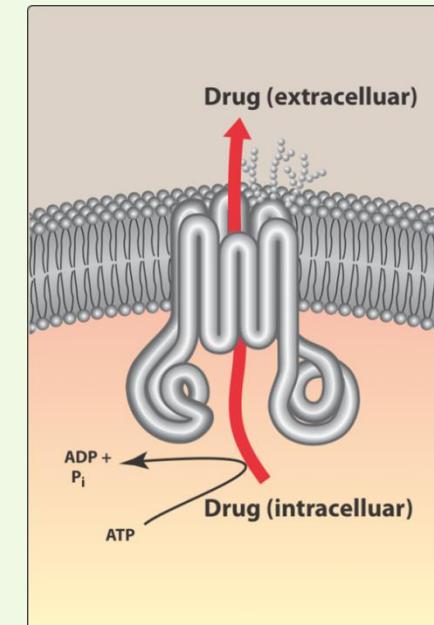


pH of selected body fluids

Fluids	pH
Gastric juice	1.0-3.0
Small intestine: Duodenum	5.0-6.0
Small intestine: Ileum	8
Large intestine	8
Plasma	7.4
Cerebrospinal fluid	7.3
Urine	4.0-8.0



2. Blood flow to the absorption site
3. Total **surface area** available for absorption
4. **Contact time** at the absorption surface
5. Expression of P-glycoprotein



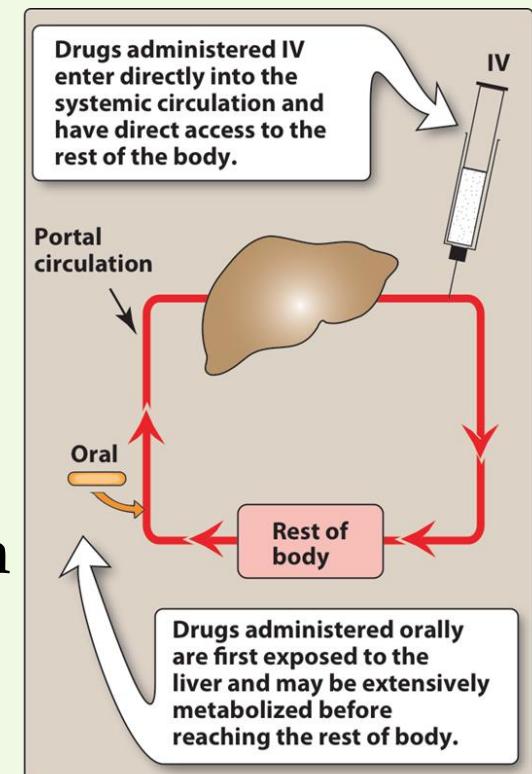


Bioavailability

Bioavailability is the fraction of administered drug that reaches the systemic circulation.

1. Factors that influence bioavailability

- a. First-pass hepatic metabolism
- b. Solubility of drug
- c. Chemical instability
- d. Nature of the drug formulation





2. Bioequivalence

Two drugs have bioequivalence if they have comparable bioavailability.

3. Therapeutic equivalence

Two similar drugs are therapeutically equivalent if they have comparable efficacy and safety.



Drug distribution

1. Blood flow

2. **Capillary permeability:** Capillary permeability is determined by **capillary structure** and by the **chemical nature** of the drug.

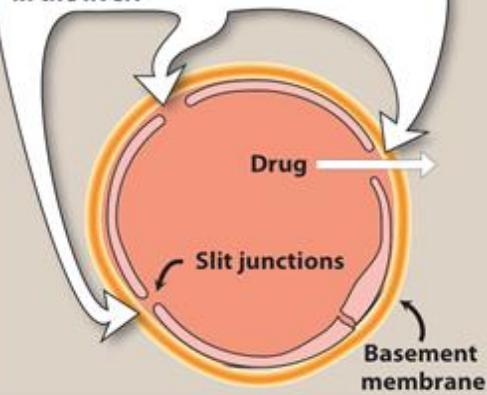
- a. Capillary structure
- b. Blood-brain barrier
- c. Drug structure



Cross-section of liver and brain capillaries

A Structure of endothelial cells in the liver

Large fenestrations allow drugs to move between blood and interstitium in the liver.



B Structure of a brain capillary

Astrocyte foot processes

Basement membrane

Brain endothelial cell

Tight junction

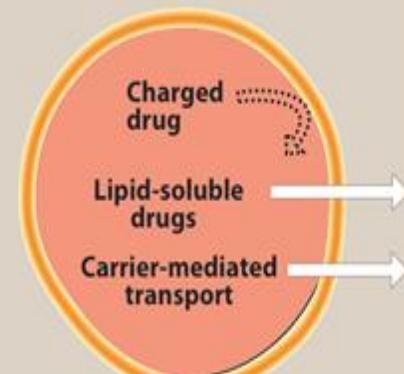
At tight junctions, two adjoining cells merge so that the cells are physically joined and form a continuous wall that prevents many substances from entering the brain.

C Permeability of a brain capillary

Charged drug

Lipid-soluble drugs

Carrier-mediated transport



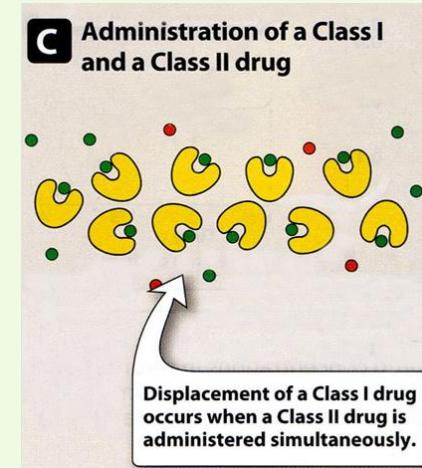
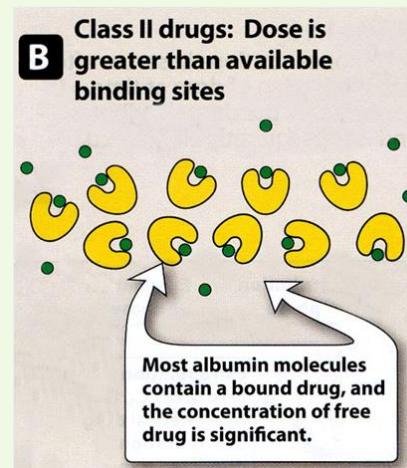
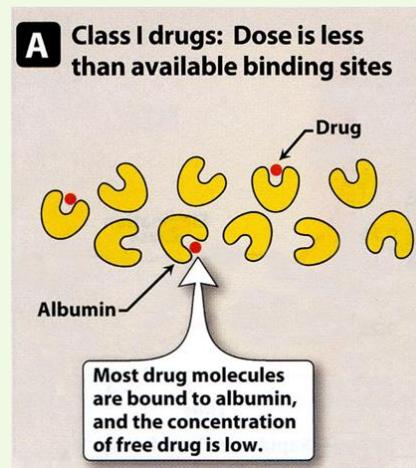


3. Binding of drugs to plasma proteins and tissues

1). Binding to plasma proteins (albumin)

Competition for binding between drugs

- a. Class I drugs
- b. Class II drugs
- c. Administration of a class I and a class II drug





2) Binding to tissue proteins:

Numerous drugs accumulate in tissues, leading to higher concentrations of the drugs in tissue than in the extracellular fluids and blood.

4. Hydrophobicity:

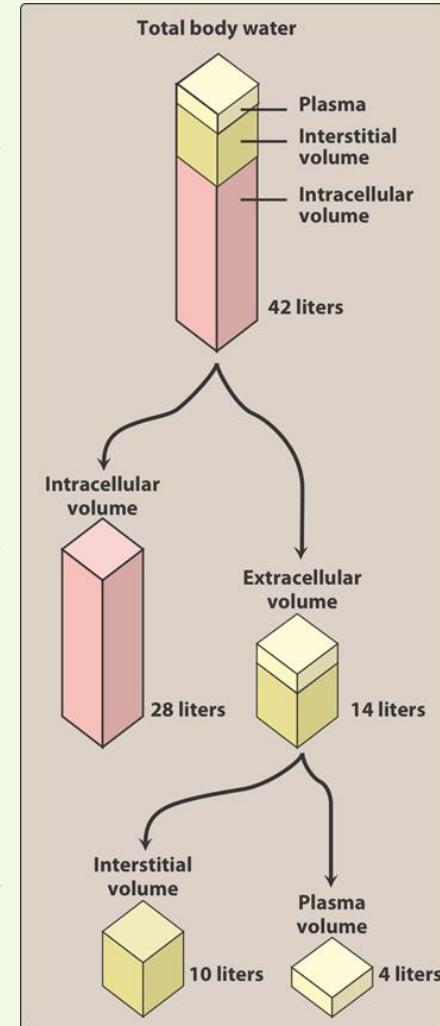
The chemical nature of a drug strongly influences its ability to cross cell membranes.



Volume of distribution (Vd)

Water compartments in the body

- a. Plasma compartment: A drug has a **very large molecular weight** or binds extensively to plasma proteins, thus is effectively trapped within the plasma (vascular) compartment.
- b. Extracellular fluid: The drug has a **low molecular weight** but is **hydrophilic**.
- c. Total body water: If the drug has a **low molecular weight** and is **hydrophobic**.
- d. Other sites: In pregnancy, the fetus may take up drugs.





Drug metabolism

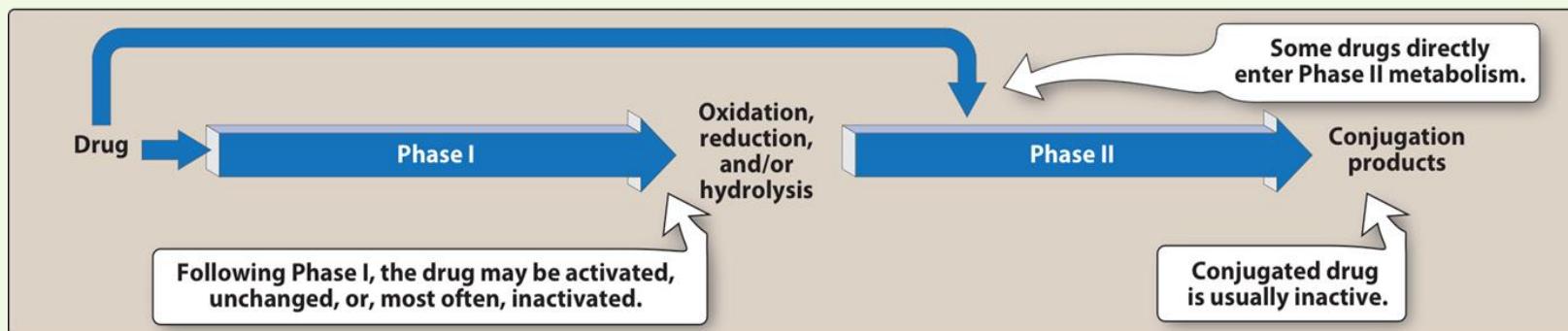
Reactions of drug metabolism

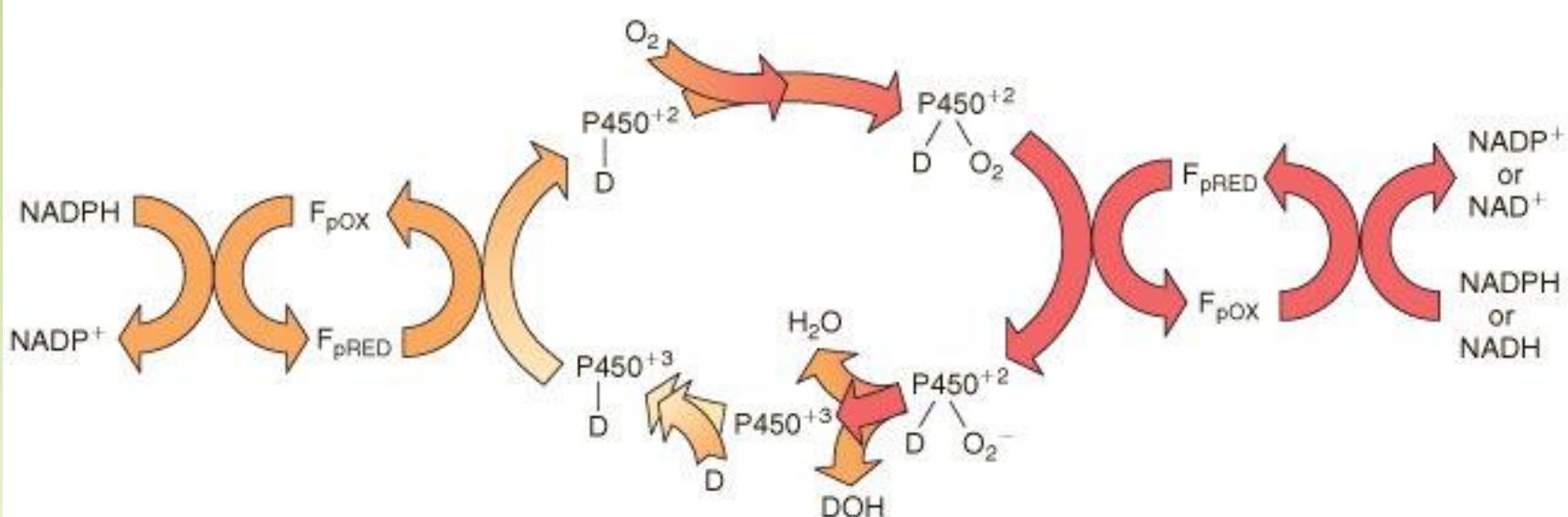
1. Phase I: (P-450 system)

Convert **lipophilic** molecules into more **polar** molecules.

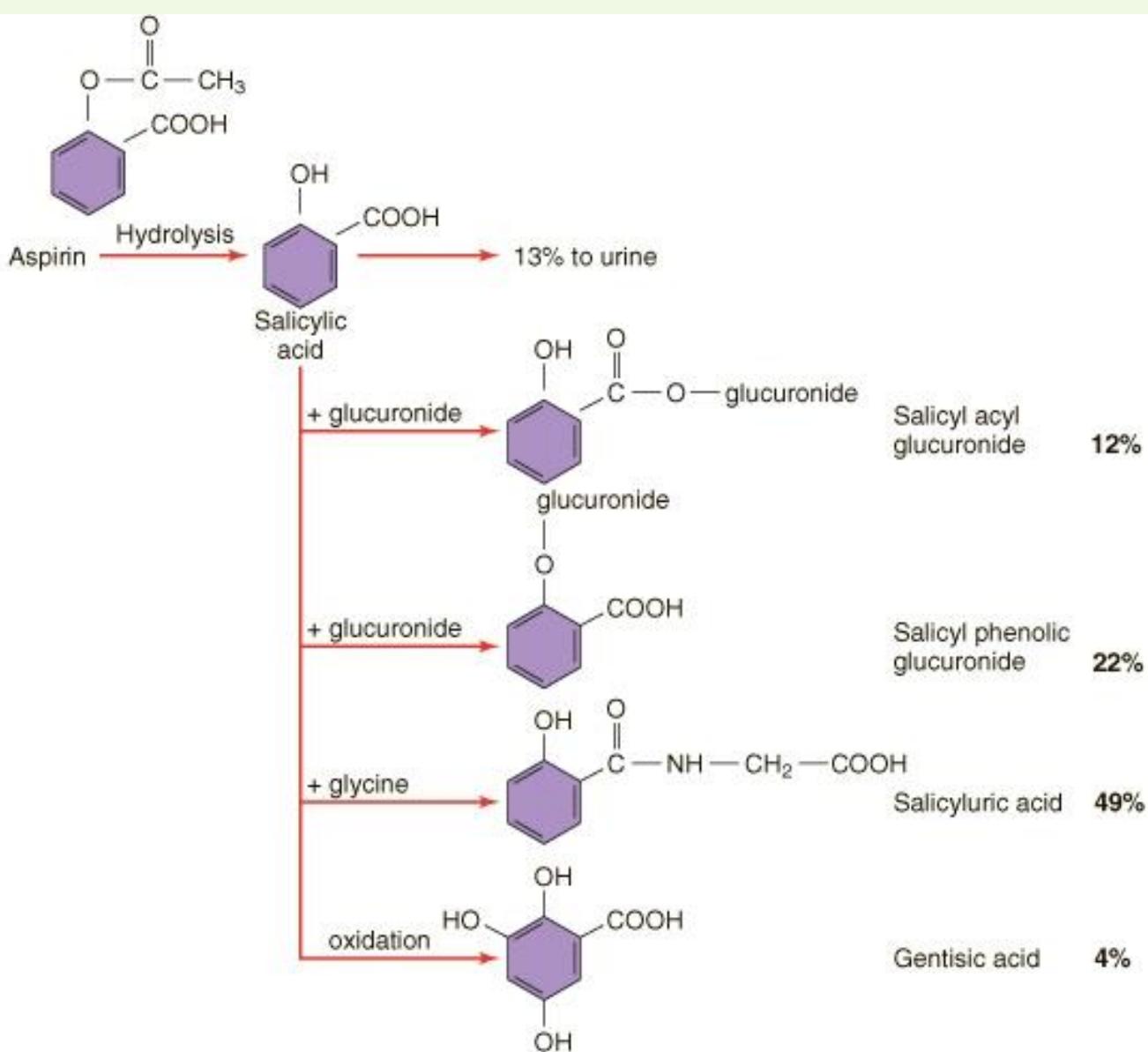
2. Phase II:

Conjugation reaction with an endogenous substrate, such as **glucuronidation**.





Simplified model of cytochrome P450 mixed-function oxidase reaction sequence. *D* is the drug undergoing oxidation to produce *DOH*. Molecular oxygen serves as the final electron acceptor. Flavin protein cofactor (F_p) systems are involved at several sites. The iron of the cytochrome P450 is involved in binding oxygen and electron transfer with changes in valence state.



Disposition of the primary metabolite of aspirin, salicylic acid, at a single dose of 4 grams (54 mg/kg of body weight) in a healthy adult. The percentage values refer to the dose. Oxidation produces a mixture of ortho and para (relative to original OH group) isomers.

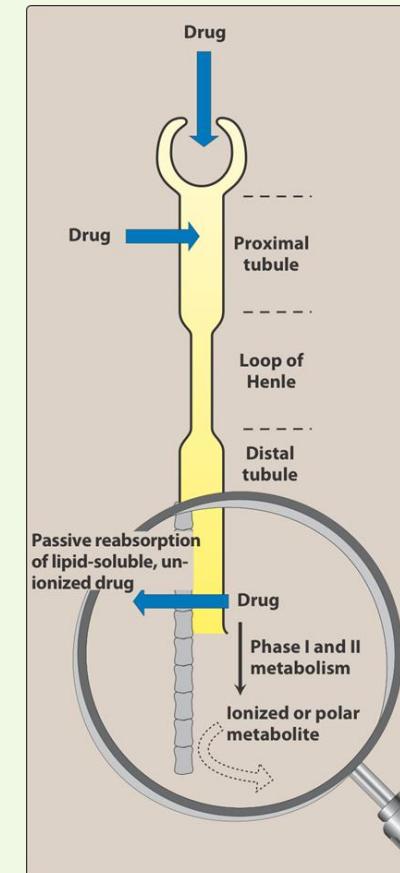


Drug elimination

The most important being through the **kidney** into the **urine**. Other routes include the **bile**, **intestine**, **lung**, or **milk** in nursing mothers.

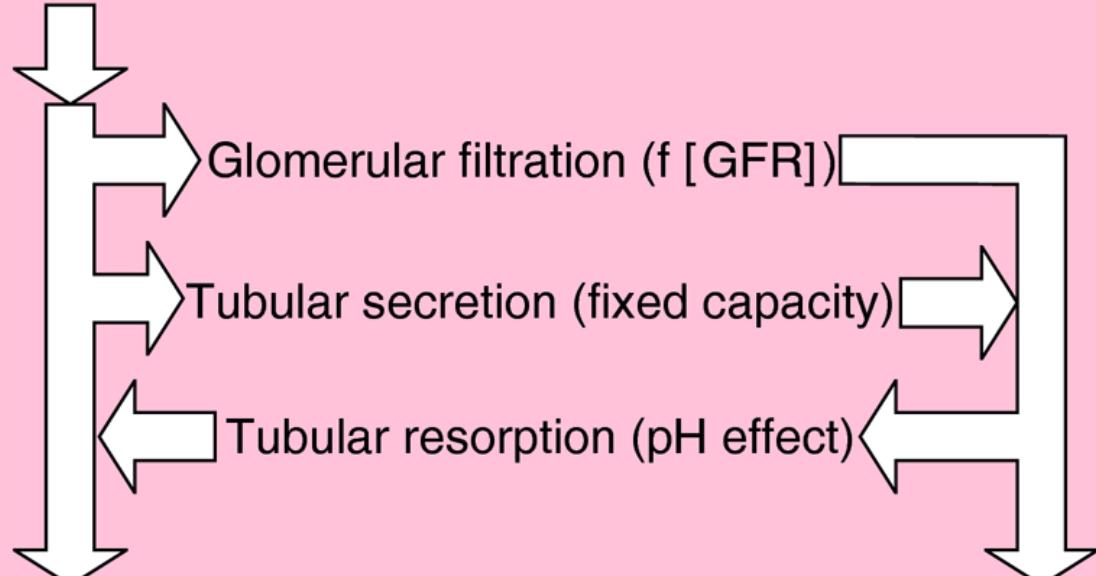
Renal elimination of a drug

- a. Glomerular filtration
- b. Proximal tubular secretion
- c. Distal tubular reabsorption
- d. Role of drug metabolism





Renal arterial blood flow



$$(Cl)_r = f (GFR) + \frac{\text{Rate of TS} - \text{rate of TR}}{C_p}$$

Summary of renal clearance (CL)_r mechanisms. C_p , Renal arterial blood concentration of drug; f , fraction of drug in plasma not bound; GFR , glomerular filtration rate of drug; TR , tubular reabsorption of drug; TS , tubular secretion of drug.



Clinical situations resulting in increased drug half-life

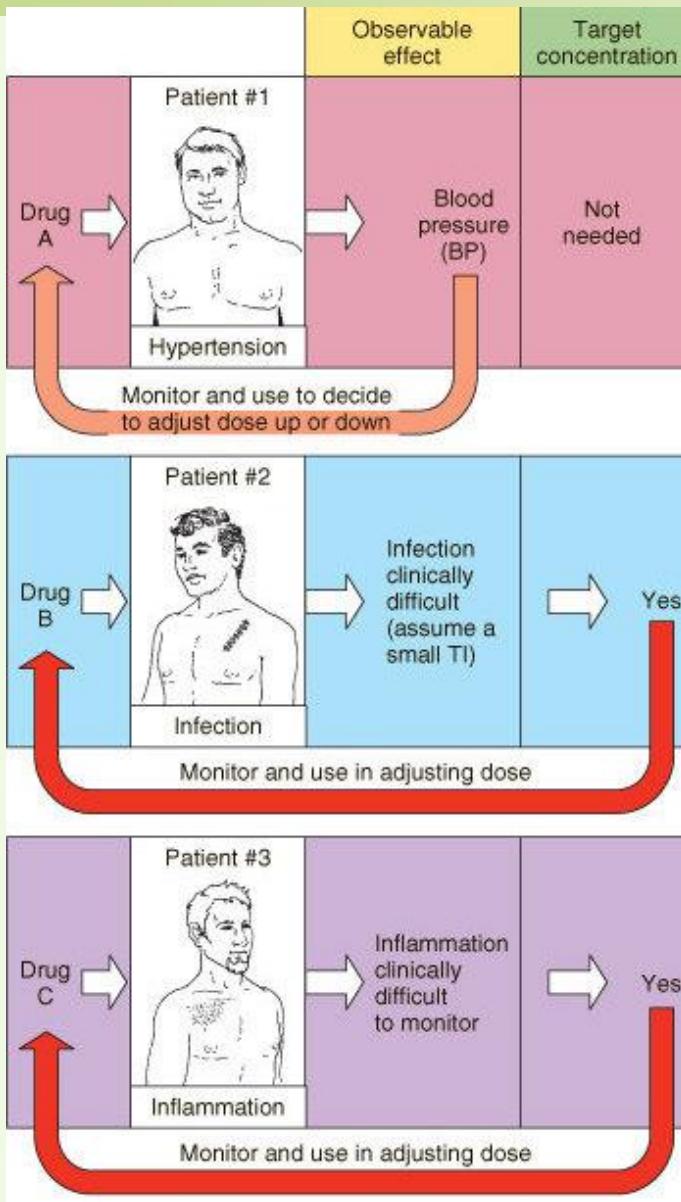
Half-life ($t_{1/2}$) is defined as the time it takes for the concentration of drug to decrease by half.

The half-life of a drug is increased by:

1. Diminished renal and hepatic plasma flow.
2. Renal diseases.
3. Decreased metabolism.

The half-life of a drug is decreased by:

1. Increased renal and hepatic plasma flow.
2. Decreased protein binding affinity.
3. Increased metabolism.



Concept of target plasma concentration of drug as an alternative to observable effect for determining whether drug input rate is sufficient or must be modified. *TI*, Therapeutic index. For a discussion of target concentration, see the text.



Pharmacodynamics

Drug-receptor interactions- lock and key hypothesis

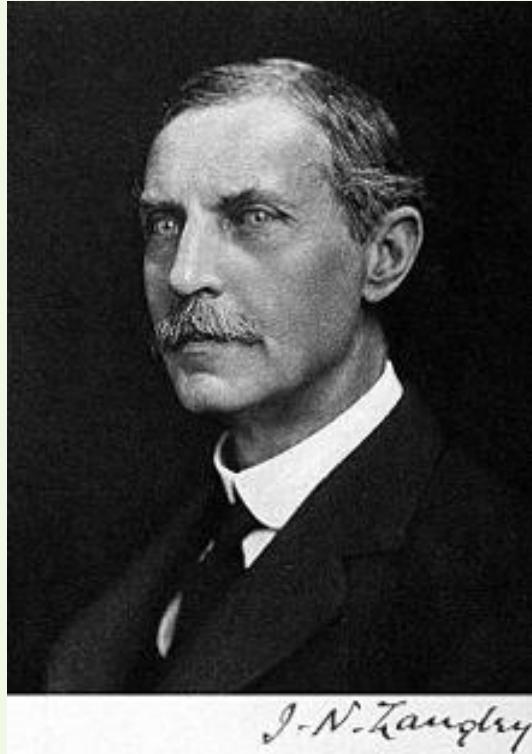
Most drugs the site of action is at a specific macromolecule, which may be a **membrane protein**, a **cytoplasmic enzyme**, or a **nucleic acid**.

Receptors

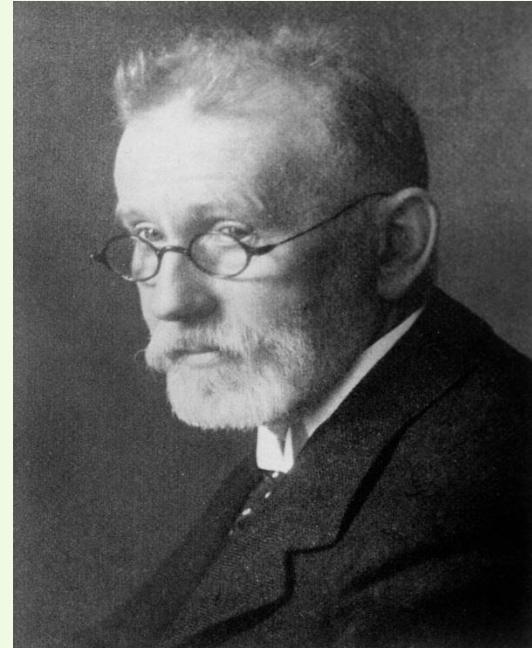
The term **receptor** is usually reserved for **proteins**, which are imbedded in a cellular or subcellular membrane and **facilitate** communication between the two sites of the membrane.



Receptor theory

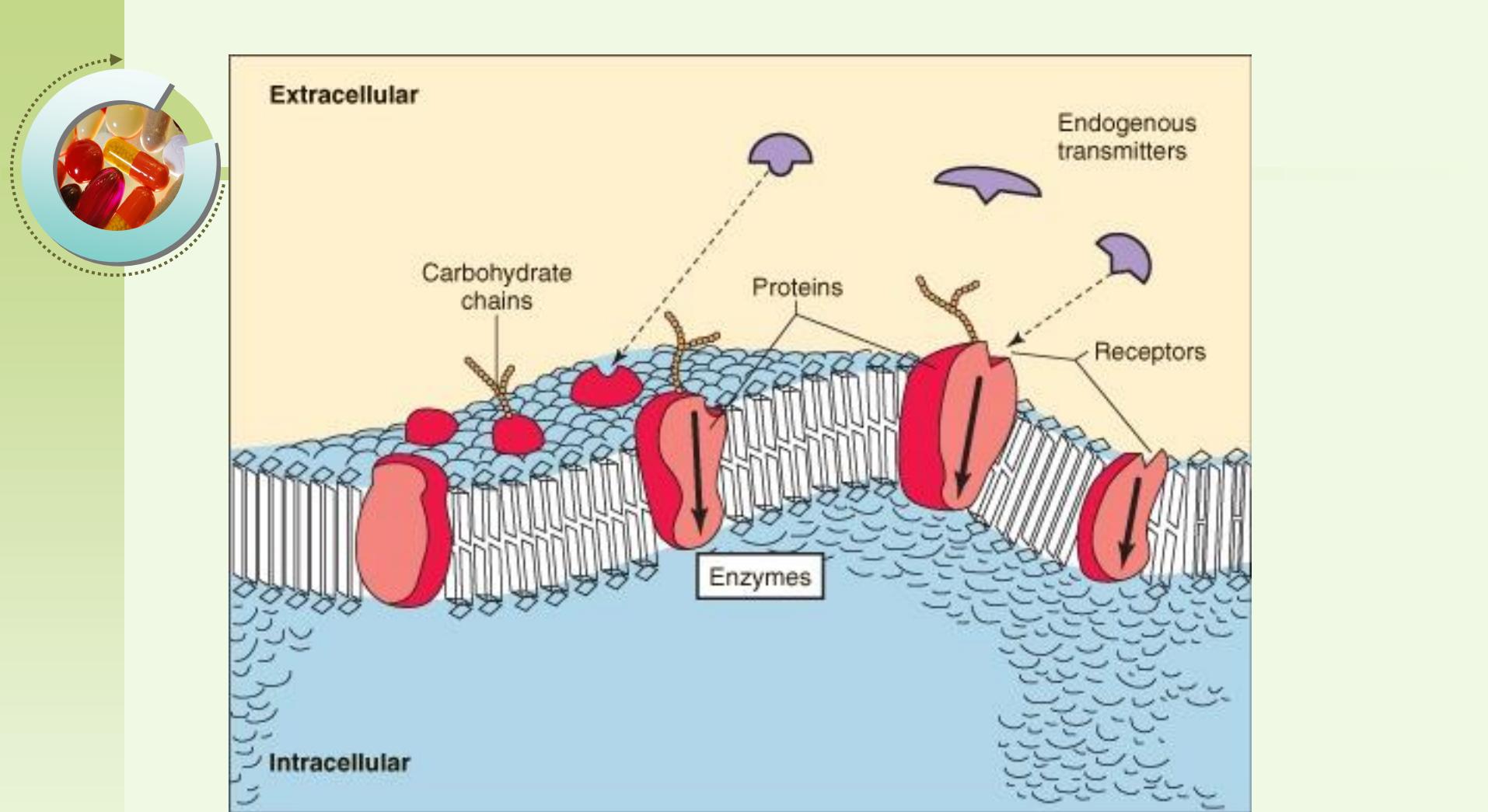


John Newport Langley
1852 – 1925



Paul Ehrlich

Paul Ehrlich
1854 – 1915



Proteins embedded in cell membranes generally extend further on both the extracellular and intracellular sides. Attached to the proteins on the extracellular side are carbohydrate (glycosylation) chains. Also shown on the extracellular side of some of the proteins are receptor sites to which endogenous transmitter compounds bind. Arrows indicate the direction of communication to the other side of the membrane.



Common features of membrane receptor

1. Receptors are proteins having one or more binding sites.
2. Binding of the endogenous ligand activates the receptor.
3. The magnitude of the transmembrane signal depends on the fraction of total receptors occupied by the ligand.
4. Drugs can enhance, diminish, or block the generation, transmission, or receipt of ligand-generated signals by several mechanisms.

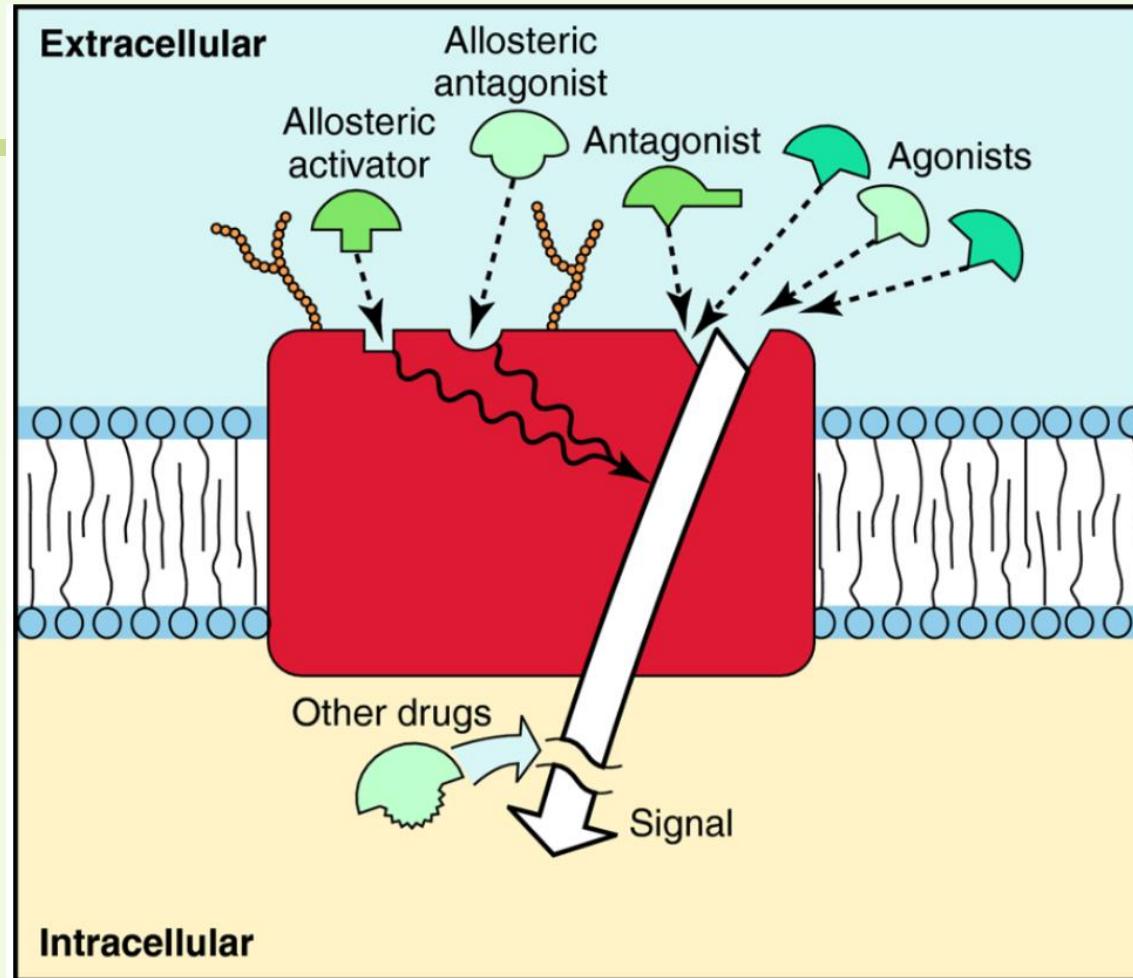
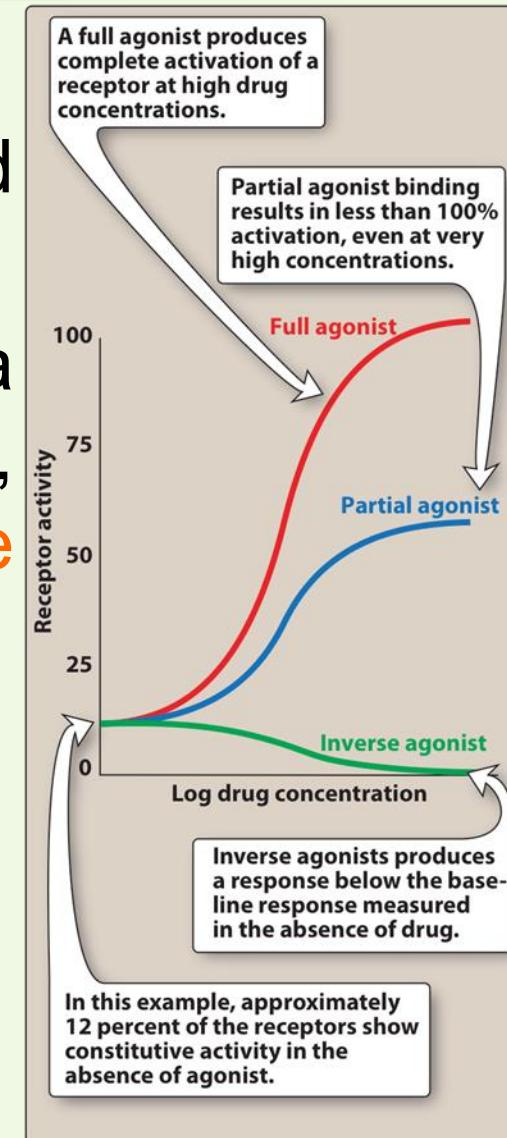


Figure 2-3 Major features of receptors. These include embedding in a membrane, glycosylated chains on the extracellular side, binding sites on the extracellular side for an endogenous transmitter (dark blue symbols) with two molecules sometimes needing to be bound (as shown here) to activate the transmembrane receptor. Drugs can use many sites on the receptor: (1) The agonist and antagonist compete with the endogenous transmitter for binding sites; (2) allosteric agonists or antagonists enhance or block the signal, respectively, by binding to allosteric sites that influence (wavy line) signal transmission; and (3) other drugs can block signal transmission within the membrane or at intracellular signal reception points.



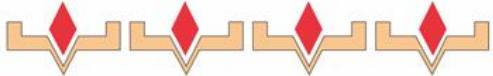
Agonists

- An agonist binds to a receptor and produces a biological response.
 - Another definition of an agonist is a drug that binds to a receptor, **stabilizing** the receptor in its **active** conformational state.
- ◆ **Full agonists**
- ◆ **Partial agonists**
- ◆ **Inverse agonists**





Full agonists & Partial agonists



High levels of agonist may activate all receptors and produce unwanted overstimulation.

Key:

Full agonist



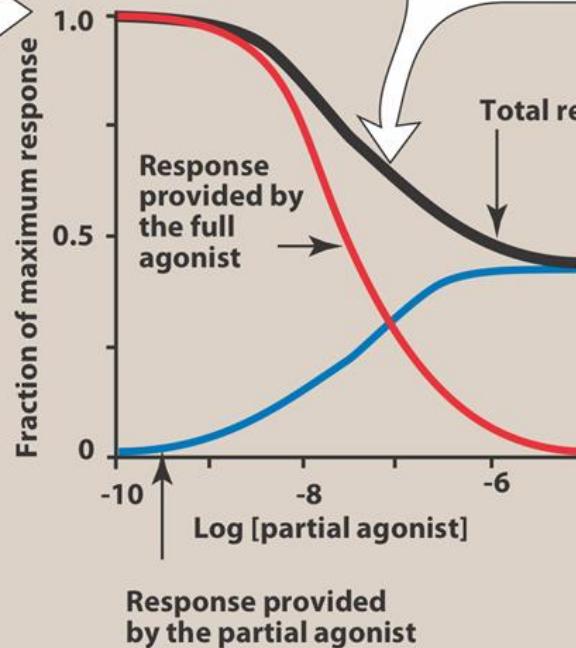
Partial agonist



Fully active receptor



Partially active receptor



The presence of partial agonist displaces some agonist, resulting in diminished receptor response.

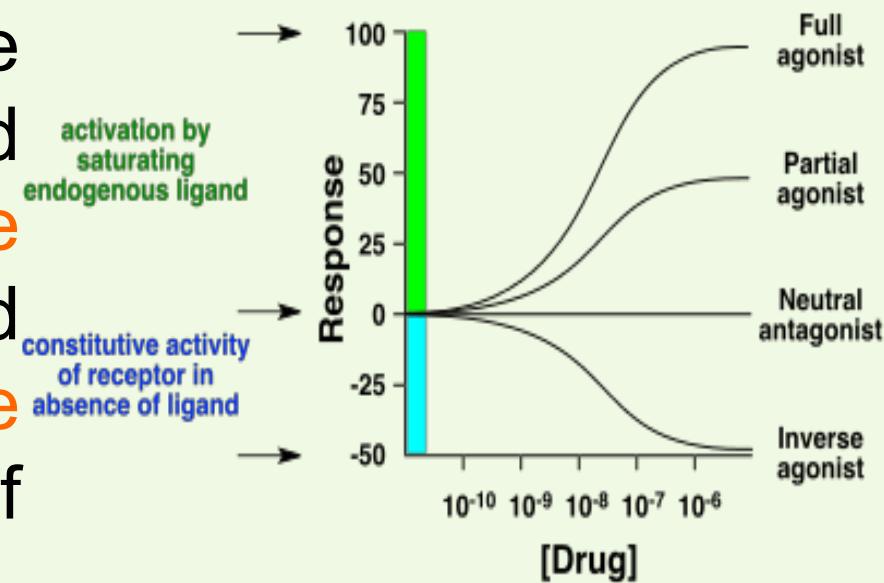


At high concentration of partial agonist, the agonist is completely displaced, and receptor activity is determined by the intrinsic activity of the partial agonist.



Inverse agonists

- Some receptors show a spontaneous conversion from R to R* in the absence of agonist, thus show a constitutive activity that is part of the baseline response measured in the absence of drug.
- Inverse agonists stabilize the inactive R form, and reverse the constitutive activity of receptors and exert the opposite pharmacological effect of receptor agonists.





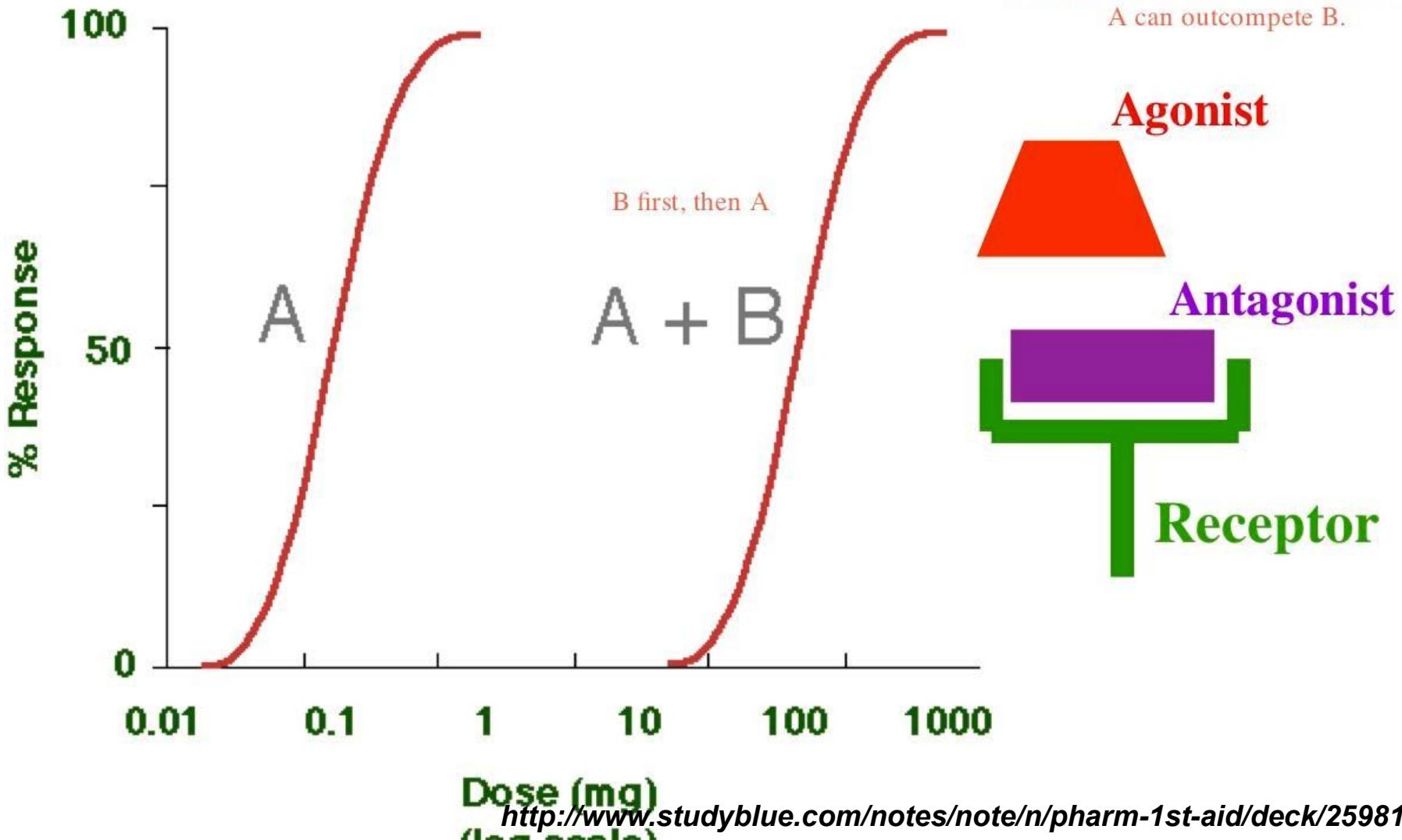
Antagonists

- Antagonists are drugs that decrease or oppose the actions of another drug or endogenous ligand. An antagonist has **no effect if an agonist is not present.**
- Although antagonists have **no intrinsic activity**, they are able to bind avidly to target receptors because they **possess strong affinity**.

- ◆ **Competitive antagonists**
- ◆ **Irreversible antagonists**
- ◆ **Functional and chemical antagonism**



Competitive antagonists



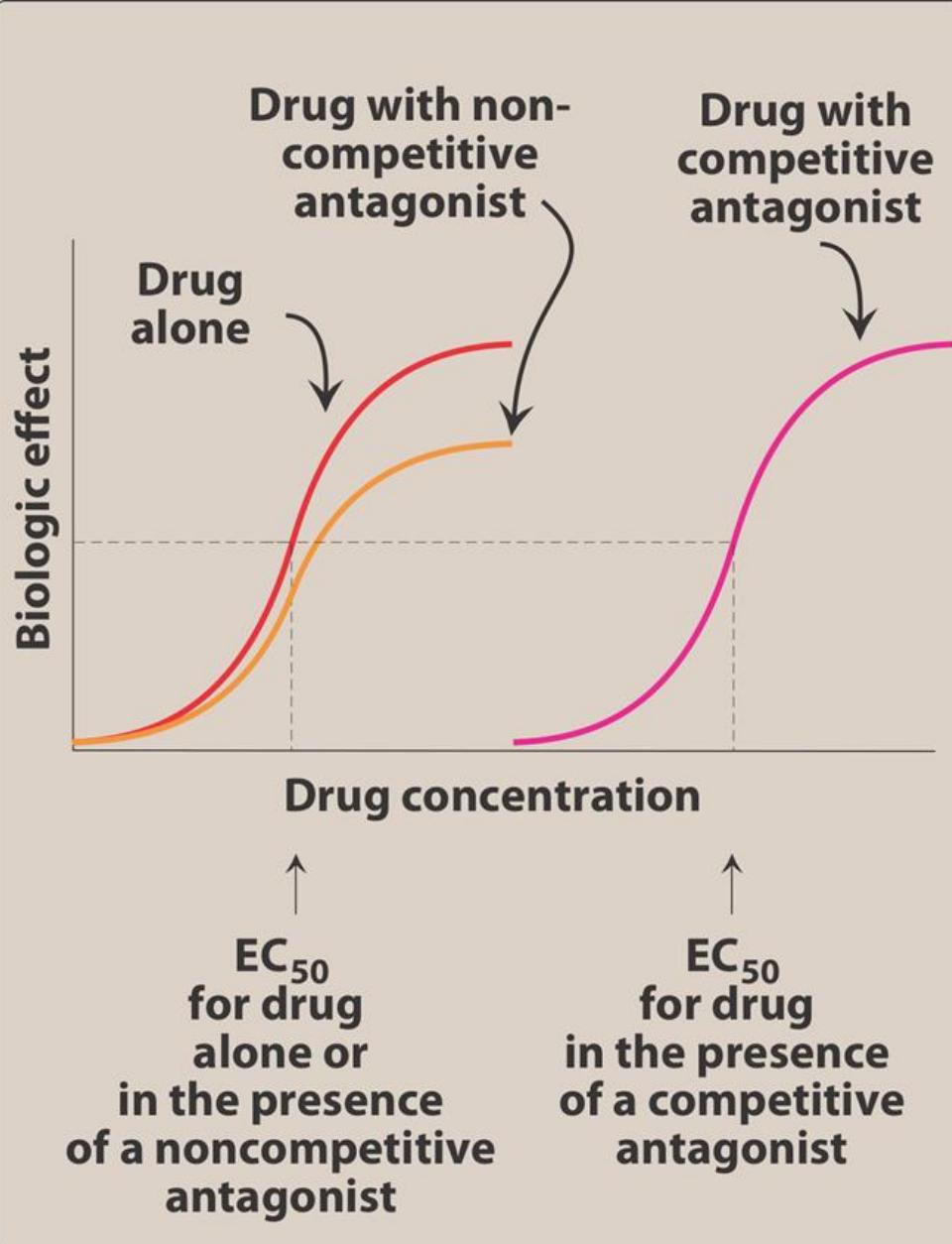


Irreversible antagonists

- An irreversible antagonist causes a downward shift of the maximum, with no shift of the curve on the dose axis.
- The effects of competitive antagonists can be overcome by adding more agonist. Irreversible antagonists, by contrast, cannot be overcome by adding more agonist.



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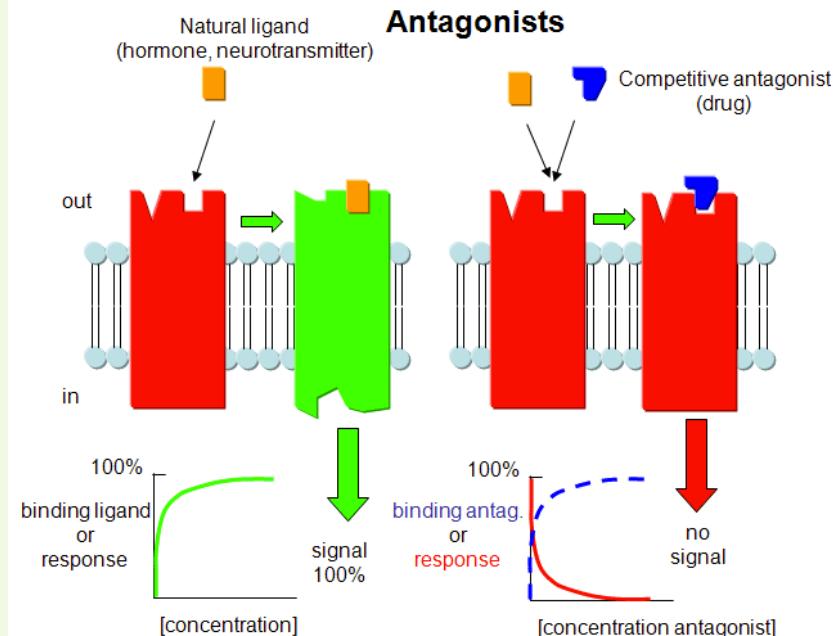
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Competitive antagonists increase the ED₅₀, whereas irreversible antagonists do not.

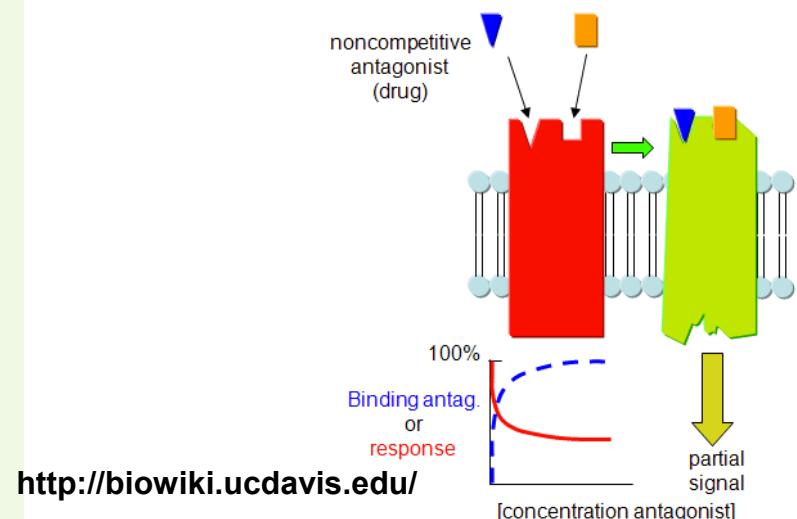


Two mechanisms by which an agent can act as a noncompetitive antagonists

A. The antagonist can bind covalently or with very high affinity to the active site of the receptor. (irreversible antagonist)



B. The second type of noncompetitive antagonist binds to a allosteric site other than the agonist-binding site.



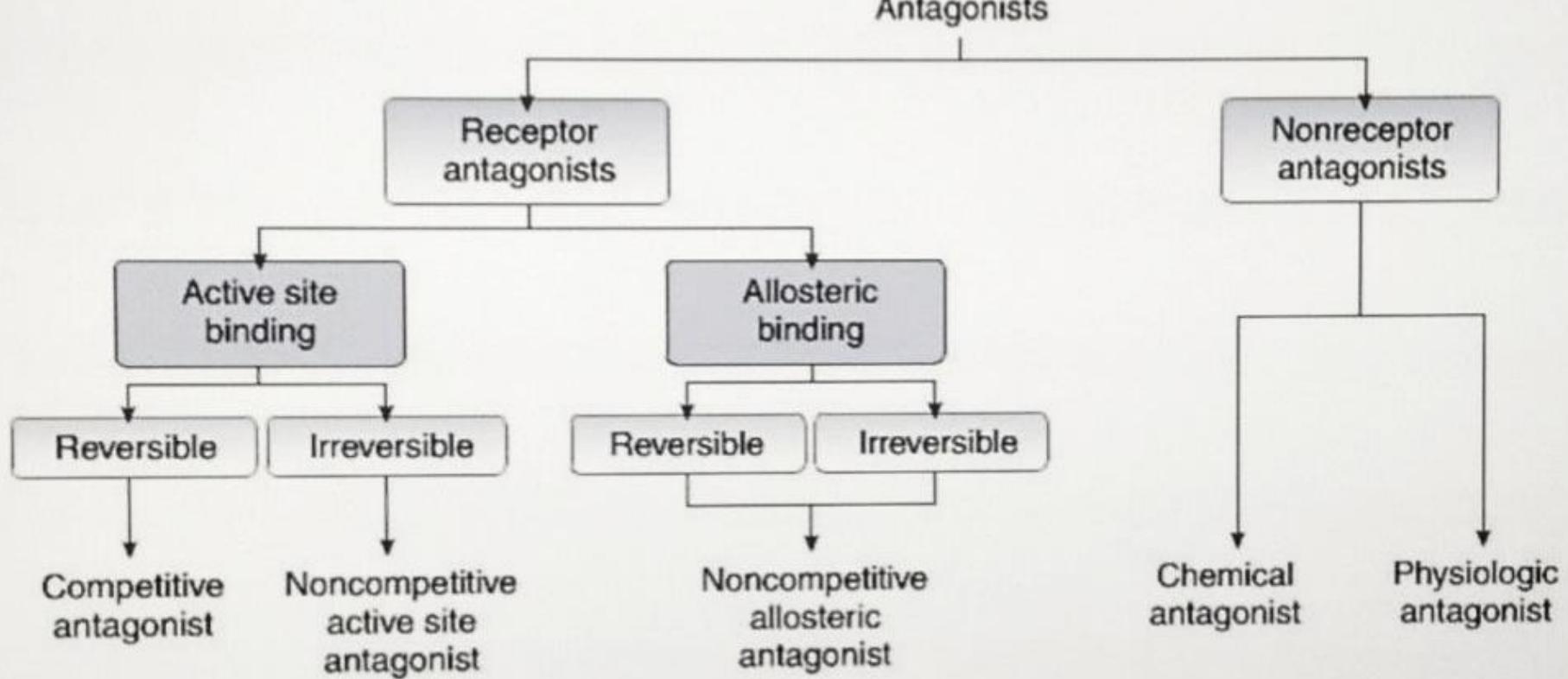


Functional and chemical antagonism

- An antagonist may act at a **completely separate receptor**, initiating effects that are **functionally opposite** those of the agonist. This functional antagonism is also known as "**physiologic antagonism**."
- A chemical antagonist prevents the actions of an agonist by **modifying or sequestering the agonist** so that it is incapable of binding to and activating its receptor.



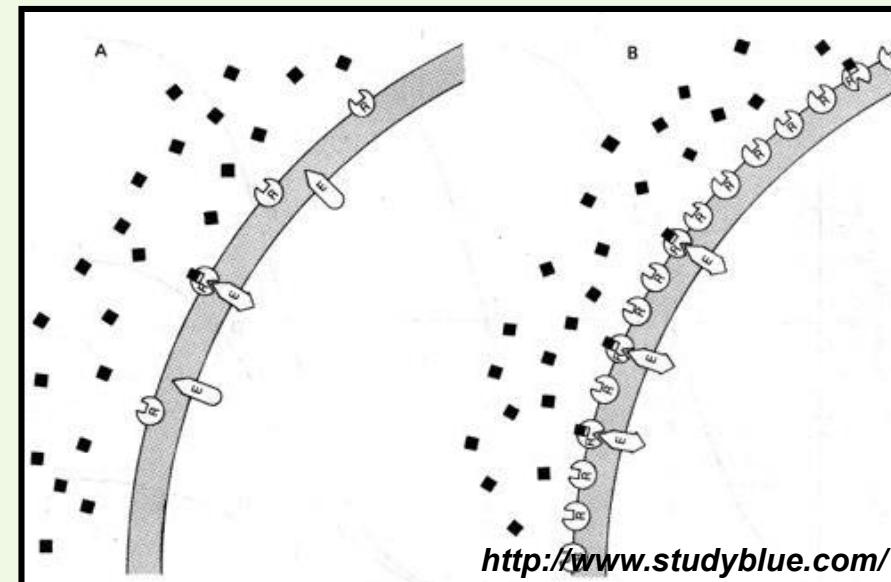
Antagonist classification





Signal amplification-Spare receptors

- More commonly, a maximal response can be achieved when **only a small fraction of receptors are occupied** by an agonist. This phenomenon defines the concept of **spare receptors**, or a receptor reserve.
- Spare receptors are important in all-or none responses, where it is especially important that **activation does not fail**.





Tissue specific actions of agonists

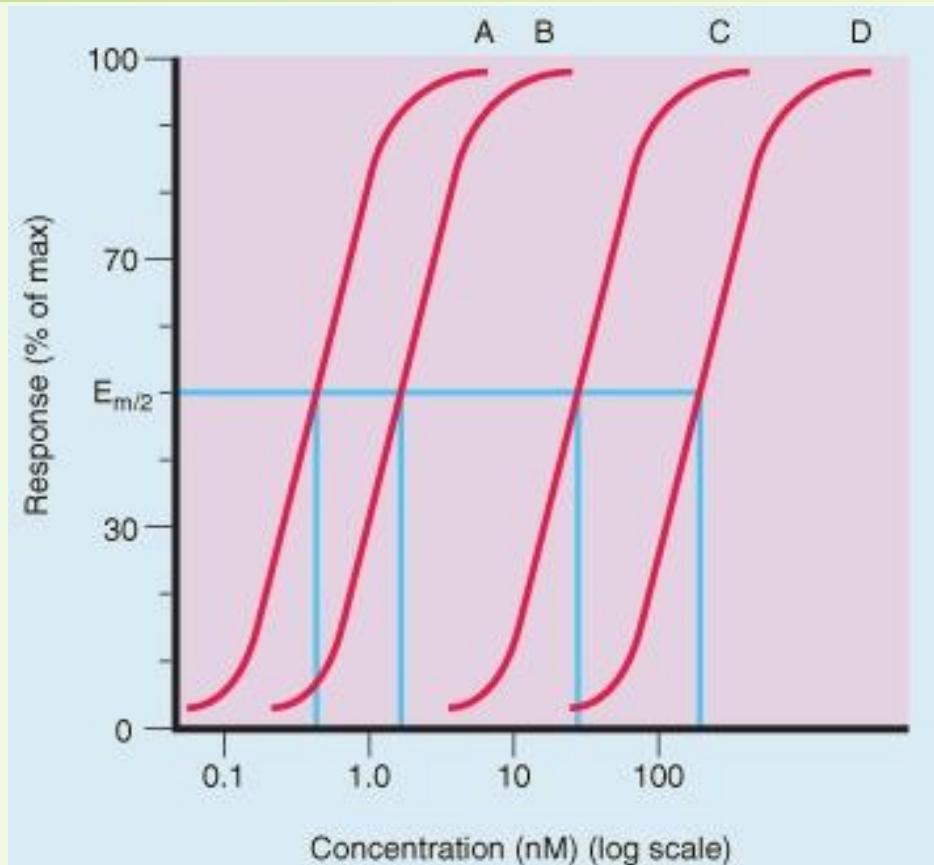


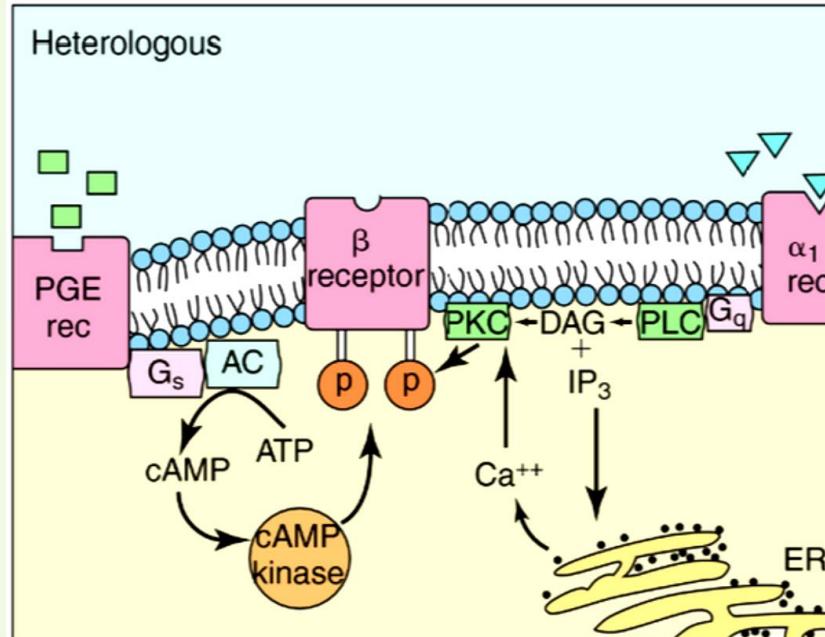
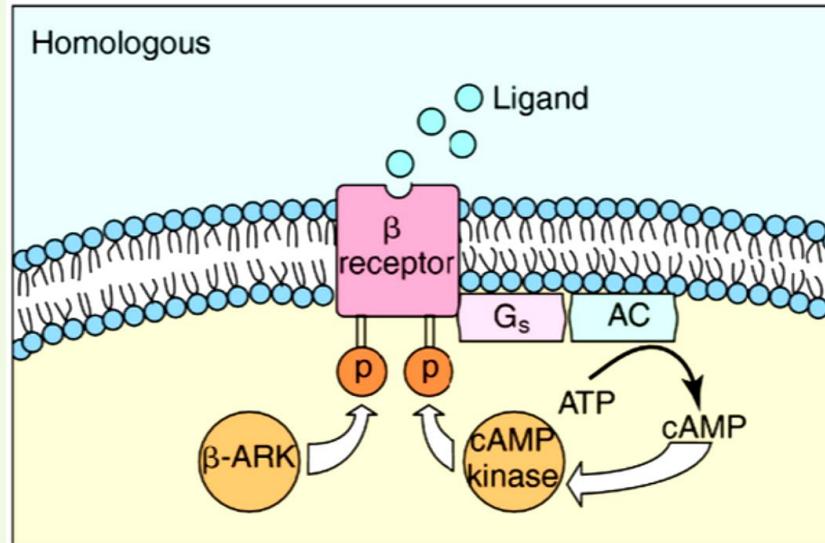
Figure 3-4 Logarithmic concentration-response curves for a single agonist acting on the same receptor subtype in tissues with different proportions of spare receptors (A, B, C, and D) and eliciting muscle contraction in vitro. Note that all tissues show the same maximum response to drug (intrinsic activity). The agonist shows its highest potency (lowest EC_{50}) at the tissue with greatest proportion of spare receptors (A), and its lowest potency at the tissue with the lowest proportion of spare receptors (D).



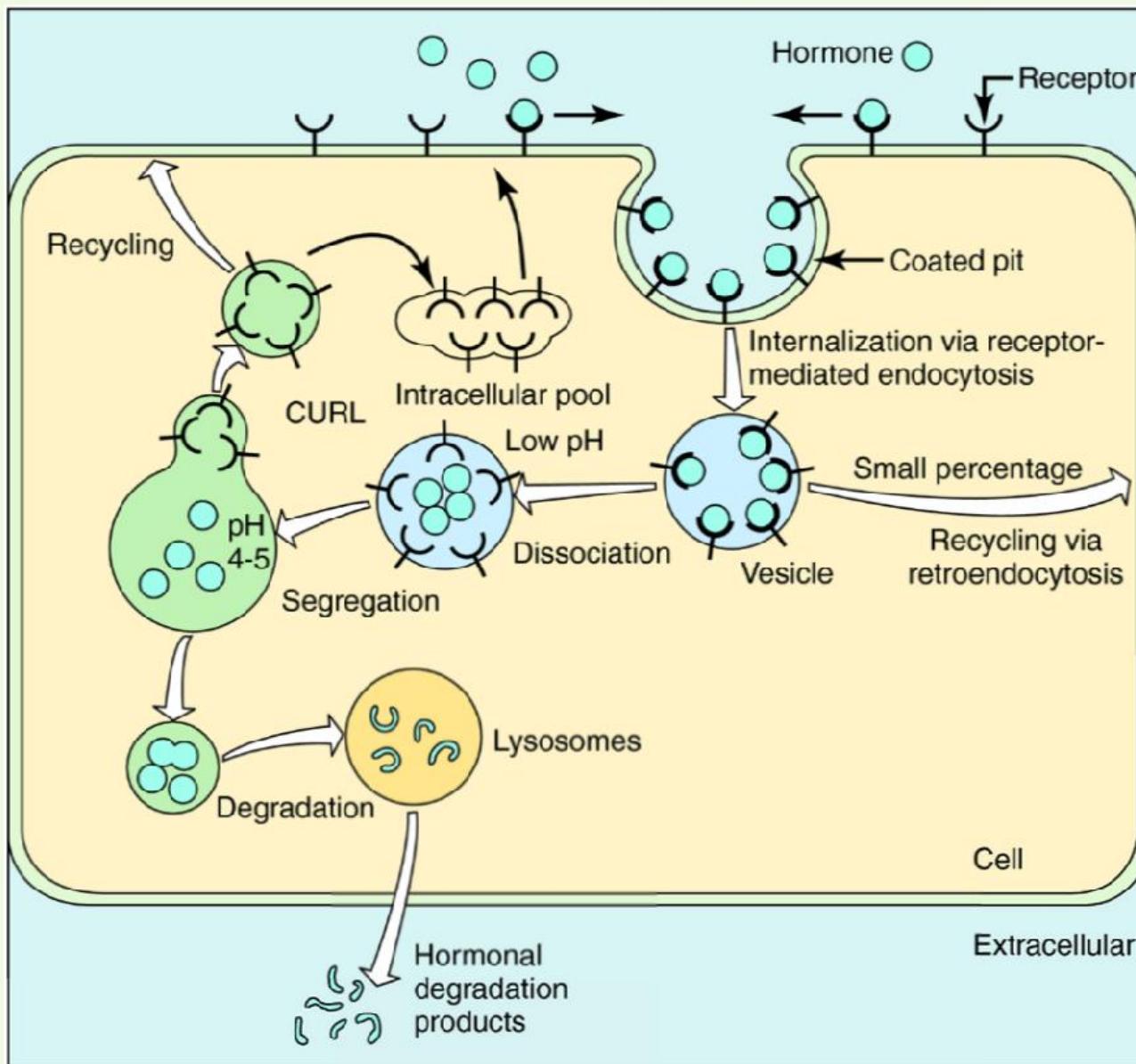
Receptor desensitization and supersensitivity

- The response of any cell to hormones or neurotransmitters is tightly regulated and can vary depending on other stimuli impinging on the cell. The number of receptors or responsiveness of the receptors themselves is regulated.
- One hormone can sensitize a cell to the effects of another hormone, and more commonly, when a cell is continuously exposed to stimulation by a transmitter or a hormone, it may become desensitized.

Phosphorylation is important in receptor desensitization.

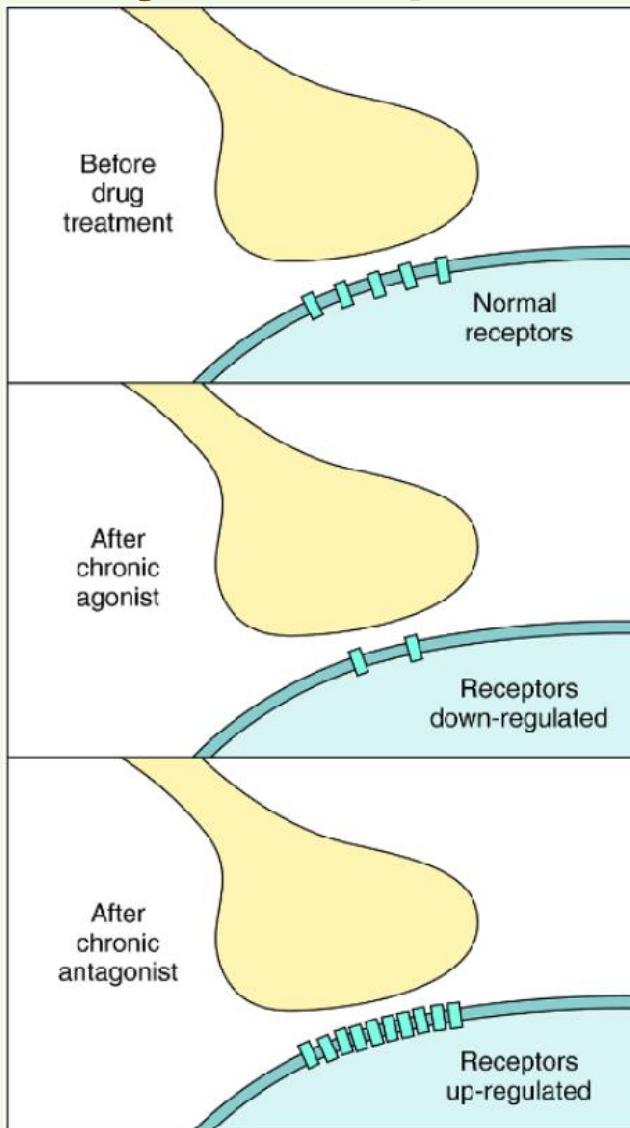


Pathways of receptor internalization and recycling.





Long-term treatment with agonists or antagonists can alter postsynaptic receptor density or responsiveness.





Receptor desensitization and turnover

1. **Tolerance**

Decrease in susceptibility to the effects of a drug due to its **continued administration**.

2. **Tachyphylaxis** : also named “acute tolerance” . Loss of response in an organ after **repeated exposure to an agonist**.

3. **Desensitization** (for the receptor):

Decrease in the responsiveness of a receptor-transmembrane signaling mechanism.



Four general mechanisms for signal transmission

1. Receptors that control **ion channels**.
2. Receptors coupled to **G-proteins** to regulate generation of intracellular second messengers.
3. Receptors consists of those having **cytosolic enzyme activity** as an integral component of their structure or function.
4. Receptors are entirely **intracellular**.

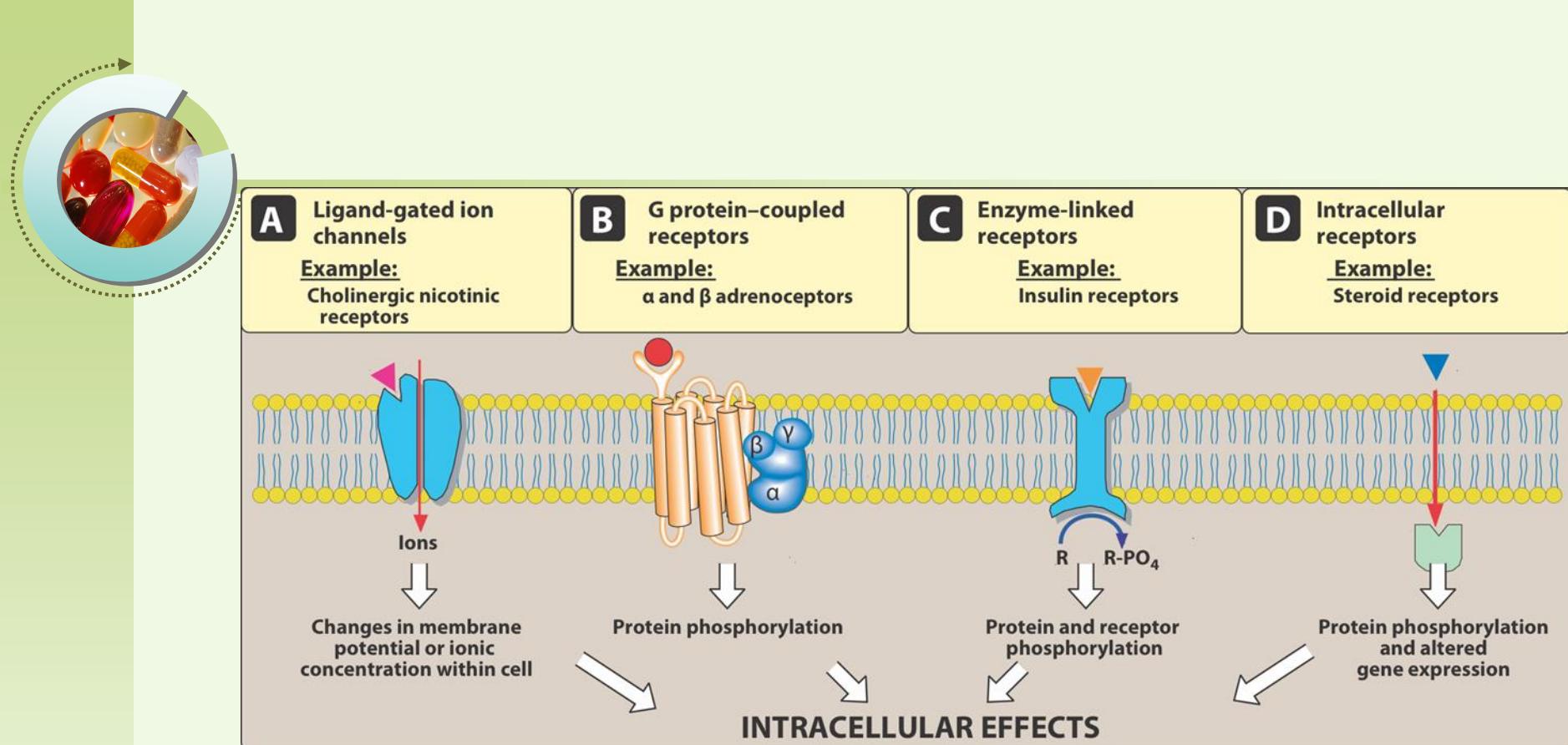
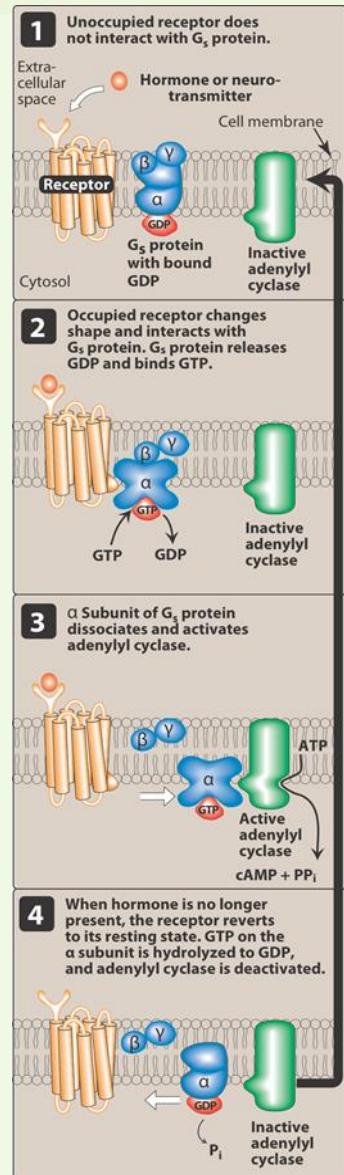
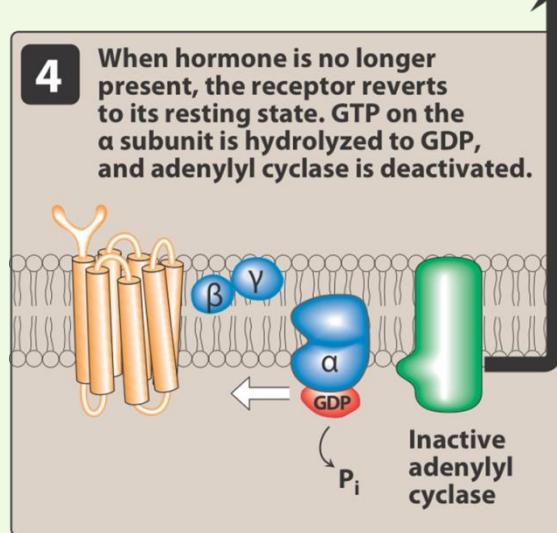
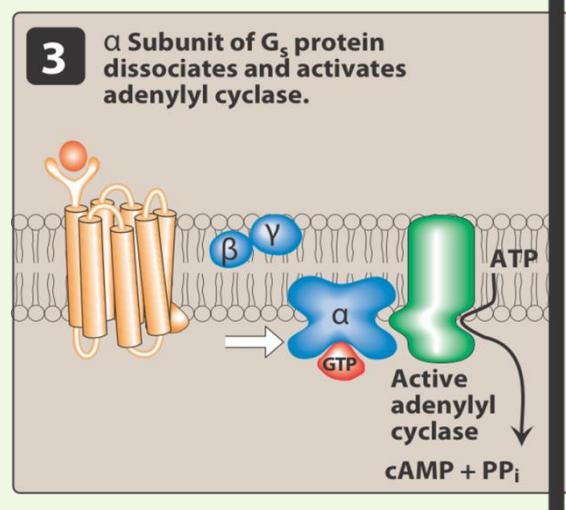
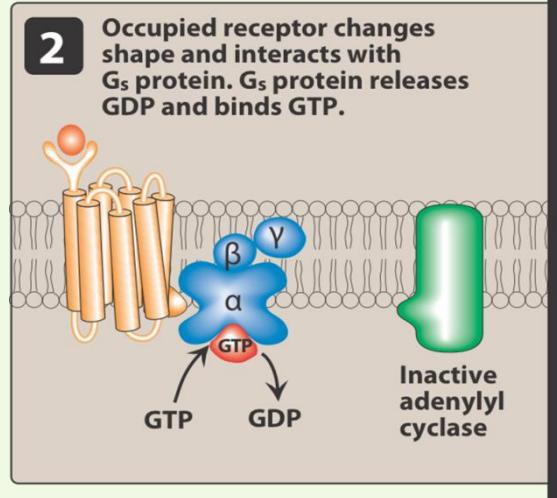
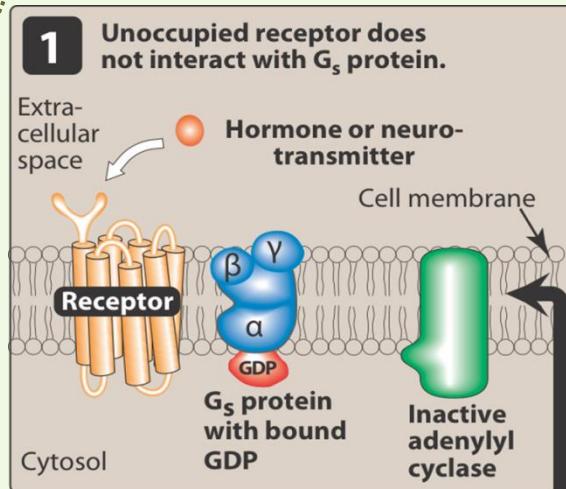
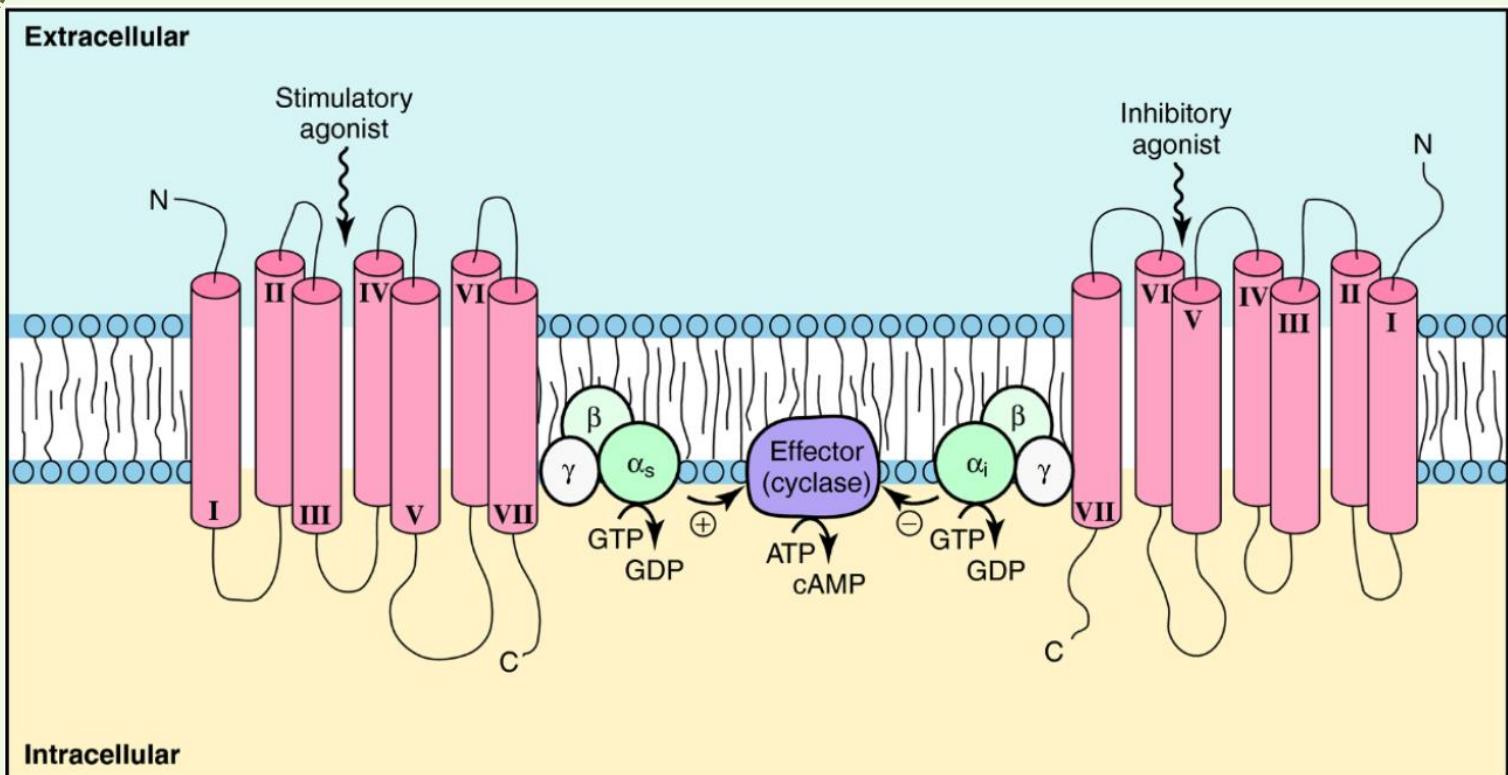


Figure 2.2 Transmembrane signaling mechanisms. A. Ligand binds to the extracellular domain of a ligand-gated channel. B. Ligand binds to a domain of a serpentine receptor, which is coupled to a G protein. C. Ligand binds to the extracellular domain of a receptor that activates a kinase enzyme. D. Lipid-soluble ligand diffuses across the membrane to interact with its intracellular receptor.

G protein-coupled membrane receptors





Structure of GPCRs and signaling molecules involved in regulation of adenylyl cyclase.



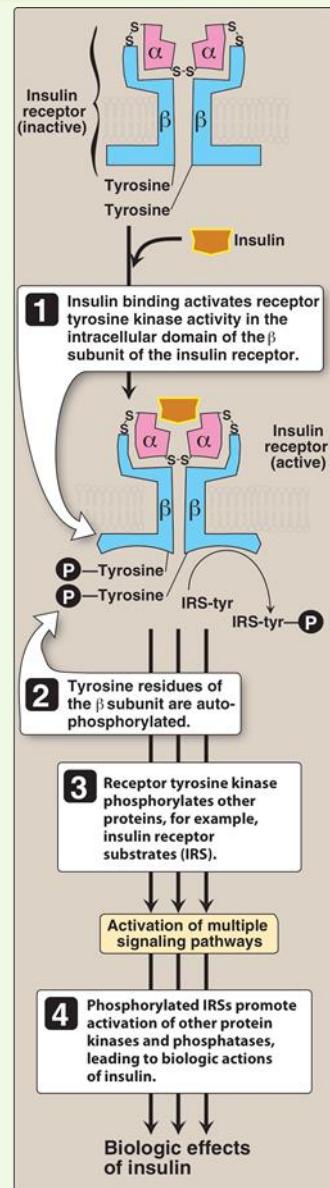
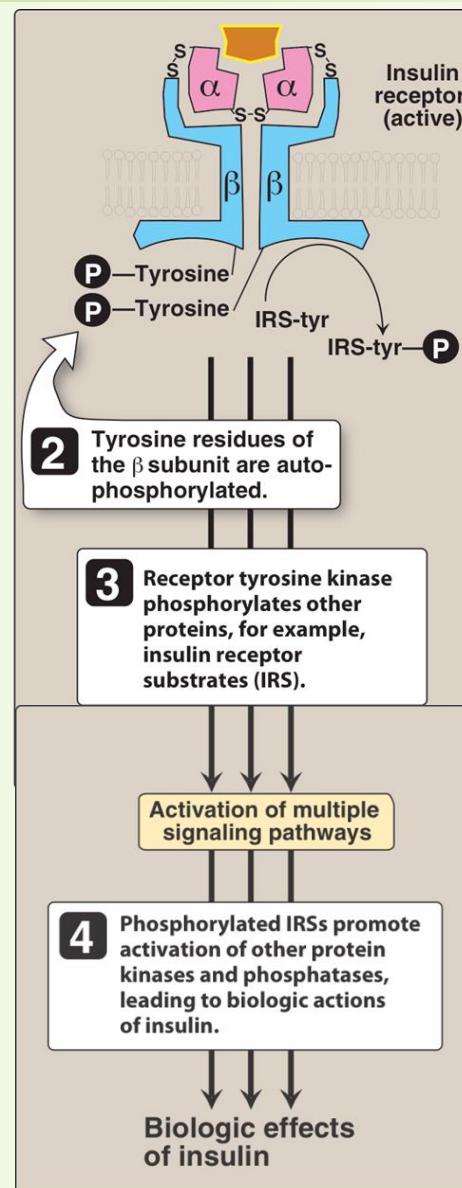
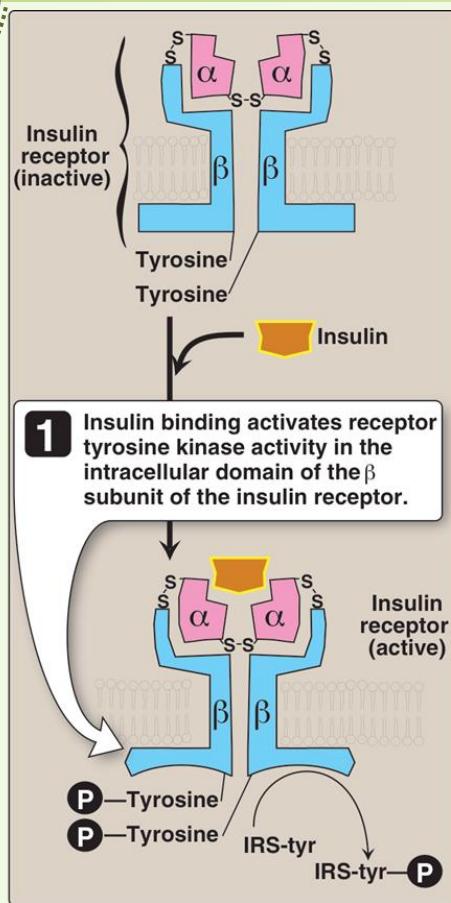
G protein-coupled receptors

G Protein	Receptors for	Effector/Signaling Pathway
G_s	β -Adrenergic amines, glucagon, histamine, serotonin, and many other hormones	\uparrow Adenylyl cyclase \rightarrow \uparrow cAMP
G_{i1}, G_{i2}, G_{i3}	α_2 -Adrenergic amines, acetylcholine (muscarinic), opioids, serotonin, and many others	Several, including: \downarrow Adenylyl cyclase \rightarrow \downarrow cAMP Open cardiac K ⁺ channels \rightarrow heart rate
G_{olf}	Odorants (olfactory epithelium)	\uparrow Adenylyl cyclase \rightarrow \uparrow cAMP
G_o	Neurotransmitters in brain (not yet specifically identified)	Not yet clear
G_q	Acetylcholine (muscarinic), bombesin, serotonin (5-HT ₂), and many others	\uparrow Phospholipase C \rightarrow \uparrow IP ₃ , diacylglycerol, cytoplasmic Ca ²⁺
G_{t1}, G_{t2}	Photons (rhodopsin and color opsins in retinal rod and cone cells)	\uparrow cGMP phosphodiesterase \rightarrow \downarrow cGMP (phototransduction)

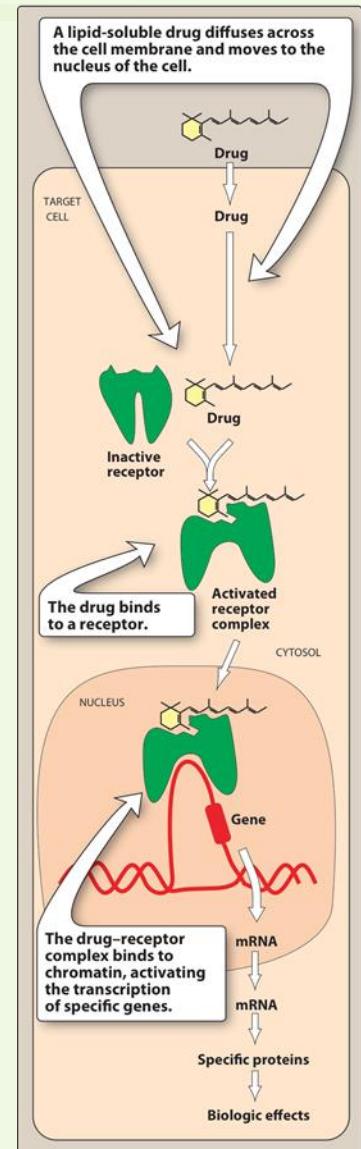
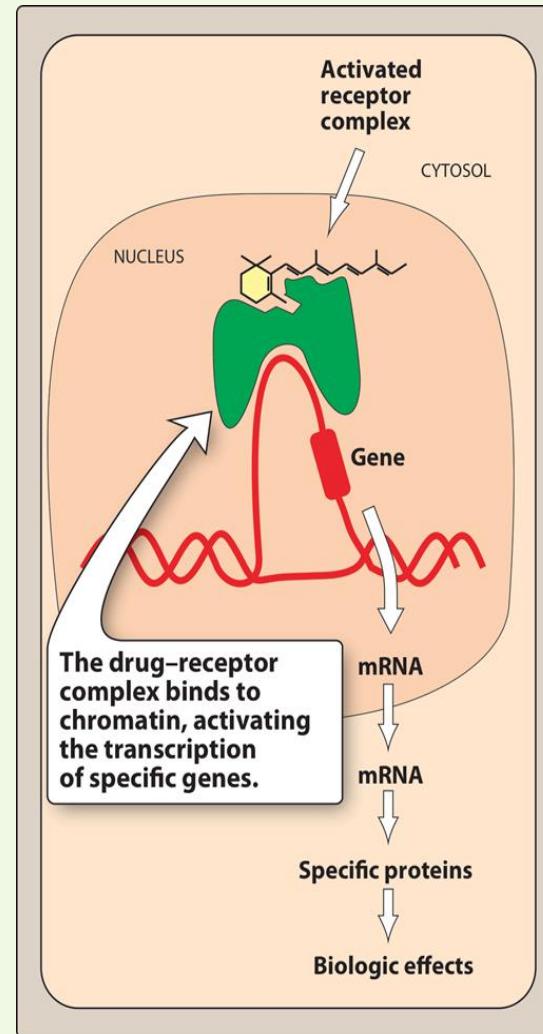
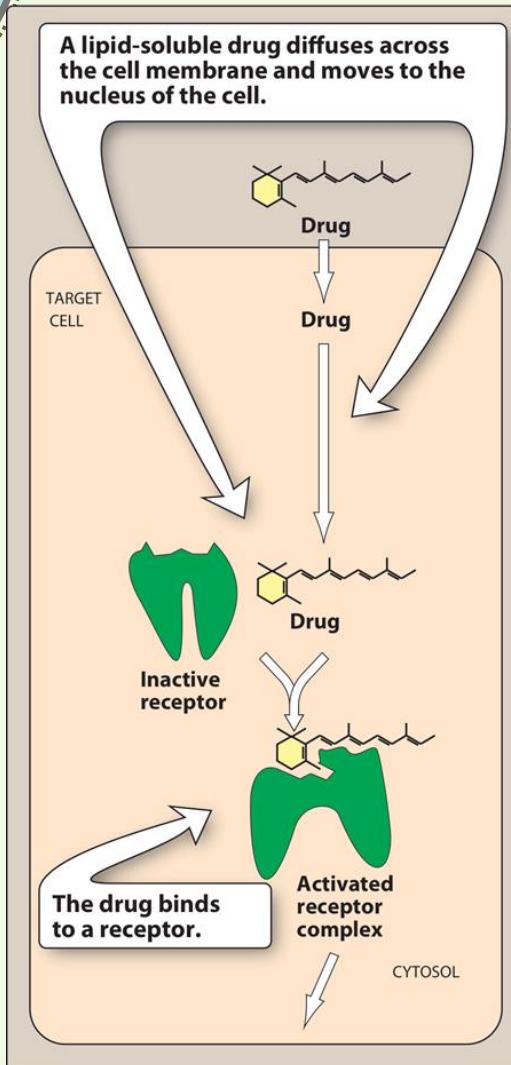
cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate.



Insulin receptor



Intracellular receptor





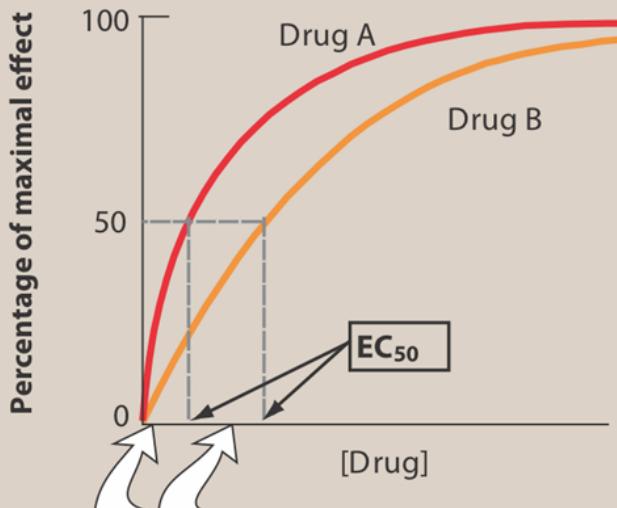
Concentration-Response relationships

- A. Effective dose (ED_{50})
- B. Lethal dose (LD_{50}), toxic dose (TD_{50})
- C. **Efficacy**: The maximal response produced by a drug (*y-axis*).
- D. **Potency**: Also termed effective dose concentration (*x-axis*).
- E. Therapeutic index: $\frac{TD_{50}}{ED_{50}}$

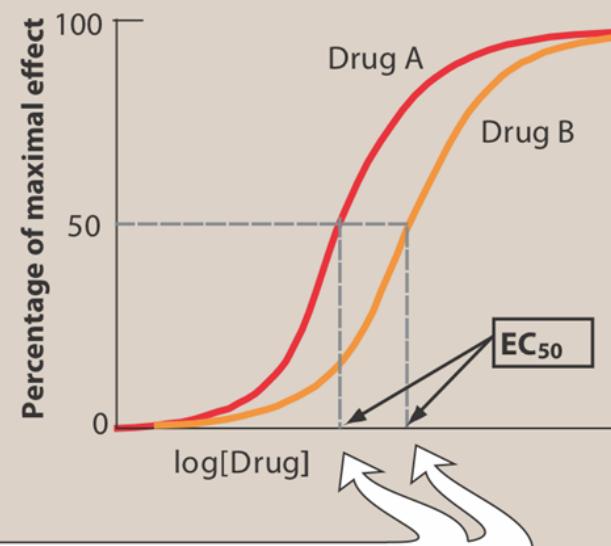
The effect of dose on the magnitude of pharmacological effect



A

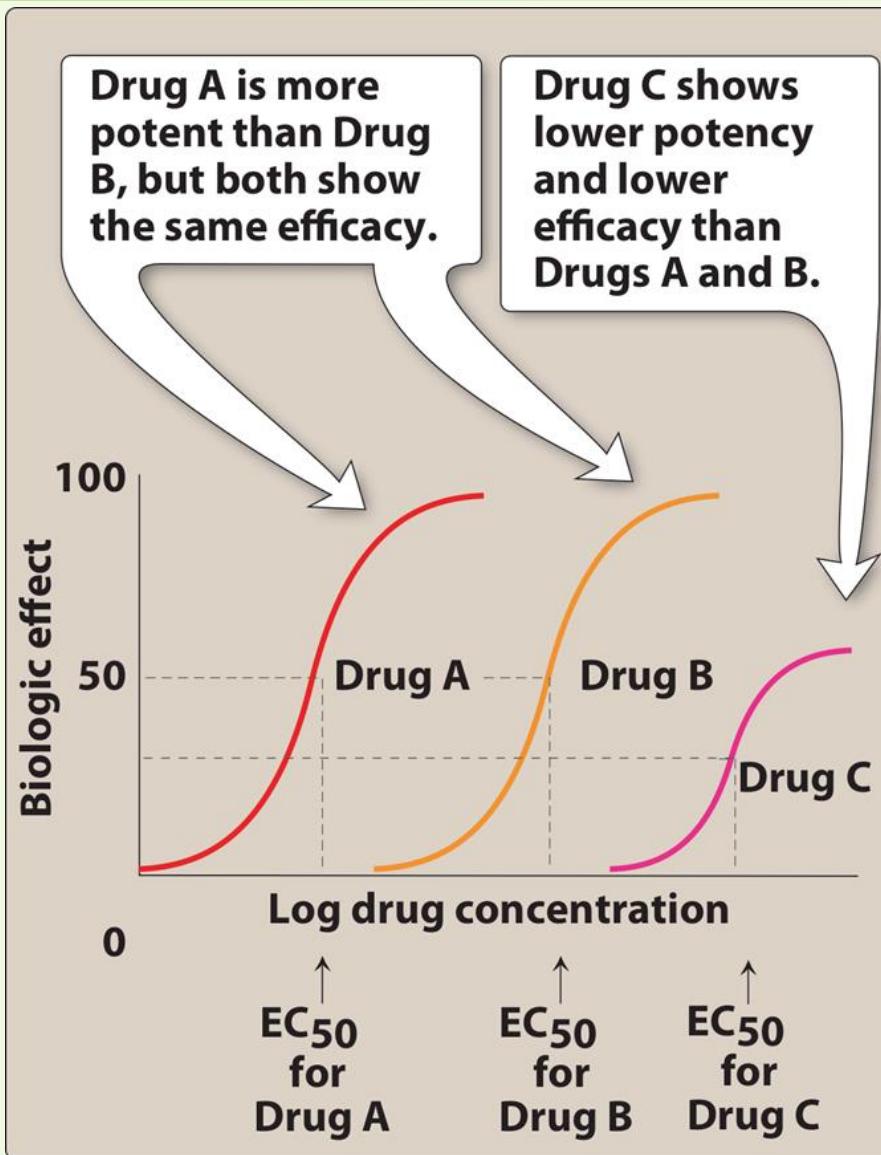


B





Typical dose-response curve for drugs showing differences in potency and efficacy. (EC_{50} =drug dose that shows fifty percent of maximal response.)





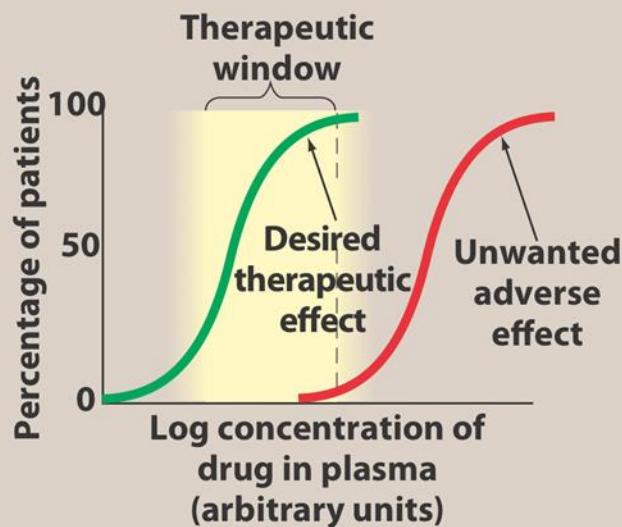
Therapeutic index

Therapeutic index =
toxic dose(TD50)/effective dose (ED50)

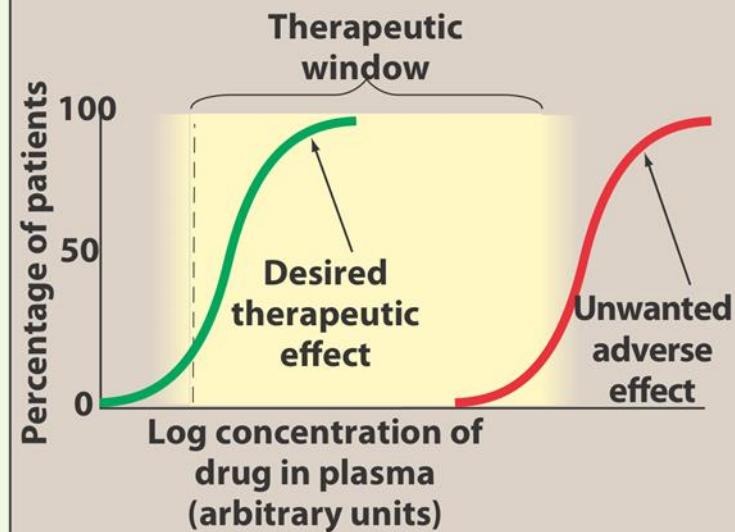
1. Warfarin (a small therapeutic index).
2. Penicillin (a large therapeutic index).



A Warfarin: Small therapeutic index



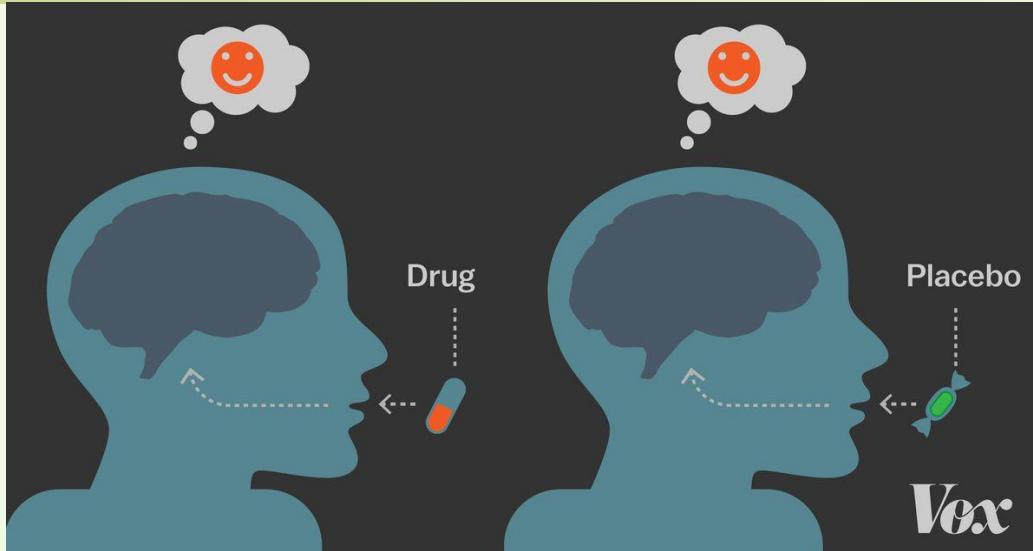
B Penicillin: Large therapeutic index



Cumulative percentage of patients responding to plasma levels of a drug.



Placebo effect



A beneficial effect in a patient following a particular treatment that arises from **the patient's expectations** concerning the treatment rather than from the treatment itself.



Thank You !

