

# Chapter 1

## Principles of Drug Absorption, Drug Disposition, and Drug Action

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**I. INTRODUCTION.** **Pharmacology** is the study of the properties of chemicals used as drugs for therapeutic purposes. It is divided into the study of pharmacokinetics and pharmacodynamics. Veterinary pharmacology focuses on drugs that are used in domestic animals. Pharmacokinetics is the study of drug absorption, distribution, biotransformation (metabolism), and excretion. Pharmacokinetic processes affect the route of administration, doses, dose intervals, and toxicities of drugs given to animals. Pharmacodynamics is the study of cell/tissue responses and selective receptor effects. In this chapter, we introduce standard concepts of pharmacokinetics and pharmacodynamics and comment on the need to be aware of species variation when considering principles of veterinary pharmacology.

## II. DRUG ABSORPTION AND DISPOSITION

**A. General principles.** An overview of the principles involved in a drug's journey in the body beginning from its administration to the pharmacologic response.

**How do drugs reach their site of action?** It is apparent from Figure 1-1 that a drug usually crosses several biological membranes from its locus of administration to reach its site of action and thereby produce the drug response. The manner by which drugs cross membranes are fundamental processes, which govern their absorption, distribution, and excretion from the animal.

- 1. Passive diffusion.** Cell membranes have a bimolecular lipoprotein layer, which may act as a barrier to drug transfer across the membrane. Cell membranes also contain pores. Thus, drugs cross membranes based on their ability to dissolve in the lipid portion of the membrane and on their molecular size, which regulates their filtration through the pores.
- a. Weak acids and weak bases.** The majority of drugs are either weak acids or weak bases. The degree to which these drugs are fat soluble (nonionized, the form which is able to cross membranes) is regulated by their  $pK_a$  and the pH of the medium containing the drug.  $pK_a = \text{pH}$  at which 50% of the drug is ionized and 50% is nonionized.
- b.** To calculate the percent ionized of a drug or to determine the concentration of a drug across a biological membrane using the **Henderson–Hasselbalch** equation one needs to know whether a drug is an acid or a base.

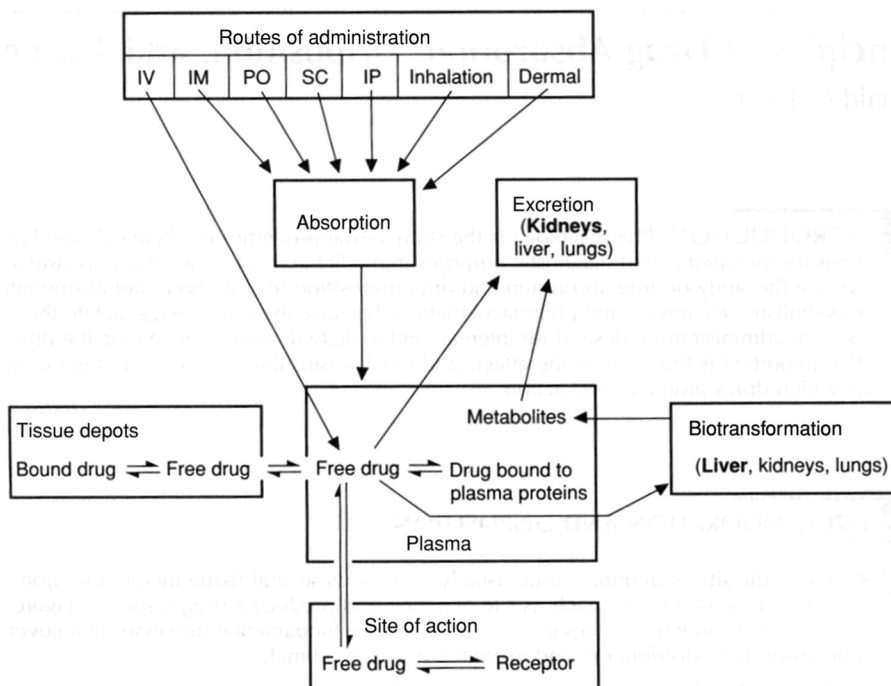
If the drug is a weak acid use:

$$pK_a = \text{pH} + \log \frac{\text{Concentration of nonionized acid}}{\text{Concentration of ionized acid}}$$

If the drug is a weak base use:

$$pK_a = \text{pH} + \log \frac{\text{Concentration of ionized base}}{\text{Concentration of nonionized base}}$$

- c.** In monogastric animals with a low stomach pH, weak acids such as aspirin ( $pK_a = 3.5$ ) tend to be better absorbed from the stomach than weak bases because of the acidic conditions. In ruminants, the pH varies with feeds and the pH is often not low.



**FIGURE 1-1.** This diagram relates what may be expected to occur to a drug in the animal following its administration (IV, intravenous; IM, intramuscular; PO, per os or oral; IP, intraperitoneal; SC, subcutaneous; inhalation, dermal). (From Figure 1-1, *NVMS Pharmacology*.)

- d. Weak bases are poorly absorbed from the stomach since they exist mostly in the ionized state (low lipid solubility) because of the acidic conditions. Weak bases are better absorbed from the small intestine due to the higher environmental pH.
- 2. Filtration**
  - a. Some low molecular weight chemicals, water, urea, and so forth, cross membranes better than predicted on the basis of their lipid solubility, suggesting that membranes possess pores/channels.
  - b. The glomerular filtration process in the kidney provides evidence for large pores, which permit the passage of large molecular weight substances but small enough to retain albumin (mw ~60,000).
- 3. Facilitated diffusion**
  - a. No cellular energy is required and it does not operate against a concentration gradient.
  - b. Transfer of drug across the membrane involves attachment to a carrier (a macromolecular molecule).
  - c. **Examples:** Reabsorption of glucose by the kidney and absorption from the intestine of vitamin B<sub>12</sub> with intrinsic factor.
  - d. This is not a major mechanism for drug transport.
- 4. Active transport**
  - a. Requires cellular energy and operates against a concentration gradient.
  - b. Chemical structure is important in attaching to the carrier molecule.
  - c. **Examples:** Penicillins, cephalosporins, furosemide, thiazide diuretics, glucuronide conjugates, and sulfate conjugates are examples of acidic drugs that are actively secreted by the proximal renal tubule. Amiloride, procainamide, quaternary ammonium compounds, and cimetidine are examples of basic drugs that are actively secreted by the proximal renal tubule cells. Intestinal absorption of 5-fluorouracil, an anticancer drug, which is transported by the same system used to transport uracil.

5. **Pinocytosis.** This is a minor method for drug absorption, but it may be important in the absorption process for some polypeptides, bacterial toxins, antigens, and food proteins by the gut.

**B. Routes of administration.** All routes of administration except intravascular (see Figure 1-1) involve an absorption process in which the drug must cross one or more membranes before getting into the blood.

## 1. Alimentary routes

### a. Oral (per os, PO)

#### (1) Advantages

- (a) Usually safest, convenient, economical, but some animals are difficult to administer this way.
- (b) May require the drug to be mixed in the food to facilitate administration.
- (c) Food may stimulate bile secretion, which will help dissolve lipophilic drugs to increase absorption.

#### (2) Disadvantages

- (a) Acidic environment of stomach and digestive enzymes may destroy the drug.
- (b) In ruminants the bacterial enzymes may inactivate the drug.
- (c) Some drugs may irritate the GI mucosa.
- (d) The presence of food may adversely alter absorption.
- (e) Some drugs are extensively metabolized by the GI mucosa and the liver before they reach the systemic circulation (e.g., propranolol) and this is referred to as the **first-pass effect**.
- (f) Antimicrobials may alter the digestive process in ruminants and other herbivores.

### b. Rectal

#### (1) Advantages

- (a) Can be used in the unconscious animal and in those vomiting.
- (b) Absorption is slower compared to the intramuscular route.
- (c) There are some drugs like diazepam and phenytoin that have an erratic oral absorption and are better given rectally.
- (d) In dogs, influence of the first-pass effect is reduced because the rectal veins bypass the portal circulation and go to the caudal vena cava.

## 2. Parenteral routes (circumvents the GI tract)

### a. Examples

- (1) **Intravenous (IV)**
- (2) **Intramuscular (IM)**
- (3) **Subcutaneous (SC)**
- (4) **Intraperitoneal (IP)**
- (5) **Spinal and subdural.** Used for regional anesthesia.

### b. Advantages

- (1) Rapid onset (IV > IM > SC), may be useful in an unconscious or vomiting patient, absorption is more uniform and predictable.
- (2) Absorption from IM and SC injection sites is mostly determined by the amount of blood flow to that site. The absorption of local anesthetics is often purposely slowed by coadministration with epinephrine, which decreases the blood flow to the injection site.

### c. Disadvantages

- (1) Asepsis is necessary.
- (2) Cause pain.
- (3) May penetrate a blood vessel during IM injection.
- (4) The speed of onset is so rapid as with IV administration that cardiovascular responses may occur to drugs, which normally have minimal effects on this system.
- (5) In food animals, discoloration of the meat or abscess formation may occur to IM injection and these may be expected to devalue the carcass.

### 3. Other routes

#### a. Dermal or topical

- (1) Degree of absorption is dependent on the drug's lipid solubility.
- (2) Abraded or damaged skin may be expected to absorb more drug than intact skin.
- (3) Animals with thin skin, like cats, may absorb drugs like corticosteroids readily if they are applied topically than animals with thicker skin.
- (4) It is convenient and allows nonskilled operators to administer the drugs by pour-on methods. For example, topical application of anthelmintics that are lipophilic, like levamisole and macrocyclic lactones, is frequently performed in this manner.

#### b. Inhalation

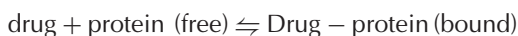
- (1) It is used for volatile or gas anesthetics. Example: isoflurane.
- (2) Response is rapid because of the large surface area of the lungs and large blood flow to the lungs.
- (3) It is reversible if the anesthetic is turned off and the animal ventilated.

### C. Drug distribution

1. **Distribution** refers to the reversible transfer of drug from one site in the body to another site.
2. In much of the body, the junctions between the capillary endothelial cells are not tight thereby permitting free (unbound to plasma proteins) drug to rapidly reach equilibrium on both sides of the vessel wall.
3. Distribution of drugs into the central nervous system (CNS) and cerebrospinal fluid (CSF) is restricted due to the **blood-brain barrier (BBB)**.
  - a. There are three processes that contribute to keeping drug concentration in the CNS low:
    - (1) In much of the CNS (except: area postrema, pineal body, posterior lobe of hypothalamus), the capillary endothelial junctions are tight and glial cells surround the precapillaries. This reduces the filtration process and requires that drugs diffuse across cell membranes to leave the vascular compartment and thereby enter the extracellular fluid or CSF. This ability to cross cell membranes is dependent upon the drug's lipid solubility.
    - (2) Cerebrospinal fluid production within the ventricles circulates through the ventricles and over the surface of the brain and spinal cord to flow directly into the venous drainage system of the brain. This process continues to dilute out the drug's concentration in the CSF.
    - (3) Active transport mechanisms are found for organic acids and bases in the choroid plexus, which transports drug from the CSF into the blood. P-glycoprotein is one transporter protein that is present in the endothelial cells of the choroid plexus (blood-brain barrier) that contributes to drug entry into and exit from the brain.
 

**Examples:** The macrocyclic lactones, ivermectin, and selamectin but less so with moxidectin, are excluded from the brain via P-glycoprotein. In some breeds of dog, particularly the Collies, P-glycoprotein is defective and ivermectin accumulates in the CNS, leading to toxicity.

Penicillin (a weak acid) concentrations in the CNS are kept low due to an active organic ion transporter system.
4. **Plasma protein binding** of drug can affect drug distribution since only the free (unbound) drug is able to freely cross cell membranes (see Figure 1-1, II A).



Acidic drugs are bound primary to **albumin** and basic drugs are bound primarily to  **$\alpha_1$ -acid glycoprotein**. Steroid hormones and thyroid hormones are bound by specific **globulins**, respectively, with high affinity.

- a. Drug-protein binding reaction is **reversible** and obeys the laws of mass action.

- b. Binding does not prevent a drug from reaching its site of action but retards/slows the rate at which it reaches a concentration sufficient to produce a pharmacologic effect.
  - c. Drug–protein binding limits glomerular filtration as an elimination process since bound drugs cannot be filtered. Example: sulfa drugs with a high degree of binding to protein are eliminated more slowly in urine than those sulfa drugs with a lower binding affinity for plasma proteins.
  - d. Binding to albumin does not totally prevent the elimination of drugs that are actively secreted by the kidney or metabolized by the liver, rather it slows the rates of metabolism and/or secretion. Binding lowers the free drug concentration but there is still release from the drug–protein complex for the metabolism or secretion.
  - e. Drug interactions may occur when two drugs are used that bind at the same site on the plasma proteins. Competition for the same site will increase the percent of drug in the free form, thereby increasing the pharmacologic/toxicological response by the displaced drug.
5. **Drug redistribution** can terminate the drug response.
- a. The biologic response to a drug is usually terminated by metabolism/biotransformation and excretion.
  - b. Redistribution of a drug from its site of action to other tissues will lower its concentration at its site of action, thereby terminating the drug response.
  - c. Drugs exhibiting the redistribution phenomenon are highly lipid soluble. Thiopental is the classic example in dogs where redistribution from the brain to less vascular area of the body, including the muscle and fat, allows recovery. In sheep and goats, however, liver biotransformation takes place at such a high rate so that in these species it is metabolism, not redistribution that dominates the duration of anesthesia. Propofol is very lipophilic and is rapidly redistributed following IV injection so that in goats and dogs anesthesia is ultrashort. Interestingly, the redistribution process varies between breeds of dogs due to the different leanness of the different breed. Very lean breeds like Greyhounds with less fat for the lipophilic anesthetics to redistribute to, take longer to recover.
6. Drug distribution from dam to fetus.
- a. Drug transfer across the placenta occurs primarily by simple diffusion.
  - b. **Drugs** cross the placenta best if they are lipid soluble (nonionized weak base or acid).
  - c. The fetus is exposed to some extent even to drugs with low lipid solubility when given to the dam.
  - d. **General rule:** Drugs with an effect on the maternal CNS have the physical–chemical characteristics to freely cross the placenta and affect the fetus. Examples: anesthetics, analgesics, sedatives, tranquilizers, and so forth.

**D.** **Drug metabolism/biotransformation** is the term used to describe the chemical alteration of drugs (xenobiotics) as well as normally found substances in the body.

### 1. Principles

- a. Following filtration at the renal glomerulus most lipophilic drugs are reabsorbed from the filtrate.
- b. Biotransformation of drugs to more water-soluble (polar) chemicals reduces their ability to be reabsorbed once filtered by the kidney. This enhances their excretion and reduces their volume of distribution.
- c. The **liver** is the most important organ for biotransformation but the lung, kidney, and GI epithelium also play a role.
- d. Drug biotransformation frequently reduces the biological activity of the drug/chemical/toxicant.
- e. Drug metabolism/biotransformation is not synonymous with drug inactivation as the parent chemical may be transformed to a chemical with greater or significant biologic activity.

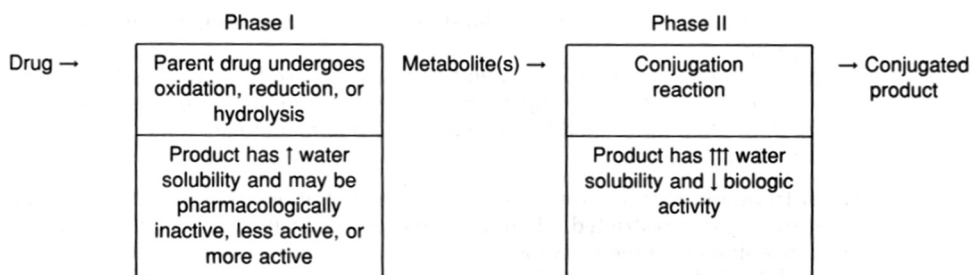


FIGURE 1-2. Phases of biotransformation. (From Figure 1-2, *NVMS Pharmacology*.)

### Example:

Acetylsalicylic acid	→	salicylate
Inactive (aspirin)		active anti-inflammatory
febantel	→	fenbendazole/oxfendazole
Inactive		active anthelmintic
Primidone	→	phenobarbital
Inactive		active anticonvulsant
codeine	→	morphine
active analgesic		more active analgesic

2. Enzymatic reactions in biotransformation usually occur in two phases (Figure 1-2):
  - a. **Phase I** biotransformation enzymes are found in the **smooth endoplasmic reticulum** of the hepatic cells (also referred to as the **microsomal enzymes** since they are found in the microsomal fraction following high-speed centrifugation).
    - (1) **Oxidation** is carried out by a family of isozymes termed cytochrome P450s.
    - (2) The enzyme system is also called a **mixed function oxidase** since one atom of oxygen is incorporated in the drug molecule and the other atom of oxygen combines with hydrogen to form water. Nicotinamide adenine dinucleotide phosphate (NADPH) provides the reducing equivalents. Examples of microsomal oxidation:
      - (a) **Side chain and aromatic hydroxylation:** pentobarbital, phenytoin, phenylbutazone, propranolol
      - (b) **O-dealkylation:** morphine, codeine, diazepam
      - (c) **N-oxidation:** acetaminophen, nicotine, phenylbutazone, pentobarbital
      - (d) **S-oxidation:** phenothiazines (acepromazine, chlorpromazine), cimetidine
      - (e) **Deamination or N-dealkylation:** lidocaine
      - (f) **Desulfuration:** thiopental
  - (3) **Nonmicrosomal oxidation**  
A few chemicals are oxidized by cytosol or mitochondrial enzymes.
    - (a) **Alcohol dehydrogenase** and **aldehyde dehydrogenase.** **Example:** ethanol, acetaldehyde, ethylene glycol
    - (b) **Monoamine oxidase.** **Example:** epinephrine, norepinephrine, dopamine, serotonin
    - (c) **Xanthine oxidase.** **Example:** theophylline
  - (4) **Oxidative metabolism.** There are considerable differences among the species in the activity of the oxidative enzymes. Generally, the difference has been attributed to differences between the kinetic parameters (Michaelis constants and Max velocity) of the species enzymes. Oxidation is higher in horses than cattle, which in turn are higher than dogs. Oxidation is lowest in cats among domestic animals. The level of oxidative enzymes is lower in very young animals. The duration of pentobarbital anesthesia in horses is much shorter than in dogs. Young calves are much more sensitive to pentobarbital and lindane than adult cattle.

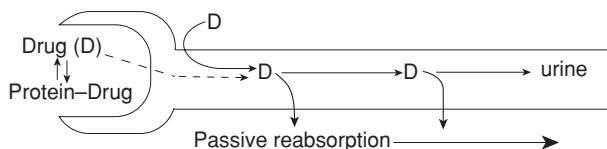
**TABLE 1-1.** Drug Conjugation Reactions

Conjugation Reaction	Drug Conjugated
Glucuronidation	Aspirin, morphine, sulfadimethoxine, digitoxin, steroids, thyroxine, phenobarbital, phenytoin, chloramphenicol, phenylbutazone
Acetylation	Sulfonamides, clonazepam, procainamide
Glutathione formation	Ethacrynic acid
Glycine formation	Salicylic acid, nicotinic acid
Sulfate formation	Catecholamines, acetaminophen
Methylation	Catecholamines, histamine

- (5) **Reduction** biotransformation reactions are **less frequent** than oxidation-type reactions. Enzymes are located in both microsomal and nonmicrosomal fractions. **Examples:** chloramphenicol and naloxone.
- (6) **Hydrolysis** reactions occur with either ester (esterases) or amide linked chemicals (amidases).
- (a) **Esterases** occur primarily in nonmicrosomal systems and are found in the plasma, liver, and other tissues. Examples of drugs hydrolyzed: acetylcholine, succinylcholine, and procaine.
- (b) **Amidases** are nonmicrosomal enzymes found primarily in the liver. Examples of drugs hydrolyzed: acetazolamide, lidocaine, procainamide, sulfacetamide, and sulfadimethoxine.
- b. **Phase II** biotransformation (conjugation) may occur to a phase I metabolite or to a parent drug/chemical. This involves the coupling of an endogenous chemical (glucuronic acid, acetate, glutathione, glycine, sulfate, or methyl group to the drug). Enzyme systems are present in the microsomes, cytosol, and in the mitochondria.
- (1) Products of phase II biotransformation have greater water solubility and are more readily excreted via the kidney.
- (2) Examples of drugs undergoing phase II biotransformation (Table 1-1).
- (3) **Species variation in phase II metabolism.** There are considerable species defects in certain conjugation reactions:
- (a) In the cat, glucuronide synthesis where the target is  $-\text{OH}$ ,  $-\text{COOH}$ ,  $-\text{NH}_2$ ,  $=\text{NH}$ ,  $-\text{SH}$  is only present at a low rate. Thus, cats often have longer plasma  $t_{1/2}$  for many drugs than other species.
- (b) In the dog acetylation of aromatic- $\text{NH}_2$  groups is absent and this affects the metabolism of sulfonamides and other drugs.
- (c) In the pig sulfate conjugation of aromatic- $\text{OH}$ , aromatic- $\text{NH}_2$  groups are only present at a low extent.
- (4) **Enterohepatic recirculation**
- (a) Drugs biotransformed via the formation of a glucuronic acid metabolite may be eliminated via the bile.
- (b) Glucuronide metabolites can be hydrolyzed by intestinal or bacterial  $\beta$ -glucuronidases, thereby releasing free drug, which can then be reabsorbed. This process can greatly increase a drug's residence in the body. This is recognized for etorphine in horses and may give rise to relapse despite initial reversal with the antagonist diprenorphine.
- (5) **Biotransformation by GI microflora.** In addition to the liver, metabolism of drugs can also take place in the rumen and GI tract by the microflora where hydrolytic activity and reductive activity may occur. Gut-active sulfonamides (phthalylsulfathiazole) require hydrolysis for the release of sulfathiazole for antimicrobial action. Cardiac glycosides are hydrolyzed in the rumen and become inactive, the chloramphenicol  $-\text{NO}_2$  group is reduced and the drug is inactivated.



**FIGURE 1-3.** Proximal renal tubule. Only drugs (D) which are free in the plasma are filtered. Once in the tubular lumen the drug may be passively re-absorbed. In the proximal renal tubule active transport mechanisms exist for secreting acid and base drugs (D) from the extracellular fluid into the renal tubule.



**E.** **Drug excretion** refers to the processes by which a drug/drug metabolite is eliminated from the body. The **kidney** is the primary organ for drug excretion.

**1. Renal excretion.** Primary mechanisms.

- a. **Glomerular filtration.** All drugs (**D**, Figure 1-3) not bound to plasma proteins are filtered.
- b. **Active tubular secretion.** In the **proximal** portion of the renal tubule **active transport** mechanisms exist for both **acidic** and **basic drugs**. Examples of drugs actively secreted into the tubule lumen are presented above. **Competition** among the acidic drugs or basic drugs can be expected to occur for the secretion process (Table 1-2).
- c. **Passive tubular reabsorption.** The lipid nature of the cellular membrane lining the tubule dictates that only **lipophilic drugs will be reabsorbed**.
  - (1) Since most drugs are weak acids or bases the degree of ionized (water soluble, non-reabsorbable) or nonionized (lipid soluble, reabsorbable) form of the drug will vary with the  $pK_a$  of the drug and the pH of the lumen urine.
  - (2) Urinary pH of carnivore animals is acidic (pH 5.5–7.0).
  - (3) Urinary pH range of herbivore animals is 7.0–8.0.
  - (4) Food will influence the urinary pH for both carnivores and herbivores.
  - (5) **Excretion** can be **enhanced** for drugs eliminated primarily by the kidney through altering the pH of the urine. For practical purposes this is limited to weak acidic or weak basic drugs with a  $pK_a$  of 5–8.
  - (6) Quaternary drugs ( $R_4-N^+$ ) are polar at all urine pH and can be expected to be eliminated rapidly, since they cannot be reabsorbed.

**2. Other routes of excretion**

- a. **Biliary secretion.** Both the parent drug and glucuronide form of the drug may be eliminated via the bile.
  - (1) **Glucuronide-drug** conjugates eliminated via the bile may be hydrolyzed by  $\beta$ -glucuronidases from gut bacteria. The free drug then may be reabsorbed giving rise to “enterohepatic recycling.”
  - (2) Transport processes exist in the liver for actively transporting acidic, basic, and neutral drugs into the bile. Since these drugs may eventually be reabsorbed from the gut lumen, biliary elimination processes tend to be less important than are renal excretion processes.

**TABLE 1-2.** Examples of Drugs Actively Secreted

Acid Drugs	Basic Drugs
Penicillin	Histamine
Ampicillin	Amiloride
Cephalosporins	Cimetidine
Thiazine diuretics	Procainamide
Furosemide	Neostigmine
Probenecid	Trimethoprim
Salicylate	Atropine
Ethacrynic acid	
Phenylbutazone	



- (3) **Role of P-glycoprotein in drug excretion.** P-glycoprotein is a transmembrane efflux pump that has a role in the “first-pass clearance” of some oral drugs. P-glycoprotein is also found in the biliary and renal tubular epithelia and thus plays a role in the “secretion” of some but not all drugs into the gut and renal tubules. As stated earlier, this protein is also found in the BBB and its effect there is to “expel” the drug from the CNS. Substrates of P-glycoprotein include azole antifungal agents, corticosteroids, cyclosporine, digoxin, diltiazem, doxorubicin, opioids, macrocyclic lactones, macrolide antibiotics, quinidine, and vincristine/vinblastine.
- b. **Milk.** While this is not a major route for drug excretion for the dam, it is important since the drugs given to the dam appear in the milk and produce residues requiring a withdrawal period if the milk is to be used for human consumption. Antimicrobial drugs given to the dam appear in concentrations sufficient to treat mastitis. **Milk is acidic relative to plasma.** Therefore, weak organic bases will diffuse from the plasma into the milk where they will become more ionized, thereby preventing passage back to the plasma. This is an example of **ion trapping**. Drugs which are basic (tylosin, erythromycin, and lincomycin) can be expected to be found in milk in higher concentrations than in the plasma.
  - c. **Saliva.** This is not a major route for excretion but is important in herbivores receiving parenteral antimicrobial drugs. Drugs enter the saliva by passive diffusion from the blood. Copious salivation by cattle and sheep and the swallowing of antimicrobial-drug-laden saliva may upset the digestive process in the rumen.
  - d. **Expired air.** This route of elimination is primarily important for volatile drugs such as gas anesthetic drugs.
  - e. **Minor routes of excretion: tears and sweat.**

**F. Pharmacokinetics** is the mathematical description of drug concentrations in the body. Frequently in pharmacokinetics, the distribution of drugs is depicted as being in a compartment, that is, a one-compartment model or in a two- or three-compartment model. Since many drugs used in veterinary medicine can be described by a two-compartment open model this will be the only model described but the reader should refer to standard textbooks for information on other pharmacokinetic models.

### 1. Two-compartment model (Figure 1-4)

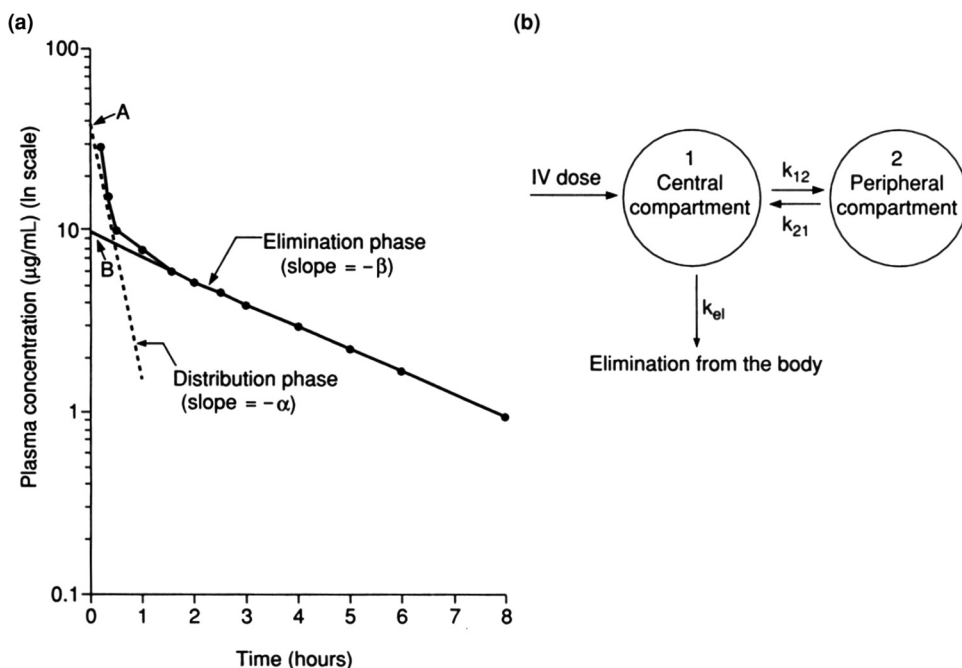
- a. Mathematically, the log-concentration–time graph can be depicted as composed of two straight lines.
  - (1) The line representing the distribution phase has an intercept “A” and a slope  $-\alpha$ .
  - (2) The line representing the elimination phase has an intercept “B” and a slope  $-\beta$ ;  $\beta$  is used to calculate the elimination half-life, see below.
- b. The theoretical plasma concentration at time zero ( $C_p^0$ ) is:  $C_p^0 = A + B$ . Units are usually  $\mu\text{g/mL}$  or  $\mu\text{g/L}$ .
- c. The apparent volume of distribution ( $V_d$ ) is a proportionality constant relating the plasma drug concentration to the total amount of drug in the body.

$$V_d = \frac{\text{Dose}}{\left(\frac{A}{\alpha} + \frac{B}{\beta}\right)\beta}$$

The apparent volume of distribution gives a measure of how well distributed the drug is within the body. A high volume of distribution like 1 L/kg for a drug implies that the drug is widely distributed throughout the body water.

- d. **Half-life** ( $t_{1/2}$ ) of a drug is the time needed for the drug concentration to be reduced by half. This value is determined during the elimination phase of the drug.

$$t_{1/2} = \frac{\ln 2}{\beta} = \frac{0.693}{\beta}$$



**FIGURE 1-4.** (a) The plasma-concentration–time graph following IV injection of a drug exhibiting two-compartment pharmacokinetics. The distribution phase is represented by the line with intercept A and slope  $-\alpha$ . The elimination phase is represented by the line with intercept B and slope  $-\beta$ . (b) A model of a two-compartment open model. The central compartment represents rapid equilibration and represents fluids such as the blood, interstitial fluid, and highly perfused organs (e.g., the lungs). The peripheral compartment reaches equilibrium more slowly and represents organs such as bone and fat.  $k_{12}$  and  $k_{21}$  are the rate constants of distribution between the central and peripheral compartments. (From Figure 1-3, *NVMS Pharmacology*.)

- (1)  $t_{1/2}$  is usually limited by the processes of biotransformation and renal excretion; sometimes it is governed by slow release from tissue sites like bone or fat.
  - (2) Indicates the time required to attain 50% of the steady state or to lose 50% of the steady state concentration.
  - (3) Has limited value as an indicator of drug residues or distribution.
- e. **Total body clearance ( $Cl_B$ )** is the volume of blood that is effectively cleared of a drug in a specified period of time.

$$Cl_B = \beta \cdot V_d = \frac{0.693 V_d}{t_{1/2}}$$

Clearance expresses the rate of drug removal from the body that is independent of  $t_{1/2}$ . Disease and infection may alter drug distribution and clearance, but not necessarily the  $t_{1/2}$  value. Therefore, the volume of distribution and clearance can be altered and thus the  $t_{1/2}$  will be altered. We can rewrite the equation as:

$$t_{1/2} = \beta \cdot V_d = \frac{0.693 \cdot V_d}{Cl_B}$$

- f. **Bioavailability ( $F$ )** is a term that describes the fraction of drug entering the systemic circulation intact from the site of administration; it is the fraction absorbed or taken up.

By definition the bioavailability of an IV dose = 100% or 1. All other routes of administration will have a bioavailability of less than one. Knowledge of  $F$

for oral dosage is particularly important. The presence of **food** may alter the bioavailability of some drugs.

$$F = \frac{(AUC)^{nIV} \cdot \text{dose}^{IV} \cdot \beta^{n,IV}}{(AUC)^{IV} \cdot \text{dose}^{nIV} \cdot \beta^{IV}},$$

where AUC is the area under the plasma concentration curve; nIV is the non-intravenous route of administration; IV is the intravenous route of administration; and  $\beta$  is the slope of the elimination phase.

**g. Determination of dosage**

Knowledge of a drug's bioavailability ( $F$ ), clearance ( $Cl_B$ ), and the average steady state concentration ( $\bar{C}_{P\infty}$ ) of a drug needed to produce the pharmacologic response permits dosage calculation.

$$\frac{F \cdot \text{dose}}{\text{Dosing interval}} = \bar{C}_{P\infty} \cdot Cl_B.$$

**G. Species variation.** Veterinarians must be aware of differences between species and also of differences that can occur among breeds.

**1. Examples of species variation**

- a. It is recognized that xylazine (an  $\alpha_2$ -adrenergic agonist) is a much more potent sedative in cattle than other species; the reason that ruminants are more sensitive to  $\alpha_2$ -agonists such as xylazine is because the difference is at the pharmacodynamics level; ruminants have  $\alpha_{2D}$ -receptors and nonruminants have  $\alpha_{2A}$ -receptors.
- b. It is recognized that morphine (a  $\mu$ -opoid agonist) is more potent in cats than dogs. In dogs, the dose is 1 mg/kg where it consistently produces sedation. In cats, the dose for analgesia is 0.1 mg/kg. Higher doses in cats may produce excitement. The excitement in cats appears to be mediated by central dopamine receptors and is inhibited by sedatives with dopamine antagonist actions like droperidol. The detailed explanation for this species difference between dogs and cats is not known.
- c. Certain breeds of dog: Great Dane and Irish Setters are more sensitive to bloat following xylazine administration due to aerophagia.
- d. Ivermectin can cause CNS depression in collies at normal doses due to a defect in the P-glycoprotein transporter which excludes ivermectin from the brain.
- e. Ivermectin should not be used in tortoises or crocodiles because of potential toxic effects; it is possible that the BBB in these species against ivermectin maintained by the P-glycoprotein is not secure.
- f. Succinylcholine, a depolarizing muscle relaxant, can be used in horses where it is broken down rapidly by the plasma esterases, but in ruminants where the esterase levels are much lower require only 0.02 mg/kg, but horses require 0.1 mg/kg.
- g. Cats have a low level of glucuronyl transferase so that the  $t_{1/2}$  of many drugs that are conjugated to glucuronide by the liver is much longer. The classic example is aspirin where the  $t_{1/2}$  in cats is 25–35 hours compared to 8 hours in dogs and 1 hour in horses.
- h. GI absorption will differ between nonherbivores animals and ruminant herbivores. The GI transit time in monogastrics animals means that oral suspensions are swept out of the intestine within 24 hours. The benzimidazoles are examples of drugs where the GI transit time in herbivores is longer than in nonherbivores. In most cases, benzimidazoles are administered once to herbivores, but to nonherbivores, in daily doses over a period of 3–5 days.
- i. Most lipophilic organic bases, like ivermectin, lincosamide, tulathromycin, erythromycin, tylosin, ketamine, metronidazole, enrofloxacin, theophylline, and trimethoprim have larger volumes of distribution in ruminants than in monogastrics animals.

2. **Drug metabolism.** The differences in the rate of elimination for drugs that are metabolized by the liver usually accounts for most of the differences in the  $t_{1/2}$  values between species. There is a wide variation in the  $t_{1/2}$  of most drugs that are eliminated mainly by hepatic metabolism.
  - a. The general trend is that cattle and horses have shorter  $t_{1/2}$  values than the dog and cats which often have longer  $t_{1/2}$  values. Cattle and horses oxidize drugs more efficiently than dogs and cats.
  - b. Because pharmacokinetic parameters including  $t_{1/2}$  values are more available for humans, it is important to appreciate that human values are usually longer than those of domestic animals (except cats), because the oxidation of drugs by liver P450 oxidative enzymes in domestic animals is usually faster than in humans.
  - c. The exceptions include the methylxanthines (e.g., theophylline) in horses and phenylbutazone in cattle, which have longer  $t_{1/2}$  values in these animals than in humans.
  - d. There are also differences between more closely related species. Cefitofur, trimethoprim, and sulfamethazine have a shorter  $t_{1/2}$  value in goats than sheep, while  $t_{1/2}$  of phenylbutazone is shorter in donkeys than horses.
  - e. The  $t_{1/2}$  of extensively metabolized drugs is shorter in mice, rats, rabbits, and guinea pigs (lab animals) than in domestic animals.
  - f. It is also important to be careful about comparing duration of action between different species of birds. There is significant variation between  $t_{1/2}$  values of chickens, turkeys, and different wild birds which is again related to differences in metabolism.
  - g. Although there are different types of cholinesterase in the tissues and blood, the overall levels in ruminants are lower than in horses and humans. This means that sheep, goats, calves, and cattle, are more sensitive to organophosphorous compounds than horses and humans. Sheep have been suggested as possible "sentinel" animals for the detection of toxic anticholinesterase (organophosphate nerve gases) because of their sensitivity.
3. **Ionized drugs.** There is much less variation in the  $t_{1/2}$  values between the species for drugs that are more ionized, and have a lower volume of distribution: renal excretion is the main route of elimination. For example, the  $t_{1/2}$  of gentamicin for cats is 82 minutes, for dogs it is very similar, 75 minutes. Penicillins and cephalosporins also have short  $t_{1/2}$  values of 30–90 minutes in different species. Thus, highly "ionized drugs" are less likely to show species variation.
4. **Cold-blooded animals.** Fish and reptiles have longer  $t_{1/2}$  values compared to mammalian species due to the much lower metabolic rates. However, the temperature of the ambient environment affects the metabolic rate of the animals and this, in turn, affects the  $t_{1/2}$  values of the drug. The  $t_{1/2}$  value of trimethoprim given IV to carp is 41 hours at 10°C but 20 hours at 24°C. Fish also have a lower renal function and more enterohepatic recycling than warm-blooded animals.
5. **Distribution and species variation.** Distribution does vary with species, but less so than  $t_{1/2}$  values. There is a significant difference between nonruminant and ruminants in the distribution of lipid-soluble organic base drugs. The rumen has a pH of 5.5–6.5 and is a large volume relative to the whole body water; because of the large capacity of the rumen, which is up to 25 liters in sheep and up to 220 liters in cattle, the phenomenon of "ion-trapping" leads to the accumulation of weak bases in the rumen fluids. This means that xylazine, furosemide, and phenylbutazone have larger volumes of distribution in ruminants so that these compounds have a greater clearance in ruminants than nonruminants.

**H. Effect of disease states on pharmacokinetic parameters.** We have seen above that the distribution of drugs ( $V_d$ ) and  $t_{1/2}$  values are key factors that affect access, concentration, and duration of action of drugs. These parameters are usually determined in healthy animals. However, veterinarians need to treat sick animals with these drugs, so **how do the pharmacokinetics change in diseased animals?**

1. **Effects of fever.** Endotoxin-induced fever can increase the extravascular distribution of ionized drugs like penicillins, cephalosporins, and aminoglycosides,

although without much effect on  $t_{1/2}$  values and renal clearance. Bacterial infections induced experimentally in pigs can increase the volume of distribution of penicillin G, ampicillin, and decrease that of oxytetracycline. The volume of distribution of the penicillins probably increases because the permeability of the inflamed tissue barriers to penicillins increases. The distribution of oxytetracycline may decrease because of binding to inflammatory exudates.

2. **Liver disease.** Drugs whose  $t_{1/2}$  values are determined by liver metabolism, that is, lipophilic drugs in general, and which undergo conjugation to convert them to more polar drugs can be affected by liver disease. Liver microsomal activity can be reduced in the presence of moderate or severe liver damage and so the effect and duration of drugs metabolized by the liver can be increased.
3. **Kidney disease.** The rates of elimination of drugs that are eliminated mostly via the kidney are decreased with renal disease. Renal blood flow affects all three renal excretion mechanisms of glomerular filtration, carrier-mediated secretion, and pH-dependent passive reabsorption.

**I. Effect of stereoisomers.** Many of the drugs that are used for therapeutic purposes have a chiral carbon so that a number of stereoisomers are possible; they are produced during the chemical synthesis of the compounds. Many of the commonly used therapeutic drugs are produced as a mixture of racemates. Because of the stereoselective nature of drug receptors, the mixture of racemates will contain the active moiety and the isomeric ballast (reduced activity racemates).

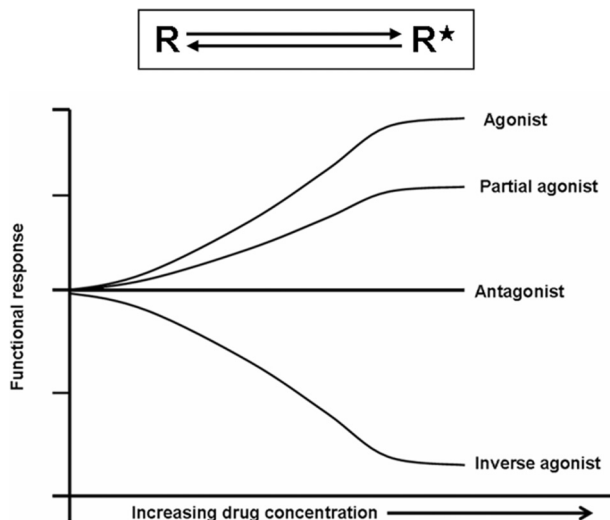
1. Tetramisole was originally produced by Jansen Pharmaceutical and subsequently the l-isomer, levamisole, was produced as the active compound and the d-isomer, dexamisole, found to be less active but contributed to toxicity of the racemic mixture.
2. Medetomidine is a racemate mixture, whereas dexmedetomidine, the d-isomer, has much more potent  $\alpha_2$ -agonistic activity than the l-isomer of medetomidine.
3. The metabolism of the stereoisomers may also be selective, favoring one isomer over others. The more potent isomer is referred to as the **eutomer** and the less potent enantiomer as the **distomer**. The stereoselective processes involved in the pharmacokinetic processes can be species-dependent and so concentration–time plots may vary between enantiomers and between the different species of animal.

### III. PHARMACODYNAMICS: MECHANISMS OF DRUG–RECEPTOR INTERACTIONS

#### A. Drugs and drug receptors

1. Many drug receptors are protein macromolecules present in cell membranes, which when activated initiate a biochemical change within the cell/tissue that in turn produces a pharmacologic response.
  - a. **Receptors bind ligands (drugs) and transduce signals (a process referred to as signal transduction)**
  - b. Drug binding to receptors uses similar **chemical bonds** as that used for enzyme–substrate interaction: hydrogen bonds coordinate covalent bonding and Vander Waals forces. Examples of covalent bonding involved in drug–receptor interactions are few in number.
  - c. Drugs have two identifiable properties: **affinity** for the receptor and **intrinsic activity**.
    - (1) **Intrinsic activity** is the property of the drug that permits it to initiate post-receptor processes, which lead to a response.
    - (a) **Agonists** are drugs that have both **affinity** and **intrinsic activity**. Examples: epinephrine, acetylcholine, angiotensin, and prostaglandin  $F_{2\alpha}$ .
      - i. **Full agonists versus partial agonists.** A *full agonist* is a drug that appears able to produce the full cell/tissue response. A *partial agonist* is a drug that provokes a response, but the maximum response is less than the maximum response to a full agonist; this is because a partial

**FIGURE 1-5.** Ligands may be classified as agonists (full, partial, and inverse) and antagonists. Both full and partial agonists stabilize the active state ( $R^*$ ) and thus increase receptor signaling, whereas inverse agonists stabilize the inactive state and thus decrease basal receptor signaling. Antagonists, which have equal affinity for both  $R^*$  and  $R$  and thus do not affect the equilibrium between the two states, but will reduce the ability of full, partial, and inverse agonists to bind to the receptor. (Modified from Leurs R. et al., *Clin. Exp. Allergy*, 32:4989–498, 2002.)



agonist has much higher affinity for the receptor, but less intrinsic activity than a full agonist. Concurrent administration of a partial agonist can reduce/antagonize the effect of a full agonist (Figure 1-5).

- ii. **Inverse agonists.** In the context of receptors which exert constitutive signaling activity, even in the absence of an agonist, *inverse agonists* are drugs that bind to the receptor, suppressing the constitutive signaling activity. Recent evidence suggests that propranolol and antihistamines are inverse agonists (Figures 1-5 and 1-6).

- (b) **Receptor antagonists** are drugs which have an **affinity** for the receptor site but which lack intrinsic activity. Antagonists block or reduce the effects of agonists (Figure 1-5).

**Examples:**

*Antagonists*

atropine ( $M_1$ – $M_5$ )  
yohimbine ( $\alpha_2$ )  
phenoxybenzamine ( $\alpha_1$ )  
diphenhydramine ( $H_1$ )  
cimetidine ( $H_2$ )  
naloxone  
naltrexone  
flumazenil  
spironolactone

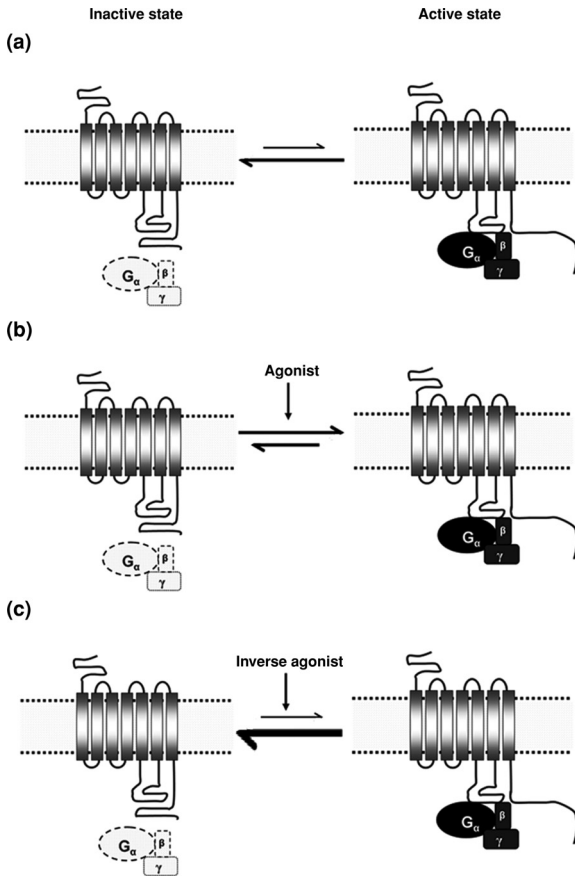
*Agonists*

cholinergic agonists  
 $\alpha_2$ -adrenergic agonists  
epinephrine  
histamine  
histamine  
opioids  
carfentanil  
benzodiazepines  
aldosterone

- i. Antagonists may act in a **competitive (these are reversible on removal, washout)** manner. Example: phentolamine-norepinephrine.
- ii. **Noncompetitive (these may be reversible or irreversible on removal, washout)** manner. The noncompetitive antagonism may be due to the antagonist binding to separate site to the agonist or due to covalent bonding. Examples: phenoxybenzamine blockade of  $\alpha_1$ -adrenergic receptors are irreversible due to covalent bonding with the receptor protein; picrotoxin antagonism of GABA receptors is reversible but noncompetitive because picrotoxin blocks the open  $Cl^-$  channel pore not the GABA binding site.

## 2. Antagonism

- a. Antagonism is the interaction between two drugs such that the response of one drug (the agonist) is reduced in the presence of the second drug (the antagonist).



**FIGURE 1-6.** Two-state model of the G protein-coupled receptor. **(a)** At rest, the inactive state isomerizes with the active state, but favors the latter. **(b)** A full agonist converts the inactive state to active state. **(c)** An inverse agonist converts more active state to inactive state than during the resting state.

There are three types of antagonism in pharmacology: **receptor**, **physiologic**, and **chemical**.

- (1) **Receptor antagonism** occurs on the same receptor protein such that two drugs, an agonist and an antagonist, compete and bind to the same receptor protein. See above for examples.
- (2) **Physiologic antagonism** occurs as the result of activating receptors with opposite physiological effects.

**Examples:**

acetylcholine	→↓	heart rate
epinephrine	→↑	heart rate
histamine	→	bronchoconstriction
epinephrine	→	bronchodilation
histamine	→↓	blood pressure
epinephrine	→↑	blood pressure

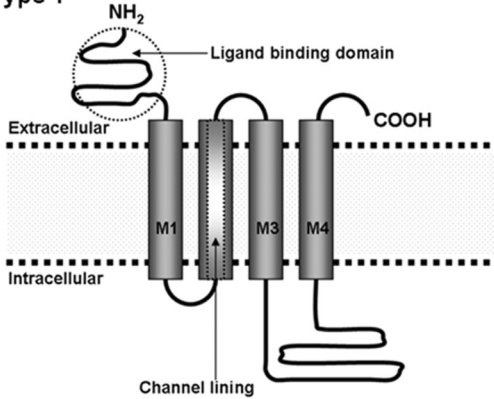
- (3) **Chemical antagonism** occurs as the result of a drug combining with two or more molecules via the formation of chemical bonds. This type of antagonism often does not require animal tissue to be demonstrated, and has been used to treat heavy metal intoxication.

**Examples:**

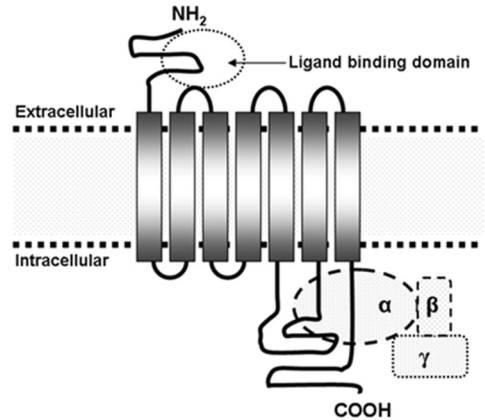
<i>Drug</i>	<i>Metal chelated</i>
Dimercaprol (BAL)	Hg, As
Penicillamine	Cu, Pb, Hg



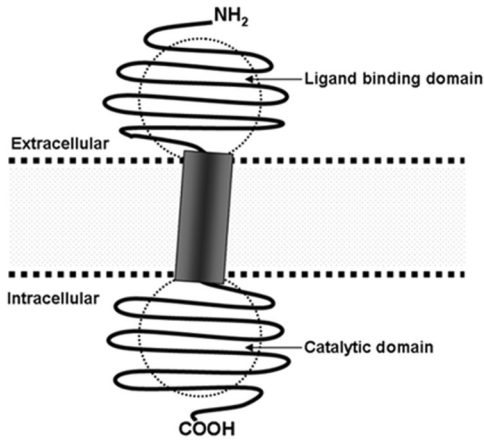
Type 1



Type 2



Type 3



Type 4

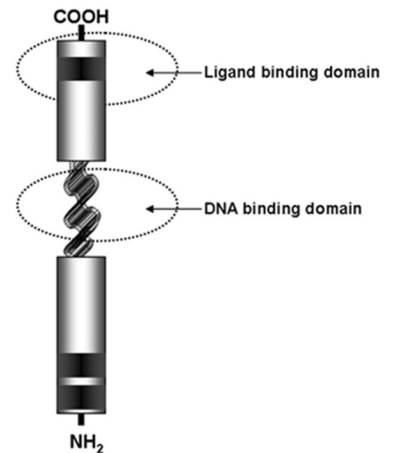
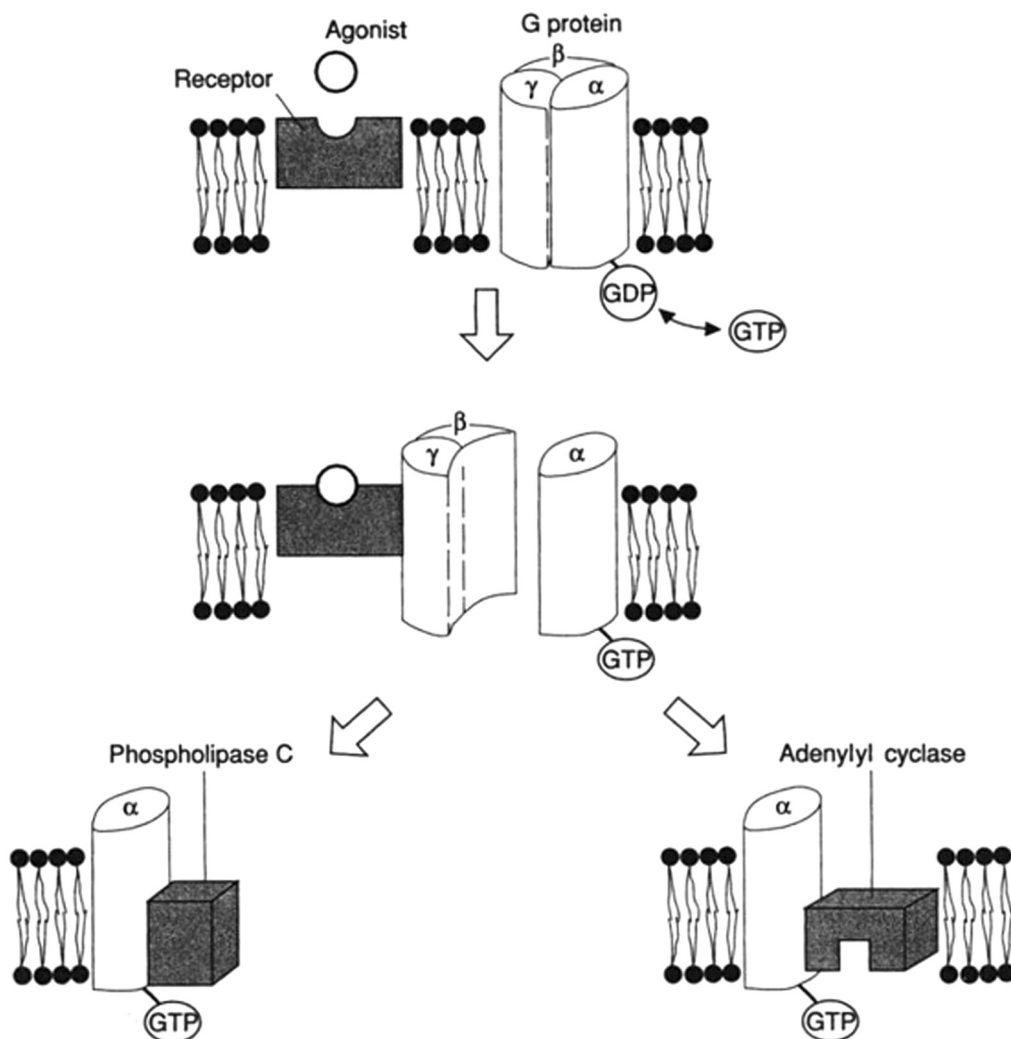


FIGURE 1-7. General structure of four receptor families.

**3. Signal transduction.** Four general types of receptor **mechanism can be described** (Figure 1-7):

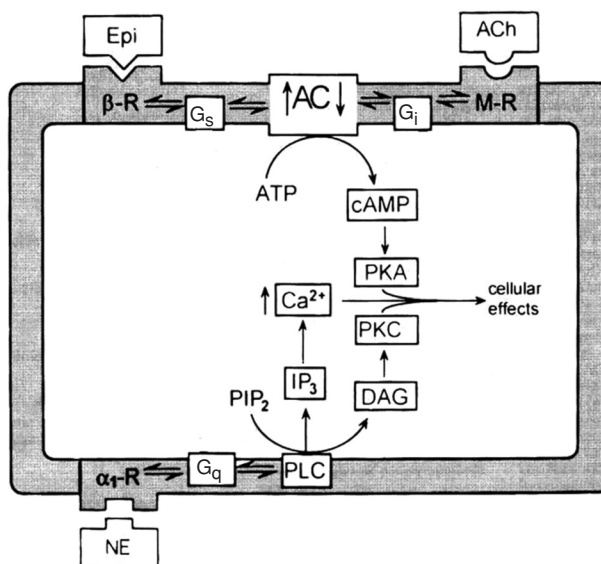
- a. **Ligand-gated ion channels (Type 1 receptor mechanisms)** regulate the flow of ions through the cellular plasma membrane channels.
  - (1) Response time is very rapid, for example, milliseconds, once the drug/ligand binds to the receptor.
  - (2) Examples of synaptic transmitters which act via ion channels: acetylcholine (at nicotinic receptors), gamma-aminobutyric acid (GABA<sub>A</sub> receptors), glycine, and glutamate (ionotropic receptors).
- b. **GTP-binding proteins (G proteins, Type 2)** couple the binding of the ligand on the cell surface receptor to intracellular second messengers. These receptors are 7-transmembrane (serpentine) receptors, which cross the plasma membrane seven times. More than 80% of receptors in animals are G protein-coupled receptors (Figure 1-8).
  - (1) Agonists (acetylcholine—on muscarinic receptor, catecholamines—on  $\alpha$ - and  $\beta$ -adrenergic receptors, and many others) acting on receptors cause the displacement of guanosine diphosphate (GDP) from the G protein and its replacement by guanosine triphosphate (GTP).
  - (2) The G protein–GTP complex in turn regulates the activity of enzymes (e.g., adenylyl cyclase, phospholipase C- $\beta$ ) or ion channels (e.g., Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup>).



**FIGURE 1-8.** G protein-coupled receptor and its effectors. When an agonist binds to a receptor that is linked to a G protein-mediated second messenger system, the conformation of the receptor in the membrane is changed, enabling it to encounter a G protein complex. When the activated receptor encounters the G protein, it induces the G protein to exchange GDP for GTP. The presence of GTP causes the  $\alpha$ -subunit to separate from the G protein and diffuse within the membrane until it encounters the effector (e.g., adenylyl cyclase, phospholipase C) that initiates the second messenger response. This response may involve regulation of enzymatic activity or opening/closure of ion channels. Hydrolysis of the GTP to GDP on  $\alpha$ -subunit returns the G protein to inactive state. (From Figure 1-4, *NVMS Pharmacology*.)

Hydrolysis of the GTP to GDP stops the activation of enzyme or ion channels.

- (3) The G protein–GTP complex may last 10 seconds whereas the initial agonist/ligand–receptor complex formation may have lasted for a few milliseconds. This leads to an **amplification** of the original agonist–receptor signal.
- (4) G proteins may **couple stimulatory responses** as well as **inhibitory responses**. Each cell may have more than one G protein type. In general, there are three G proteins:  $G_s$ ,  $G_{i/o}$ , and  $G_q$  (Figure 1-9).



**FIGURE 1-9.** Signal transduction pathways for G protein-coupled receptors (R). Activation of  $\beta$ -adrenergic receptor ( $\beta$ -R) by epinephrine (Epi) involves a stimulatory G ( $G_s$ ), which activates adenylyl cyclase (AC) to synthesize cyclic AMP (cAMP); cAMP activates protein kinase A (PKA). Acetylcholine (ACh) binds a muscarinic-2 receptor (M-R) linked to an inhibitory G ( $G_i$ ), which inhibits AC and hence PKA. Activation of  $\alpha_1$ -R by norepinephrine (NE) activates another G ( $G_q$ ), which in turn activates phospholipase C- $\beta$  (PLC). PLC hydrolyzes  $PIP_2$ , a membrane phospholipid to form  $IP_3$  and diacylglycerol (DAG).  $IP_3$  releases  $Ca^{2+}$  from the endoplasmic reticulum, whereas DAG activates protein kinase C. PKA and PKC phosphorylate various cellular constituents that, in concert with elevated cytosolic  $Ca^{2+}$  levels, elicit characteristic changes in the cellular functions. (From Fig. 5.9 of Adams' *Veterinary Pharmacology and Therapeutics*, 8th ed.)

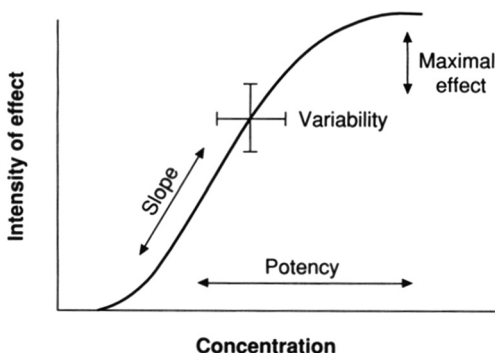
- (a)  **$G_s$  protein couples to adenylyl cyclase**, which increases the formation of cyclic AMP. Cyclic AMP activates protein kinase A, which phosphorylates cellular constituents. **Examples:** glucagon, glucagons-like peptide 1,  $\beta$ -adrenergic agonists,  $D_1$ - and  $D_5$ -dopaminergic agonists, 5-HT<sub>4</sub> agonists, gonadotropins, thyrotropin, vasopressin  $V_2$ -agonists, ACTH, and many other hormones/drugs use this mechanism.
  - (b)  **$G_{i/o}$  protein couples negatively to adenylyl cyclase**, thereby decreasing the formation of cyclic AMP. In addition,  $G_{i/o}$  protein can close  $Ca^{2+}$  and open  $K^+$  channels. **Examples:**  $\alpha_2$ -adrenergic agonists,  $M_2$ - and  $M_4$ -muscarinic agonists,  $D_2$ -,  $D_3$ -,  $D_4$ -dopaminergic agonists, 5HT<sub>1</sub>-agonists, opioids, GABA<sub>B</sub>-agonists, somatostatin, neuropeptide Y, and many other hormones/drugs use this mechanism.
  - (c)  **$G_q$  protein couples to phospholipase C- $\beta$** , which increases the formation of inositol 1,4,5-triphosphate ( $IP_3$ ) and diacylglycerol (DAG).  $IP_3$  elevates intracellular  $Ca^{2+}$  concentrations by increasing  $Ca^{2+}$  release from the endoplasmic reticulum and  $Ca^{2+}$  influx through store-operated calcium (SOC) channels. DAG activates protein kinase C, which phosphorylates cellular constituents. Vasopressin  $V_1$ -agonists, oxytocin, muscarinic  $M_1$ - and  $M_3$ -agonists,  $\alpha_1$ -adrenergic agonists, bradykinin, and many other hormones/drugs use this mechanism.
- c. Kinase-linked receptors (Type 3 receptor mechanism)**
- (1) **Receptors with tyrosine kinase activity.** Some hormones (e.g., **insulin, certain growth factors**) have tyrosine kinase as a part of the plasma membrane receptor. The insulin receptor is used as an example to explain how the tyrosine kinase receptor works (see Figure 12-5).

- (a) The activated insulin receptor (tyrosine kinase) phosphorylates its substrates [e.g., insulin receptor substrate (IRS) 1-4].
- (b) Activated IRS is thought to phosphorylate a number of cellular constituents including phosphoinositol-3 kinase (PI3-kinase), which can activate other cellular proteins including glucose transporter 4 (GLUT4) in the skeletal muscle cells and adipocytes, leading to increased glucose transport into these cells.
- (2) **Cytosolic tyrosine kinase (also see Figure 12-1).** Growth hormone, prolactin, leptin, and cytokines also have the plasma membrane receptors. Activation of these receptors will lead to the phosphorylation of Janus kinase (JAK), a form of tyrosine kinase present in the cytosol. Activation of JAK, in turn, phosphorylates the signal transduction and activation of transcription (STAT) proteins. The phosphorylated STATs form dimers, and move into the nucleus where they act as transcription factors.
- (3) **Guanylyl cyclase–protein kinase G.** Guanylyl cyclase catalyzes cyclic GMP formation from GTP. The plasma membrane receptors of atrial natriuretic peptide (ANP) and guanylin have guanylyl cyclase activity. In addition, nitric oxide (NO) can activate cytosolic guanylyl cyclase. Cyclic GMP activates protein kinase G, which mediates many effects, including closure of  $\text{Na}^+$  and  $\text{Ca}^{2+}$  channels, and opening of  $\text{K}^+$  channels.
- d. **Intracellular receptors (Type 4 receptor mechanisms)** Steroid hormones (including vitamin D) and thyroid hormone ( $\text{T}_3$ ) bind to these receptor proteins. Corticosteroid receptors are in cytosol and the receptors of other steroid hormones and  $\text{T}_3$  are in nucleus. Activated receptor proteins form dimer and move to the promoter region of the DNA, altering transcription processes (and thereby changing protein synthesis; see Figure 12-3).

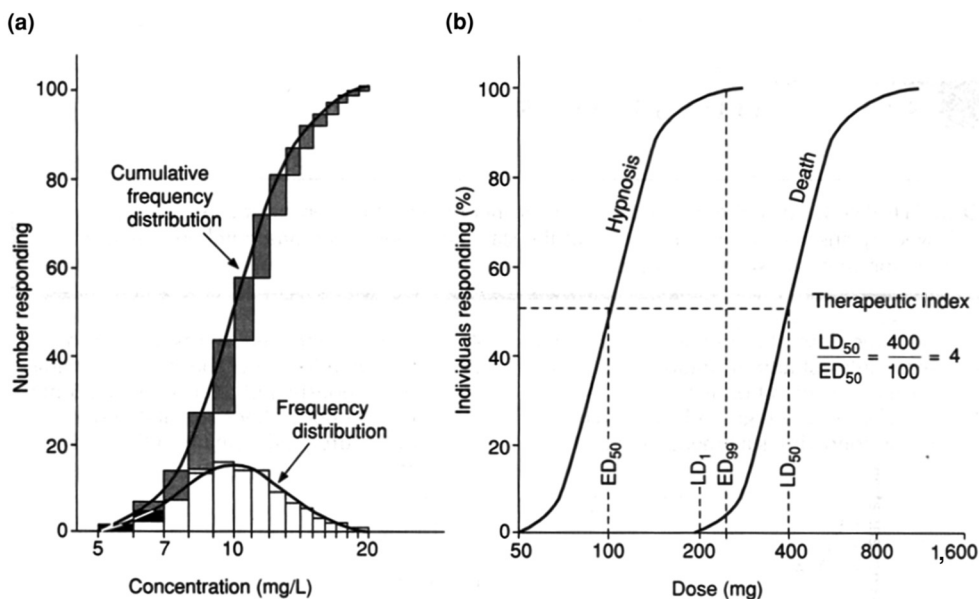
## B. Dose–response relationships

### 1. Graded dose–response relationships

- a. **The response is measured in an individual animal or tissue.** Increases in the dose produce increases in the response. Example: progressive increases in epinephrine dose produce increases in cardiac output and vasoconstriction, which lead to increases in blood pressure (Figure 1-10).
- b. **Drug concentration–effect relationships** have four important characteristics: **potency**, **slope**, **maximum efficacy**, and **individual variation**.
  - (1) **Potency** refers to the dose (concentration) of a drug needed to produce the effect. Potency is not an important property of a drug, provided the formulated form of the drug can be conveniently administered. The smaller the dose to produce the effect, the greater the potency. Assume drug [A] and drug [B] have similar pharmacological activity. The fact that drug [A] is five times more potent than drug [B] does not automatically make drug [A] the drug of choice. Strong consideration must also be given to side effects,



**FIGURE 1-10.** The log dose–effect relationship, showing the four characteristic variables. (From Figure 1-5, *NVMS Pharmacology*.)



**FIGURE 1-11.** (a) The effective concentration to produce a quantal response was determined in each of 100 subjects. The number of subjects who required each dose is plotted, giving a log normal frequency distribution (bars with diagonal lines). The stippled bars demonstrate that the normal frequency distribution, when summated, yields the cumulative frequency distribution—a sigmoid curve that is a quantal concentration–effect curve. (b) Quantal dose–response curves for the useful action and death action of a drug. ED<sub>50</sub> is the dose needed to treat 50% of the population. LD<sub>50</sub> is the dose which will kill 50% of the population. (From Figure 1-6, *NVMS Pharmacology*.)

toxicities, cost, duration of action, and so forth, in deciding which of the two drugs to use.

(2) **Slope** is of both practical and theoretical importance. Drugs that act on a common receptor (e.g., norepinephrine and phenylephrine acting on the  $\alpha_1$ -adrenoceptor) have dose–response curves with parallel slopes. Drugs that have steep slopes for their concentration–response relationship curves are potentially more difficult to use, since small increases in the dose may produce toxicity.

(3) **Variability** in the response can be expected from a specific dose and variation in dosage may be required to produce a given response.

(4) **Maximum effect** is the maximum response possible for that effector.

## 2. Quantal dose–response relationships

a. A **quantal** response is based on an **all or none response** (death, pregnant, vomit, and convulsion). The assumption is made that individual animals respond to the maximum possible or not at all. Thus, dose is not expressed as to the intensity of the effect but to the **frequency** with which any dose produced the all-or-none response. The **frequency distribution curve** is shown in Figure 1-11.

b. Quantal dose–response relationships are used to establish the useful drug effect and the toxic (death) drug effect curves.

(1) **Therapeutic index** is a ratio used to evaluate the safety of the drug. Using information available from Figure 1-11 the therapeutic index (TI) can be calculated:

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

Theoretically, the larger the TI the safer the drug. However, if the effectiveness and lethality curves are not parallel, the TI may be misleading.

- (2) **Standard safety margin** is a more conservative measure of a drug's safety than is TI and is used to relate the therapeutic effect in all animals without the risk of producing a hazardous effect. The standard safety margin is the percent by which the  $ED_{99}$  must be increased before an  $LD_1$  is reached.

$$\text{Standard safety margin} = \frac{LD_1 - ED_{99}}{ED_{99}} \cdot 100$$

- (a) Assume 10 mg/kg of a drug is effective in 99% of the animal population and that a dose of 100 mg/kg will cause toxicity in 1% of the same population.

$$\text{Standard safety margin} = \frac{100 - 10}{10} \cdot 100$$

The dose which is effective in 99% of the population must be increased by 900% to produce a toxic effect in 1% of the population.

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