Drug distribution
Lec. 1

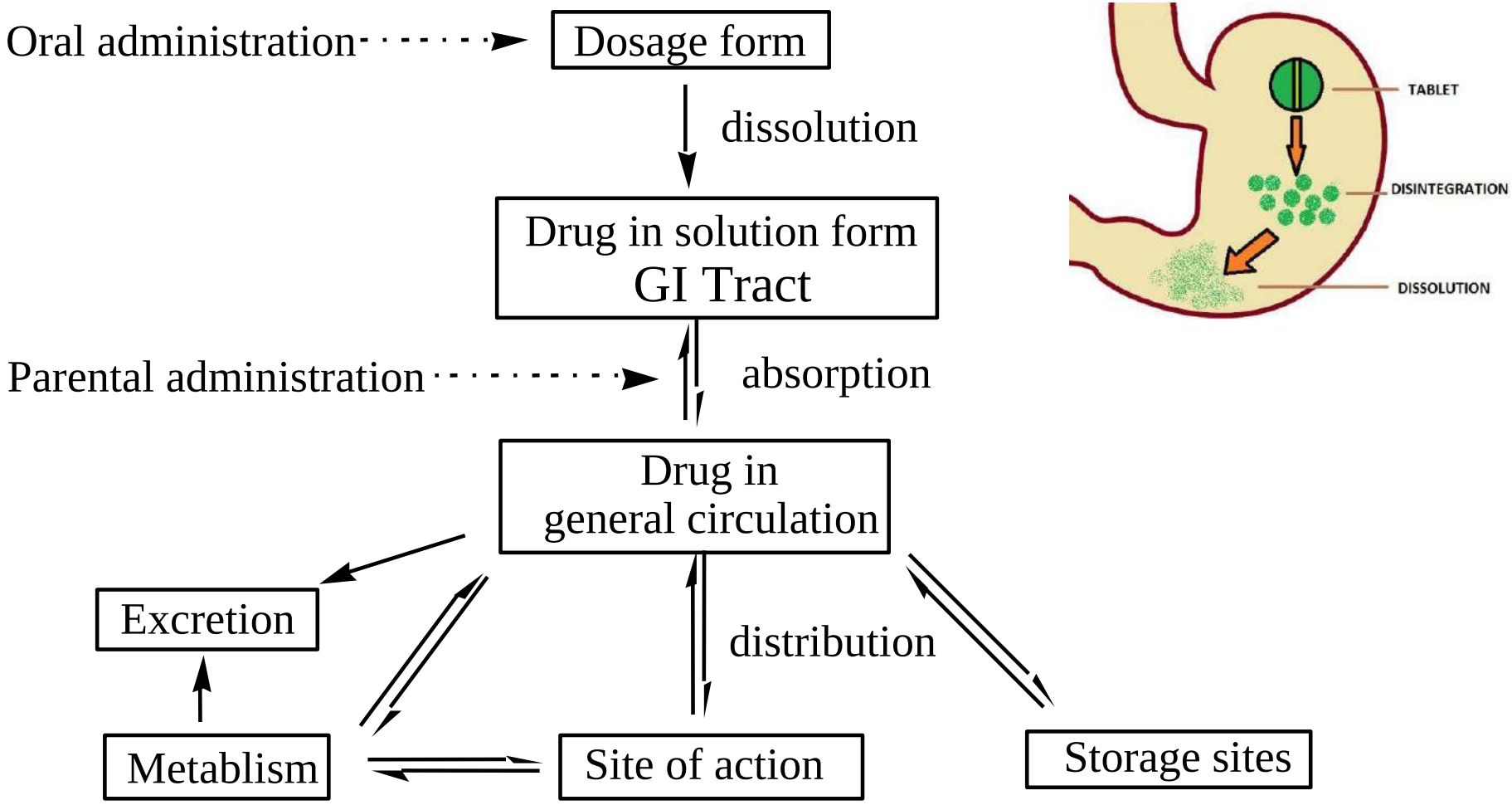
Drug Distribution after Oral Administration

- Drug is a chemical molecule
- To reaches its site of action, drug must pass through many barriers, survive alternate sites of attachment and storage, and avoid significant metabolic destruction

Distribution **after Oral Administration**

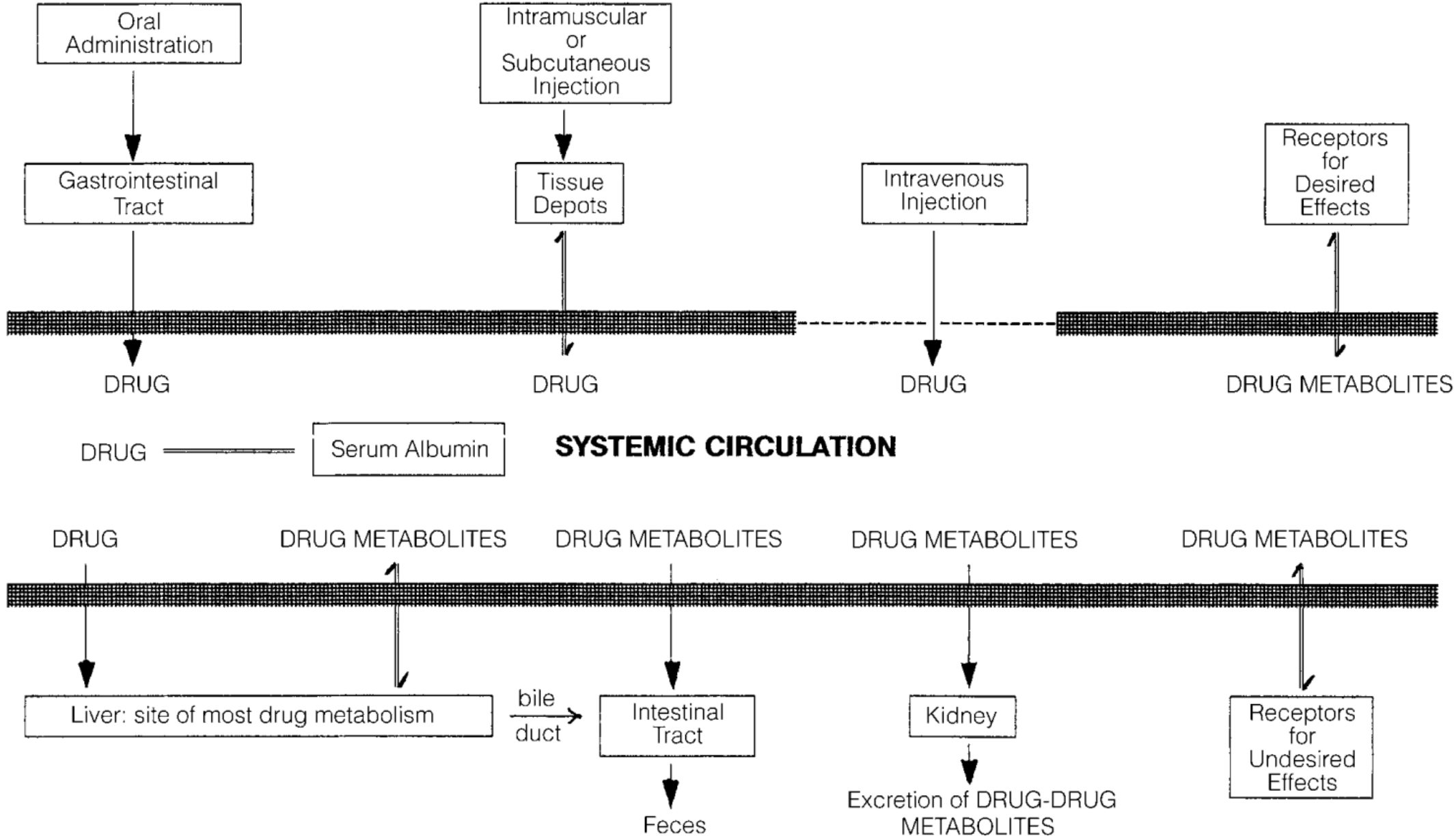
- drug must go into **solution** to pass through the gastrointestinal mucosa.
- Even drugs administered as true solutions may not remain in solution as they enter the acidic stomach and then pass into the alkaline intestinal tract.

Sequence of events after drug administration



FYI

Reservoir for lipid soluble drug



Summary of drug distribution.

Drug Distribution after Oral Administration

The ability of the drug to dissolve is governed by several factors, including:

- ❑ Its chemical structure
- ❑ Variation in particle size and particle surface area
- ❑ Nature of the crystal form
- ❑ Type of tablet coating
- ❑ Type of tablet matrix

} Drug dissolve slowly/quickly

- By varying the dosage form and physical characteristics of the drug, it is possible to have a drug dissolve quickly or slowly.
- **Chemical modification** is also used to a limited extent to **facilitate a drug reaching its desired target**.

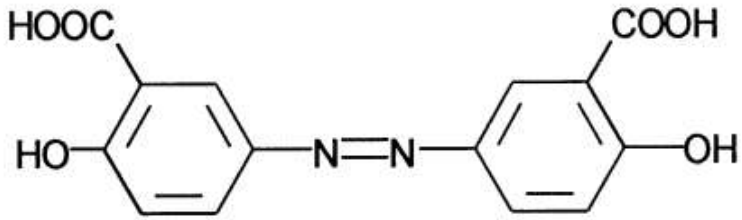
❑ In the GIT, a large number and variety of digestive and bacterial enzymes, → degrade the drug molecule

➢ leading to necessitating an alternate route

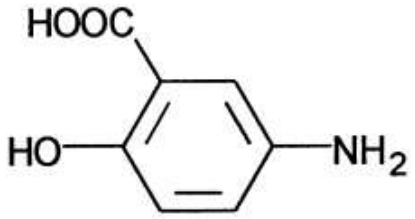
Drug Distribution /Prodrug Approach

❑ Example of Chemical modification used to facilitate a drug reaching its desired target

- Mesalamine (5-aminosalicylic acid) is not effective orally because it is metabolized to inactive forms before reaching the colon.
- Osalazine
  - treatment of ulcerative colitis
  - This drug is a dimer of the pharmacologically active Mesalamine.
  - The dimeric form passes through a significant portion of the intestinal tract before being cleaved by the intestinal bacteria to two equivalents of Mesalamine.

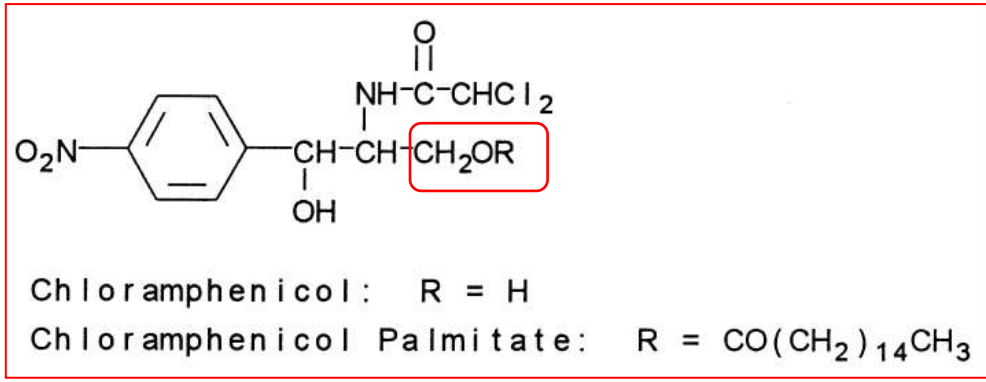


Olsalazine



Mesalamine

Drug Distribution /Prodrug Approach



- ❑ Same digestive enzymes can be used to be advantageous
- ❑ Chloramphenicol
  - is **water soluble** enough (2.5 mg/mL) to come in contact with the taste receptors on the tongue → producing an unpalatable **bitterness**.
  - To **mask** this intense bitter taste, the **palmitic acid moiety** is **added** as an ester of the primary hydroxyl of chloramphenicol (i.e. chloramphenicol palmitate) → This **reduces** the parent drug's **water solubility** (1.05 mg/mL), enough so that it can be formulated as a **suspension** that passes over the bitter taste receptors on the tongue.
  - Once in the intestinal tract, the **ester linkage** is hydrolyzed by the digestive **esterases** to the active antibiotic chloramphenicol and the very common dietary fatty acid palmitic acid.

Drug Distribution after Oral Administration

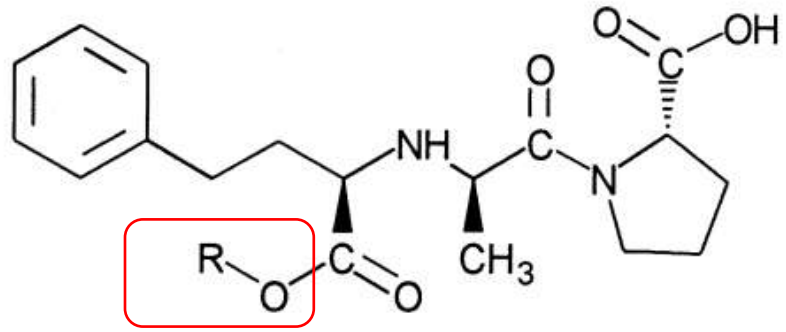
- Olsalazine and chloramphenicol palmitate are examples of prodrugs.
- Most **prodrugs** are compounds that are **inactive in their native form** but are easily metabolized to the active agent.
- Olsalazine and chloramphenicol palmitate are examples of prodrugs that are cleaved to smaller compounds, one of which is the active drug.

Drug bioavailability/Prodrug Approach

- the prodrug approach is used to **enhance the absorption** of a drug that is poorly absorbed from the gastrointestinal tract

Enalapril

- is the **ethyl ester** of enalaprilic acid, an active inhibitor of angiotensin-converting enzyme (ACE) (antihypertensive agent)
- **ester prodrug** is much more readily absorbed orally than the pharmacologically active carboxylic acid.



Enalapril: R = C_2H_5

Enalaprilic Acid: R = H

Distribution after Oral Administration

Drug should pass through the gastrointestinal mucosal barrier into venous circulation to reach the site of the receptor. This involves distribution or partitioning between:

- ❑ The aqueous environment of the GIT
- ❑ The lipid bilayer cell membrane of the mucosal cells
- ❑ Possibly the aqueous interior of the mucosal cells
- ❑ The lipid bilayer membranes on the venous side of the GIT
- ❑ The aqueous environment of venous circulation

Parenteral Administration

- bypassing the intestinal barrier (advantages)
- Indicated for:
  - Patients who, because of illness, cannot tolerate or are incapable of accepting drugs orally.
  - Some drugs are so rapidly and completely metabolized to inactive products in the liver (first-pass effect) that oral administration is precluded.

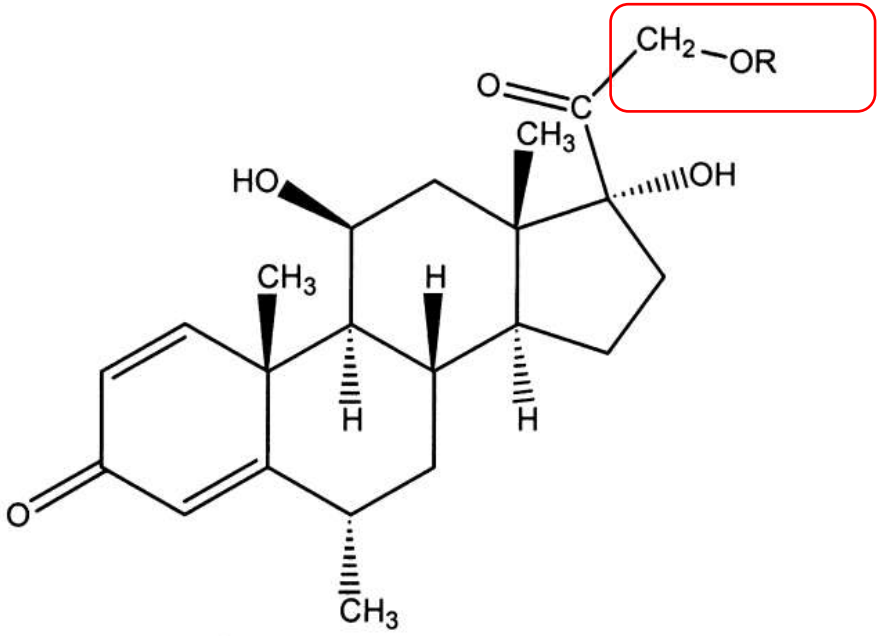
Drug distribution/Parenteral Administration

The obstacles:

- drug directly into the circulatory system → rapidly distributed → unwanted places including tissue depots and the liver (biotransformations)
- subcutaneous and IM **slow** drug distribution (must diffuse from the site of injection) → depot.
- BBB which is
  - composed of membranes of tightly joined epithelial cells lining the cerebral capillaries which protects the brain from exposure to a large number of metabolites and chemicals.
  - parenterally administered drugs may not cross the BBB
  - bypass the BBB through Intraspinal (local anesthetics) and intracerebral routes will place the drug directly into the spinal fluid or brain

Drug Formulation/ Prodrug Approach

The prodrug approach used to alter the solubility → increase the flexibility in formulating dosage forms



Methylprednisolone: R = H

Methylprednisolone Acetate: R = $C(=O)CH_3$

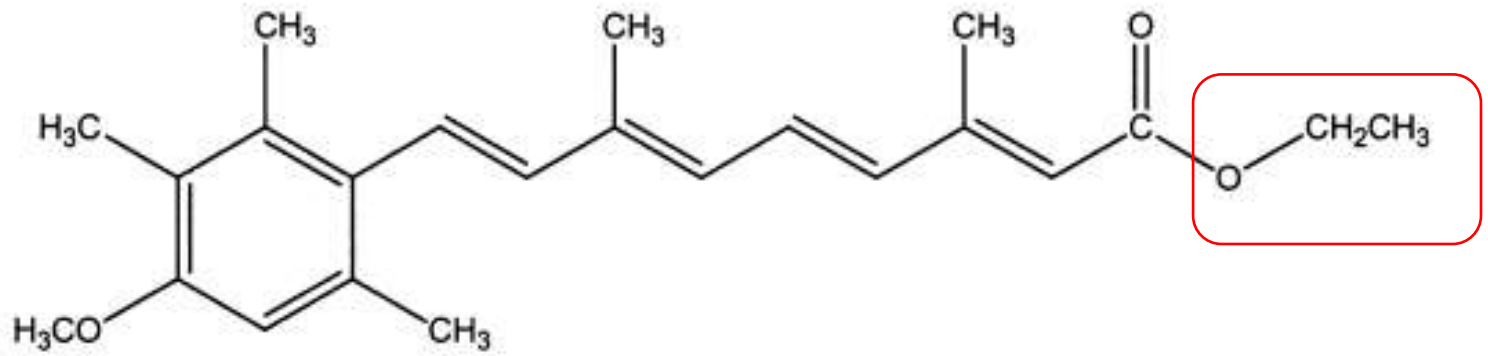
Methylprednisolone Sodium Succinate: R = $C(=O)CH_2CH_2COO^-$ Na^+

- ❑ Methylprednisolone: slightly water-insoluble (tablets
- ❑ Methylprednisolone **acetate**
  - water-insoluble (topical **ointments** and sterile aqueous suspensions for **IM injection**.
  - **Esterases** hydrolyzed to the active methylprednisolone
- ❑ Methylprednisolone sodium **succinate**
  - water-soluble sodium salt succinate ester (**oral, intravenous,** and **intramuscular**)
  - **Esterases** hydrolyzed to the active methylprednisolone

Drug distribution/Parenteral Administration

Prodrug approach alter biodistribution and biological half-life

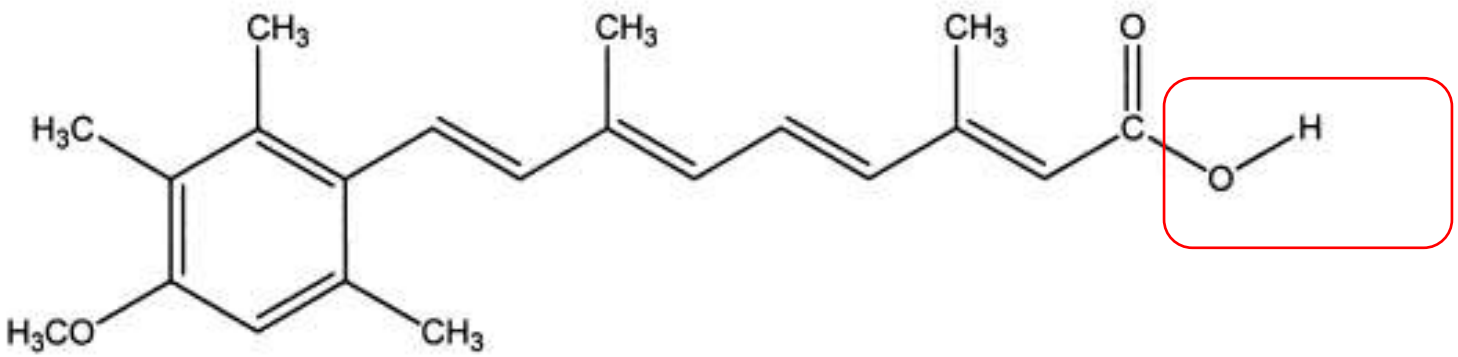
- **Etretinate** and **Acitretin** are two drugs based on the **retinoic acid** structure used systemically to treat psoriasis, a nonmalignant hyperplasia.
- **Etretinate** has a 120-day terminal half-life after 6 months of therapy.
- **Acitretin**, the active metabolite, has a 33-96 hour terminal half-life. (shorter half-life)
  - Both drugs used systemically to treat psoriasis, a nonmalignant hyperplasia.
  - Both potentially teratogenic)
- Acitretin, is recommended for a woman who would like to become pregnant, because it can clear from her body within a reasonable time frame.



Etretinate

Esterase

CH_3CH_2OH



Acitretin

Protein Binding

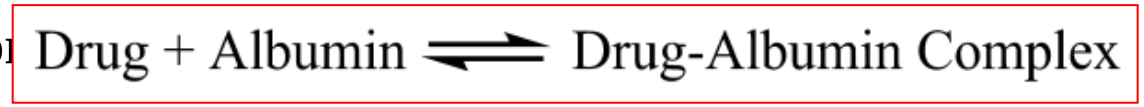
- Once the drug enters the systemic circulation→ stay in solution/bound to the serum proteins, (albumin)
- The drug bound to albumin not be available to the sites of biotransformation, the pharmacological receptors, and excretion.

- Protein binding can have a profound effect on the drug's effective **solubility**, **biodistribution**, **half-life** in the body, and **interaction** with other drugs.

Protein Binding

1. Drug's effective solubility:

   - A drug with poor water solubility that therapeutic concentrations of the unbound (active) drug normally cannot be maintained still can be a very effective agent.
   - The albumin–drug complex acts as a **reservoir by providing large enough concentrations of free drug to cause a pharmacological response at the recepto**r



2. Drug's biodistribution.

   - Protein binding limit access to certain body compartments.
   - The placenta is able to block passage of proteins from maternal to fetal circulation.
   - Thus, **drugs** that normally would be expected to **cross the placental barrier** and possibly harm the fetus are retained in the maternal circulation, **bound to the mother's serum proteins**.

Protein Binding

3. Half-life in the body and duration of action:

The drug–protein complex:

$$\text{Drug} + \text{Albumin} \rightleftharpoons \text{Drug-Albumin Complex}$$

- preventing rapid excretion of the drug (too large to pass through the renal glomerular membranes
- limits the amount of drug available for biotransformation
- limits interaction with specific receptor sites.

- example, the large, polar trypanocide **Suramin** remains in the body in the protein-bound form for as long as 3 months (t1/2 = 50 days).
- The maintenance dose for this drug is based on weekly administration.
- At first, this might seem to be an advantage to the patient, but when the **patient have serious adverse reactions**, a **significant length of time** will be **required** before the concentration of drug falls below toxic levels.

Protein Binding

4. Interaction with other drugs:

- significant drug–drug interactions that result when one drug displaces another from the binding site on albumin.
- a large number of drugs can displace the anticoagulant warfarin from its albumin binding sites.

→ increases the effective concentration of warfarin at the receptor,

→ increased prothrombin time (increased time for clot formation) and potential hemorrhage.

Tissue Depots

- The drug can be stored in tissue depots. (fat constitutes some 20% to 50% of body weight)
- The more lipophilic the drug, the more likely it will concentrate in these pharmacologically inert depots.
- The **ultra–short-acting**, lipophilic barbiturate thiopental's **concentration** rapidly **decreases** below its effective concentration following administration?
  - It disappears into tissue protein, **redistributes into body fat**, and then slowly diffuses back out of the tissue depots but in concentrations too low for a pharmacological response.

Tissue Depots

- Thus, only the **initially administered** thiopental is present in high enough concentrations to **combine with its receptors.**
- The **remaining** thiopental **diffuses** out of the tissue depots into systemic circulation, in concentrations too small to be effective, which then is metabolized in the liver, and is excreted.
- In general, structural changes in the barbiturate series that favor partitioning into the lipid tissue stores (**more lipophilic**) decrease duration of action but increase central nervous system (CNS) depression.
- barbiturates contain more polar side chains (**more hydrophilic**) :
  - with the slowest onset of action and longest duration of action contain the **more polar side chains**.
  - enters and leaves the CNS slower than the more lipophilic thiopental.

Drug Metabolism

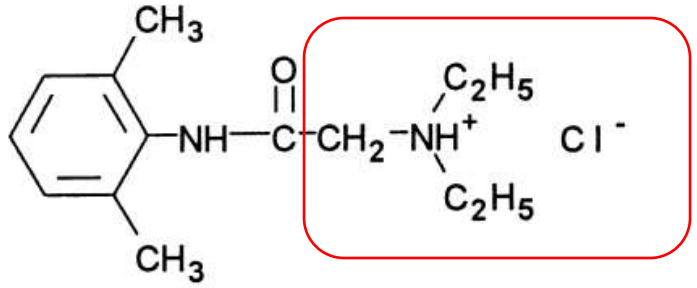
- All substances in the circulatory system, including drugs, metabolites, and nutrients, will pass through the liver.
- Most molecules **absorbed from the gastrointestinal tract** enter the portal vein and are initially transported to the liver.
- A significant proportion of a drug will partition or be transported into the hepatocyte, where it may be metabolized by hepatic enzymes to inactive chemicals during the initial trip through the liver, by what is known as the **first pass effect**.

Drug Metabolism

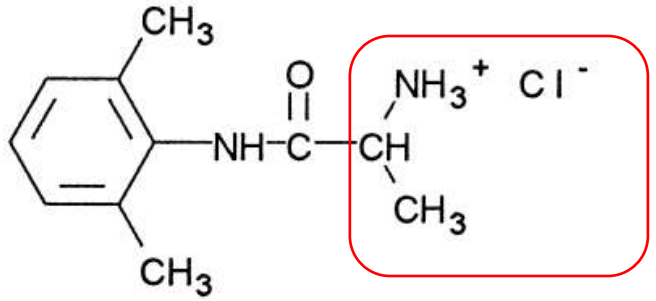
- Lidocaine
  - is a classic example of the significance of the first-pass effect.
  - Over 60% of this local anesthetic antiarrhythmic agent is metabolized during its initial passage through the liver, resulting in it being impractical to administer orally.
  - When used for cardiac arrhythmias, it is administered intravenously.
- Advantage of rapid metabolism:
  - This rapid metabolism of lidocaine is **useful** when **stabilizing a patient** with cardiac arrhythmias
  - When Lidocaine should be administered intravenously in too much quantities, toxic responses will tend to decrease (NO toxic response) because of rapid biotransformation to inactive metabolites.

Drug Metabolism

- Lidocaine
  - An understanding of the metabolic labile site on lidocaine led to the development of the primary amine analog **tocainide**.
  - lidocaine's half-life of less than 2 hours, tocainide's half-life is approximately 15 hours, with 40% of the drug excreted unchanged.



Lidocaine



Tocainide

Drug Metabolism

- A study of the metabolic fate of a drug is required for all new drug products. Where we have different situation:

1. Active parent drug converted to inactive metabolites. Example lidocaine.
2. An inactive parent drug that is converted to an active metabolite (Prodrug)
    - the nonsteroidal anti-inflammatory agent **sulindac** being reduced to the active **sulfide metabolite**
    - the immunosuppressant **azathioprine** being cleaved to the purine antimetabolite **6-mercaptopurine**, and purine and pyrimidine antimetabolites
    - antiviral agent **acyclovir** being converted to their nucleotide form **acyclovir triphosphate**.

Drug Metabolism

3. Often both the parent drug and its metabolite are active.
   - about 75% to 80% of phenacetin (now withdrawn from the U.S. market) is converted to acetaminophen.
   - In the tricyclic antidepressant series, imipramine and amitriptyline are N-demethylated to desipramine and nortriptyline, respectively.

Drug Metabolism

- Although a drug's metabolism can be a source of hindrance for the medicinal chemist, pharmacist, and physician and lead to inconvenience and compliance problems with the patient, it is fortunate that the body has the ability to metabolize foreign molecules (xenobiotics).
- Otherwise, many of these substances could remain in the body for years especially certain lipophilic chemical pollutants, including the once very popular insecticide dichlorodiphenyltrichloroethane (DDT).
- After entering the body, these chemicals reside in body tissues, slowly diffusing out of the depots and potentially harming the individual on a chronic basis for several years.

Excretion

- **Kidney** is the main route of **excretion** of a drug and its metabolites.
- For some drugs, enterohepatic circulation, in which the drug reenters the intestinal tract from the **liver** through the bile duct and be excreted in the feces.
- **Milk of nursing mothers** and therfore they must be worried, because drugs and their metabolites can be excreted in human milk and be ingested by the nursing infant.

❑ Several variables make dosing regimens must be more frequent:

- If the situation does not favor formation of the drug–receptor complex, higher and usually more frequent doses must be administered.
- If partitioning into tissue stores or metabolic degradation and/or excretion is favored, it will take more of the drug and usually more frequent administration to maintain therapeutic concentrations at the receptor.

The Receptors

- The receptor components appear to be mainly protein.
- The nature of the amide link in proteins provides a unique opportunity for the formation of multiple internal hydrogen bonds, as well as internal formation of hydrophobic, van der Waals, and ionic bonds by side chain groups, leading to such organized structures.
- An **organized protein structure** would hold the amino acid side chains at relatively **fixed positions** in space and available for specific interactions with a small molecule (ligands or drugs).
- Pharmacological response consists of a drug binding to a specific receptor.
- Many drug receptors are the same as those used by endogenously produced ligands (cholinergic agents and synthetic corticosteroids interact with the same receptors as acetylcholine and cortisone bind to them)

The Receptors

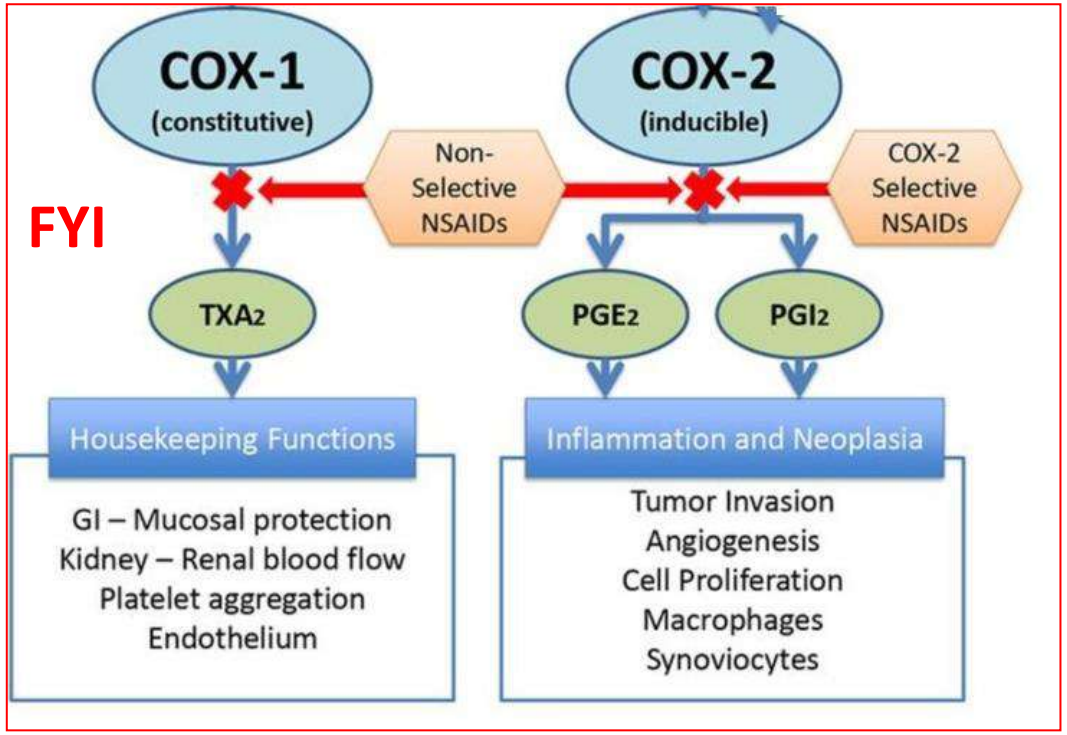
- Binding of drugs to receptors may produce desired or undesired effects. This is depending on

1. The biological distribution of these receptors.

❑ Example, the nonsteroidal anti-inflammatory drugs

➢ combine with the desired **cyclooxygenase** receptors at the site of the **inflammation** and

➢ combine with undesired **cyclooxygenase** receptors in the **gastrointestinal mucosa**, causing severe discomfort and sometimes ulceration.



The Receptors

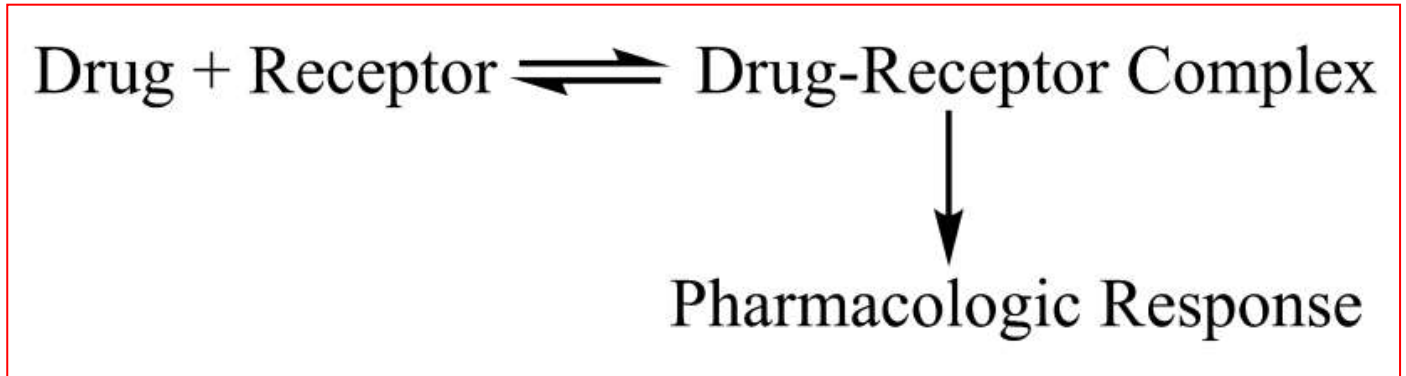
- Binding of drugs to receptors may produce desired or undesired effects. This is depending on

2. Biological distribution of drugs, i.e. the organs and tissues that can be reached by the drug and contain these receptors.
    - Unlike the first generation antihistamines, the second-generation antihistamines, like fexofenadine, are claimed to cause less sedation because it does not readily penetrate the blood-brain barrier.

The Receptors

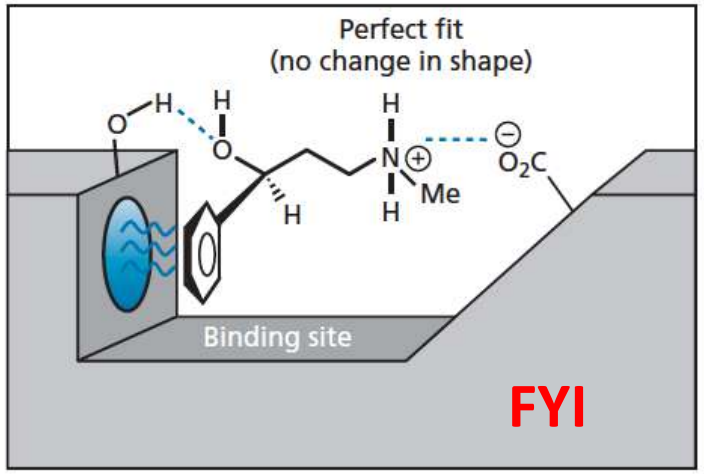
3. Various receptors with similar **structural requirements** are found in several organs and tissues

- ❑ Example, tamoxifen is:
  - an estrogen antagonist in the mammary gland and an agonist in the uterus and bone.
- ❑ In contrast, raloxifene:
  - does not appear to have much agonist property in the uterus but, like tamoxifen, are an antagonist in the breast and agonist in the bone.
- ❑ Drug-receptor interaction is an equilibrium process, equation below.
  - A good ability to fit the receptor favors binding and the desired pharmacological response
  - In contrast, a poor fit favors the reverse reaction and the amount of drug bound to the receptor is too small which leads to a much smaller pharmacological effect.



The Receptors

- Many variables contribute to a drug's binding to the receptor. These include:
  - **The structural classes**, since most drugs that belong to the same pharmacological class have certain structural features in common.
  - **The 3D shape of the molecule**. Very slight changes in structure could cause significant changes in biological activity. These structural variations could increase or decrease activity or change an agonist into an antagonist.
  - **The types of chemical bonding involved** in the binding of the drug to the receptor.



The Receptors

- The initial receptor model was based on a rigid lock-and-key concept, with the drug (key) fitting into a receptor (lock).
- It has been used to explain why certain structural features produce a predictable pharmacological action.
- **Recent model must realize** that both the drug and the receptor can have **considerable flexibility**.
- The **receptor** can **undergo an adjustme**nt in 3D structure when the **drug** makes **contact**, i.e. the drug docks with the receptor.

The Receptors

- The fit of drugs onto or into macromolecules
  - is **not always an all-or-none process** as pictured by the earlier lock-and-key concept of a receptor.
  - Rather, it appears to be a continuous process, as indicated by regular **increase and decrease** in biological activity of a **homologous series of drugs**.

- Drug-receptor association may produce **productive changes** in the configuration of the macromolecule, leading to **agonist** responses.

- Similarly, strong drug-receptor associations may lead to **unproductive changes** in the configuration of the macromolecule, leading to an **antagonistic** or blocking response.