Topic #1:
Basic Principles of Pharmacology

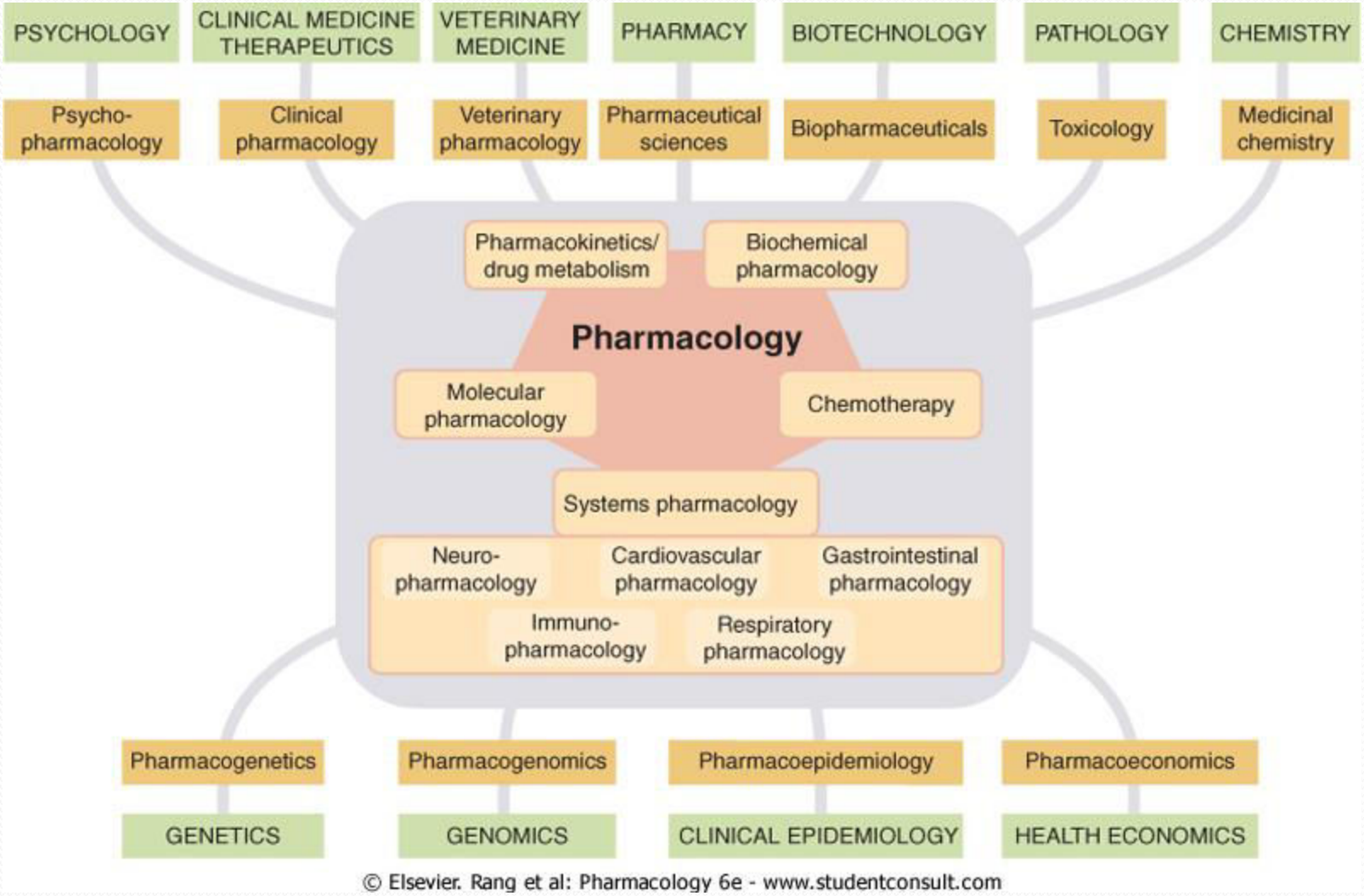
Second Semester 2013/2014

What is Pharmacology?

From the Greek *pharmakon* (drug), *logia* (study of)

"The study of **substances** that **interact** with **living systems** **through chemical processes,** especially by:

- binding to regulatory molecules
- and activating or inhibiting normal body processes"



Pharmacology today with its various subdivisions. Interface disciplines (brown boxes) link pharmacology to other mainstream biomedical disciplines (green boxes)

General principles of pharmacology

The nature of drugs

- Drug is a **chemical substance** of known structure that brings about a change in biologic function through its chemical actions
- To **count as a drug**, the substance must be **administered** as such**, rather than released by** physiological mechanisms

General principles of pharmacology

The nature of drugs

- The drugs may be:

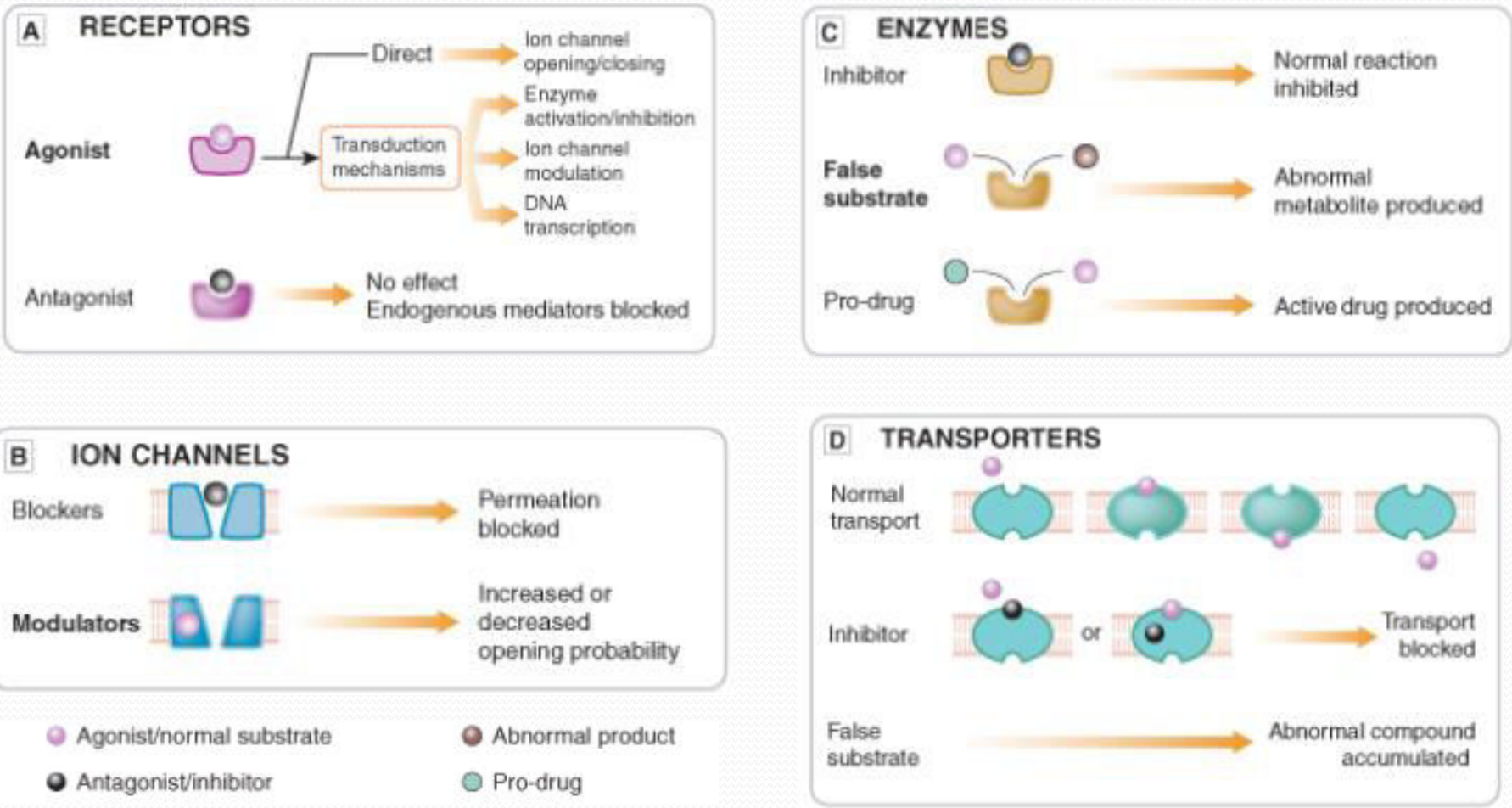
1) **Endogenous substances** synthesized within the body (e.g., hormones)

2) **Xenobiotics:** chemicals not synthesized in the body

General principles of pharmacology

The nature of drugs

- Drug molecule must 'bound' to drug targets (particular constituents of cells and tissues….**produce an effect**)
- Four main kinds of **regulatory protein** (primary drug targets):
  - **Receptors**
  - **Enzymes**
  - **Carrier molecules (transporters)**
  - **Ion channels**



Types of targets for drug action

The nature of drugs

- In order for a drug to **interact with it's target**, a drug must have the appropriate:

1) Size
2) Electrical Charge
3) Shape
4) Atomic composition

- A **practical drug** must have the **appropriate properties** to be:

5) Transported from its site of administration to its site of action

6) Inactivated or excreted from the body at a reasonable rate so its actions will be of appropriate duration

Drug size

- The molecular size of drugs varies from very small (lithium ion, MW 7) to very large (alteplase [t-PA], a protein of MW 59, 050)
- Most drugs have molecular weights **between 100 and 1000:**
  - To **achieve specificity**, a drug molecule should in most cases be at least 100MW in size
  - Drugs **much larger than MW 1000** will **not diffuse readily into the compartment where they** will have **their effect**

The physical nature of drugs

- At room temperature:
  - Solids (aspirin, atropine)
  - Liquids (nicotine, ethanol)
  - Gaseous (nitrous oxide)……????
- These factors often determine the best route of administration
- Many drugs are weak bases or acids: pH differences in various compartments in the body may alter the degree of ionization of such drugs

Drug Reactivity and Drug-Receptor Bonds

- Drugs interact with targets with a variety of chemical forces/bonds:
  - Covalent: very strong and irreversible effects last until synthesis of new receptors
  - Electrostatic: more common, varies from **strong** linkages between permanently charged **ionic molecules** to **weake**r hydrogen bonds and **very weak induced** dipole interactions (van der Waals)
  - Hydrophobic: **weak**, important in the interaction of **highly lipid soluble drugs with the lipids of the cell membran**e and interaction of drugs with internal wall of receptor "pockets"

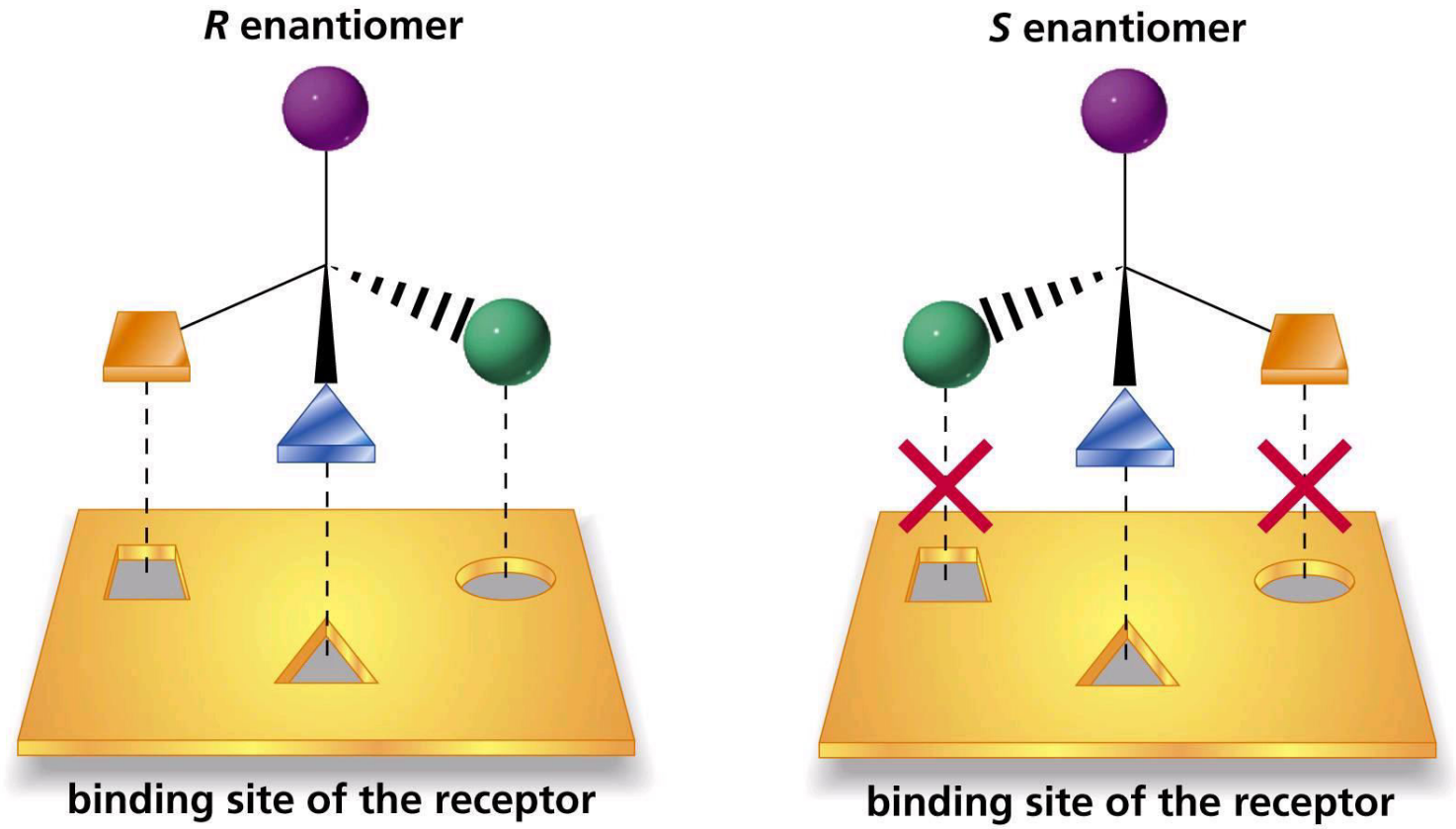
Drug shape

- The shape of a drug molecule must be such as to permit binding to its target/receptor site

- Ideally, the **drug's shape** is **complementary** to that **of the receptor site** in the same way that a key is complementary to a lock (**Lock and Key phenomenon)**

Drug shape

- **Chirality (stereoisomerism):**
- >50% of all useful drugs are chiral molecules…..exist as enantiomeric pairs
- **EX.:** One enantiomer is **more potent** than the other (e.g. S-methacholine is over 250 time more potent than R-methacholine)
- **EX.: The duration of action** of the enantiomers may be different…….due to different susceptibility to drug-metabolizing enzymes (**WHY?**)
- ~50% of chiral active ingredients are still administered as racemic mixture


R enantiomer
binding site of the receptor
S enantiomer
binding site of the receptor

Receptor & Drug → Rational Drug Design

- It implies the ability to **predict** the appropriate molecular structure of a drug on the basis of information about its biologic receptor
- Previously, drugs were developed through random testing of chemicals or modifications of drugs already known to have some effect
- In the past 3 decades many receptors were isolated and characterized
- Computer programs available to optimize drug structure

Drug-Body Interactions

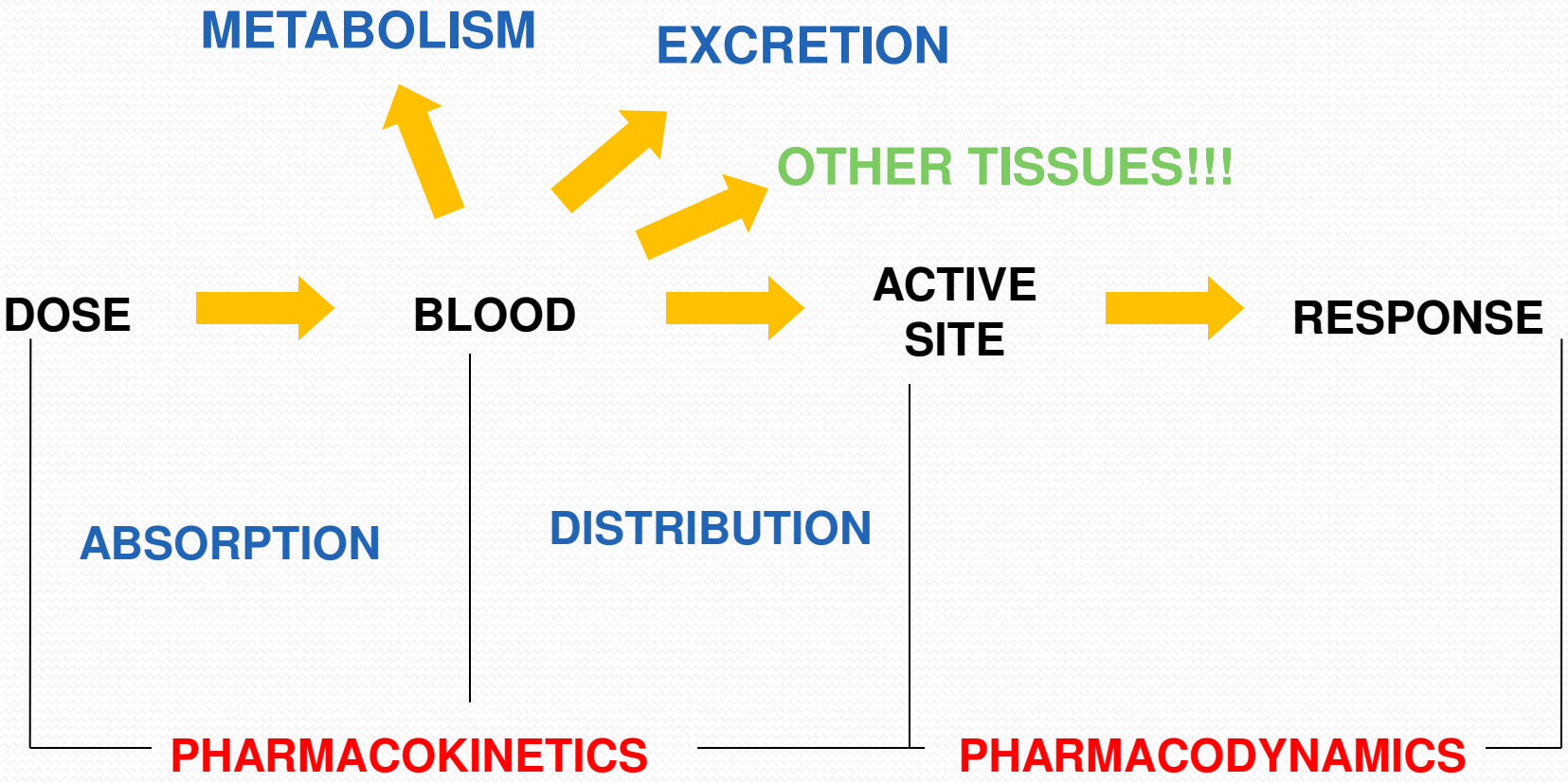
- The time course of therapeutic drug action in the body can be understood in terms of ***pharmacodynamics*** and ***pharmacokinetics***

- Pharmacodynamics: the **actions** of the **drug on the body**
- Pharmacokinetics: the **actions of the body** on the **drug** and includes absorption, distribution, and elimination

Pharmacokinetic principles

- In order to work, drugs need to achieve ADEQUATE CONCENTRATION in their SITE OF ACTION/ TARGET TISSUE
- Physiologic factors influencing drug concentration:

1. Absorption: Movement of a drug from its site of administration into the central compartment (blood stream)
2. Distribution: Drug movement to various sites/ site of action
3. Biotransformation/metabolism: Alteration of chemical structure of drug
4. Excretion: Ability of living system to remove a drug and its biotransformation products (metabolites) from the internal environment

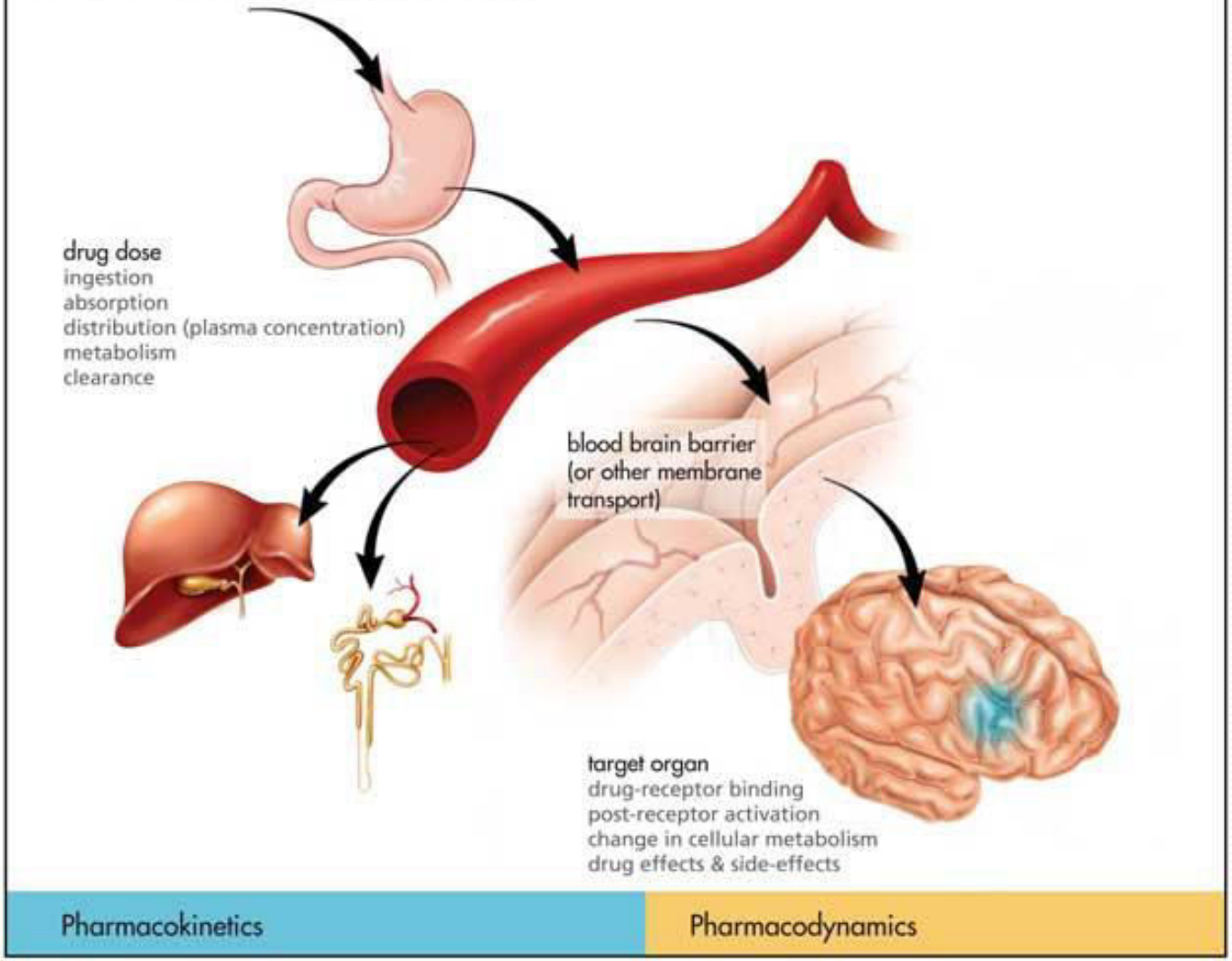

METABOLISM
EXCRETION
OTHER TISSUES!!!
DOSE
BLOOD
ACTIVE SITE
RESPONSE
ABSORPTION
DISTRIBUTION
PHARMACOKINETICS
PHARMACODYNAMICS

a. Permeation

- For a drug to produce effect on the site of action, it should be able to **cross/ translocate/ penetrate** through the various barriers/ membranes between the site of administration to the site of action (PERMEATION)

Figure 1:

Pathway of Drug Delivery and its Effect



a. Permeation

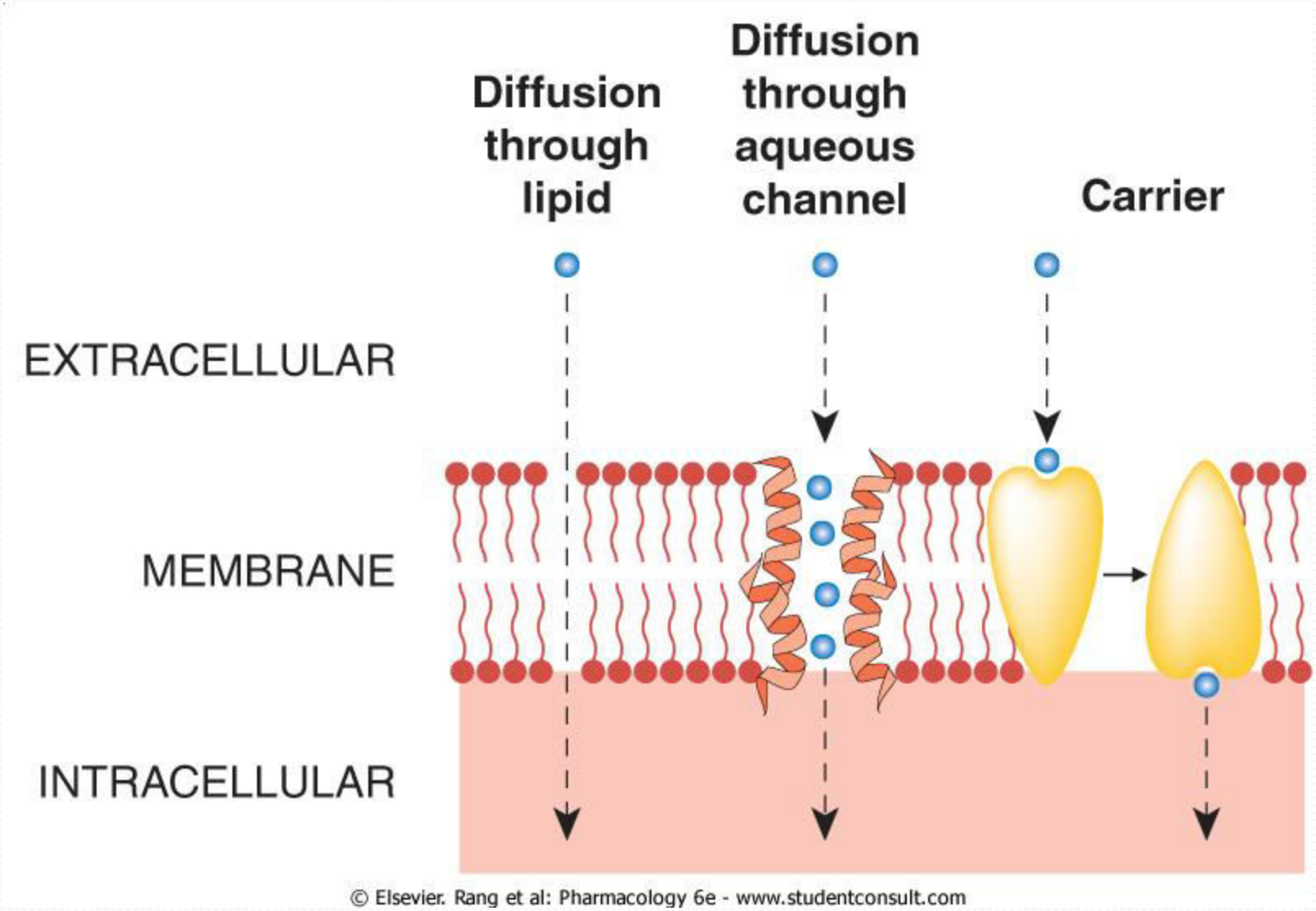
- There are four main ways by which drugs/ molecules cross through the various barriers

1. Aqueous diffusion
2. Lipid diffusion
3. Special carriers
4. Endocytosis and exocytosis

a. Permeation

1) Aqueous diffusion

- Is the **movement** of molecules through the **watery extracellular** and **intracellular spaces**
- Passage of large molecules (20,000-30,000MW)
- Occurs **in larger aqueous compartments** in the body (interstitial space, cytosol, etc..) and across epithelial lining of blood vessels through **aqueous pores or channels**
- Driven by **concentration gradient of drug-downhill movement- Ficks Law** (molecules per unit time)
- **NOT** for drug bound to plasma protein**??**



Routes by which solutes can traverse cell membranes. (Molecules can also cross cellular barriers by pinocytosis.)

a. Permeation

2) Lipid diffusion

- Is the **passive movement** of molecules through **membranes** and **other lipid structures**
  - Is the **most important limiting factor for drug permeation** because of the **large number** of **lipid barriers** that **separate aqueous compartments**
  - **Lipid soluble drugs** readily move across most biologic membrane due to their solubility in the membrane bilayer
  - The **lipid: aqueous partition coefficient** of a drug determines how readily the molecule moves between aqueous and lipid media
  - Weak acids & weak bases**??**

a. Permeation

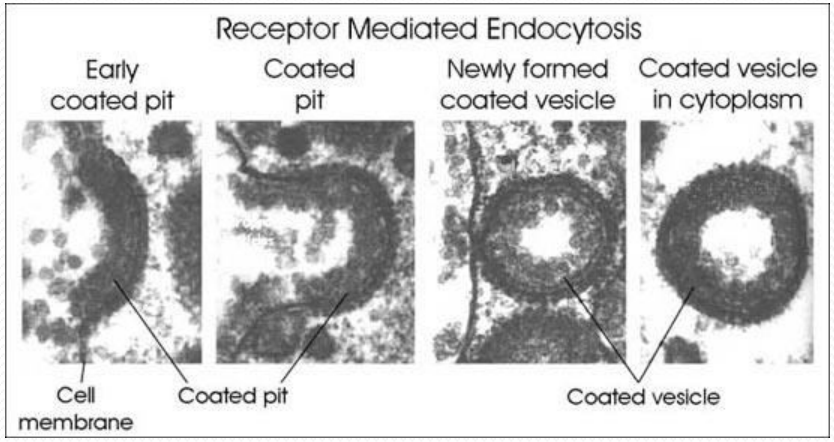
3) Special carriers

- Involves **specific carrier protein** that span over the membrane
- For **large** or **lipid-insoluble** substances
- E.g.: peptides, amino acids, glucose
- Movement: **active transport (require energy**) or **facilitated diffusion (does not require energy)**
- It is *saturable* and *inhibitable (unlike passive diffusion)*
- **ABC (ATP bining cassette) transporters: ex: P-GLYCOPROTEIN; MultiDrug Resistance protein**

a. Permeation

4) Endocytosis and exocytosis

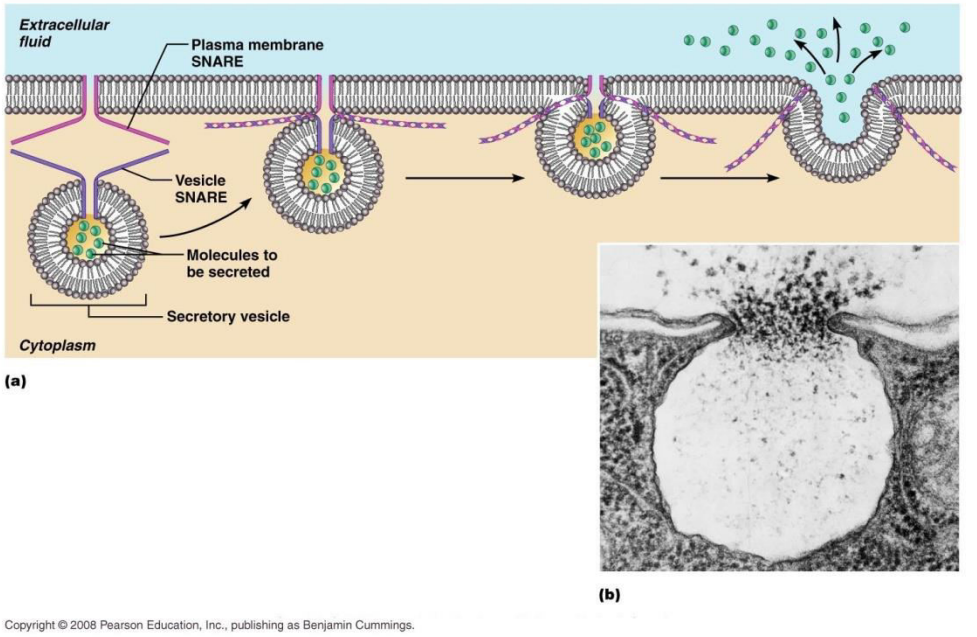
- This type of drug delivery transports **drugs of exceptionally large size** across the cell membrane
- **Endocytosis**: involves the **engulfment** of a drug molecule by the cell membrane and **transport** into the cell by **pinching off** the **drug-filled vesicle inside** the membrane (e.g. vitamin B12)



a. Permeation

4) Endocytosis and exocytosis

- Exocytosis:
- Is the reverse process of endocytosis and is responsible for the secretion of many substances from the cells (large or insoluble substances) (e.g. neurotransmitter)
- It involves the fusion of the storage vesicle with the cell membrane and the expulsion of its content into the extracellular space



Exocytosis

b. Fick's law of Diffusion

- Describes the **passive flux** of molecules down a concentration gradient:

$$\text{Flux} = (C_1 - C_2) \times \frac{\text{Area} \times \text{Permeability coefficient}}{\text{Thickness}}$$

Where C_1 is the h**igher** conc.;

C_2 **i**s **the lower conc**.;

area is the **area across** which the **diffusion is** occurring.

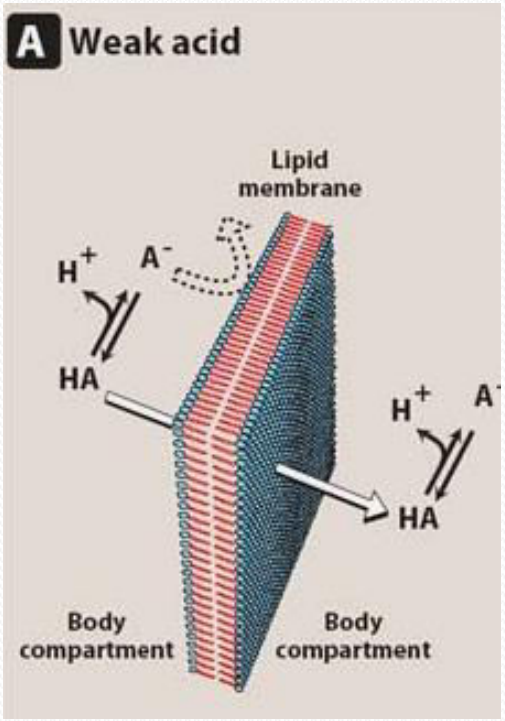
In the case of lipid diffusion, the **lipid:aqueous partition** coefficient is a major determinant of mobility of the drug

C. Ionization of weak acids and weak bases: Henderson-Hasselbalch equation

- Most drugs are either week acids (HA) or weak bases (BH^+) that are present in solution as both the non-ionized and ionized species.
- The nonionized molecules usually are more lipid-soluble and can diffuse readily across the cell membrane.
- In contrast, the ionized molecules usually are unable to penetrate the lipid membrane because of their low lipid solubility.
- Drug mobility is determined by lipid to water/aqueous partition coefficient

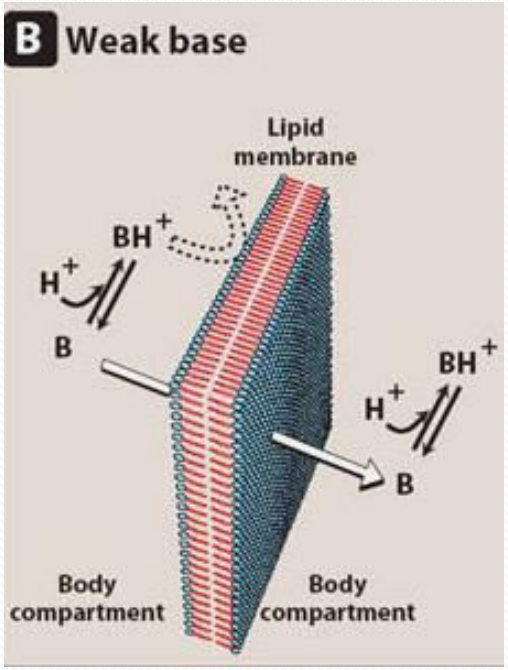
C. Ionization of weak acids and weak bases: Henderson-Hasselbalch equation

- Weak acid (HA): a neutral molecule that can reversibly dissociate into an anion (A^-) and a proton (H^+)
- Weak acids need to become protonated (uncharged) to be more lipid soluble



C. Ionization of weak acids and weak bases: Henderson-Hasselbalch equation

- **Weak base (BH^+):** a neutral molecule that can form a cation (BH^+) by combining with a proton (H^+)
- Weak bases need to become unprotonated (uncharged) to be more lipid soluble



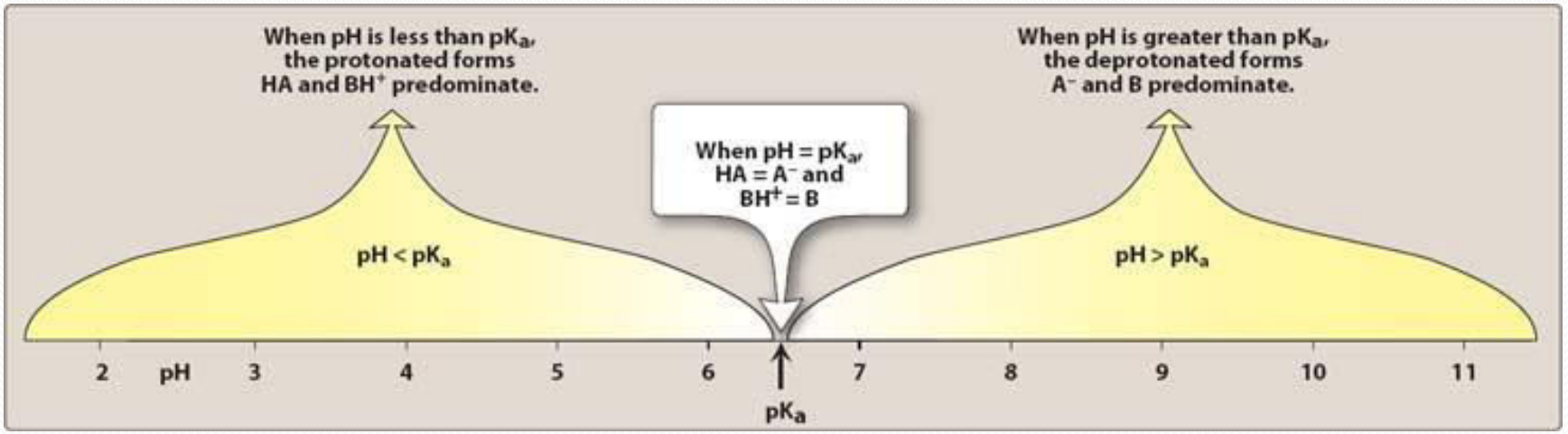
Henderson-Hasselbalch Equation

- The effective concentration of the permeable form of the drug is determined by the relative concentration of the charged and uncharged forms
- The **ratio between the two forms** is determined by **the pH** and **the strength of the weak acid or base**, represented by
- The relationship of pK_a and the ratio of acid-base concentration to pH is expressed by the Henderson-Hasselbalch Equation

$$pH = pK_a + \log \frac{[\text{nonprotonated species}]}{[\text{protonated species}]}$$

$$\text{For acids: } pH = pK_a + \log \frac{[A^-]}{[HA]}$$

$$\text{For bases: } pH = pK_a + \log \frac{[B]}{[BH^+]}$$



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

$$\text{Log}\ \frac{\text{Protonated}}{\text{Unprotonated}} = pKa - pH$$

Aspirin and gastric pH??

Table 3-1; P. 11

Henderson-Hasselbalch Equation

- Equation is **clinically important** when it is necessary to **accelerate the excretion of drugs by the kidney** – in the case of an overdose by changing the pH of the urine (increase ionized state to "trap" drug in urine)

    - Excretion of **weak acids** may be accelerated by **alkalinizing the urine** – **giving bicarbonate** I.V. (charged is more)

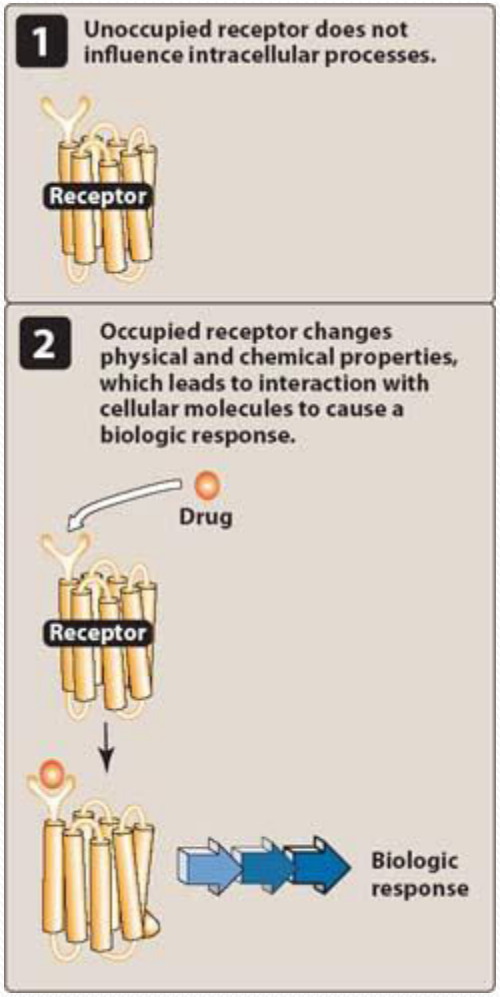
    - **Excretion** of **a weak base** may be accelerated by a**cidifying the urine** - giving ammonium chloride I.V.

Pharmacodynamic principles

- The *pharmacodynamic* properties determine the group/class in which a drug is classified and determine whether that group is appropriate therapy for a particular symptom or disease

Pharmacodynamic principles

- Most drugs exert their effects, both beneficial and harmful, by **interacting with receptors**
- Receptors binds drugs and initiate events leading to **alterations in biochemical or biophysical activity** of a cell and consequently, the function of an organ



Pharmacodynamic Principles

- To function as a receptor in the body, the endogenous target must be:

1) Selective in choosing ligands (drug molecules) to bind

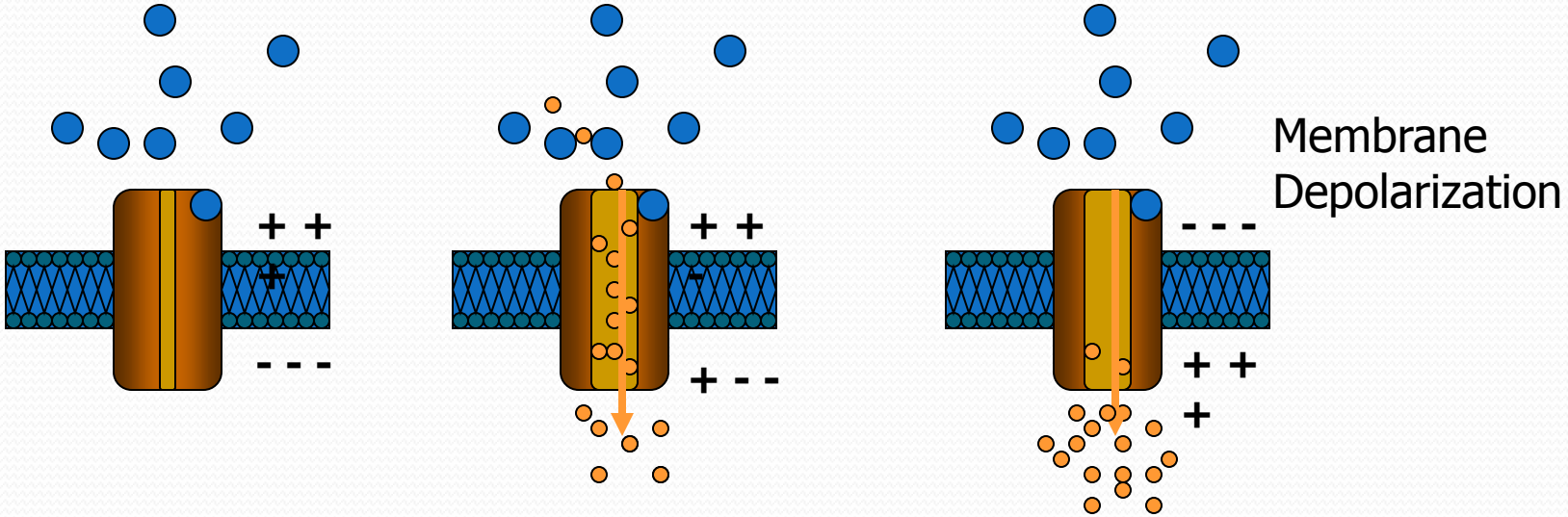
2) Change its function so that the function of the biologic system (cell, tissues, etc..) is altered

Pharmacodynamic Principles

- Inert binding sites are endogenous non-regulatory molecules that can bind a drug molecule, however, *will result in no change of biologic function*
  - Example: Plasma albumin and b-globulin
  - Significance of binding- will affect distribution of drug in the body and determine the amount of free drug in the circulation

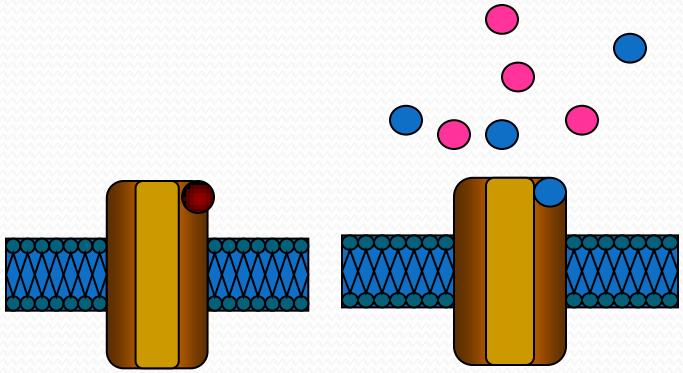
A. Types of drug-receptor interactions

I. Agonist drugs: a drug is said to be an agonist when it binds to and activates the receptor which directly or indirectly brings about the effect

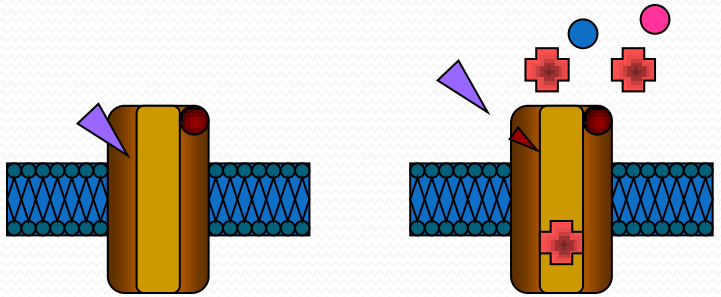


A. Types of drug-receptor interactions

II. Antagonist drugs: a drug is said to be an antagonist when it binds to a receptor and prevents (blocks or inhibits) a natural compound or a drug to have an effect on the receptor



Competitive



Non-competitive

A. Types of drug-receptor interactions

III. Partial agonist drugs: a drug is said to be a partial agonist when it binds to a receptor and causes a partial response (graded response *vs.* all or no response)