

2 Drug Disposition and Response

Robert B. Raffa

Objectives

- Review basic principles of pharmacokinetics related to the absorption, distribution, metabolism, and elimination of drugs and nutrients.
- Discuss factors that can affect these processes.
- Review basic principles of pharmacodynamics and the quantification of drug and nutrient action.
- Highlight potential pharmacokinetic and pharmacodynamic sites of drug–nutrient interactions.

Key Words: Bioavailability; elimination; pharmacokinetics; pharmacodynamics

1. INTRODUCTION

This chapter presents an overview of drug disposition (pharmacokinetics) and drug action (pharmacodynamics) as a basis for understanding drug–nutrient interactions. *Pharmacokinetics* is the term used to describe the disposition of a drug throughout the body – that is, the drug’s absorption, distribution, metabolism, and excretion (ADME). *Pharmacodynamics* is the term used to describe a drug’s effect and how that effect is produced (its mechanism of action). A drug–nutrient interaction is medically significant if either the patient’s response to the drug or the patient’s nutritional status is affected adversely. Therefore, this chapter highlights processes that can contribute to either outcome.

2. PHARMACOKINETICS

A substance can produce an effect only if it can reach its physiological target(s) in sufficient concentration. Hence, the extent and rate of disposition of a drug or a nutrient is important for understanding or predicting the magnitude or the duration of their effect or possible interaction. Several factors affect the absorption and distribution of drugs and nutrients.

From: *Handbook of Drug-Nutrient Interactions*

Edited by: J.I. Boullata, V.T. Armenti, DOI 10.1007/978-1-60327-362-6_2

© Humana Press, a part of Springer Science+Business Media, LLC 2009

2.1. Absorption

The route by which a substance is introduced into the body affects its pharmacokinetics (1,2,3).

2.1.1. SYSTEMIC ROUTES

Systemic routes of administration are those that deliver the substance with the intent of producing a systemic (on the whole system) effect, rather than a local effect (for example, on the skin). A subdivision of the systemic route of administration is *parenteral*, which refers to systemic routes other than *alimentary* routes (e.g., oral, sublingual, buccal, or rectal). Systemic routes of administration provide an opportunity for drug–nutrient interaction at several levels, including the rate at which drug substance or nutrient is available for absorption (e.g., dissolution rate, degree of ionization, adsorption); the extent of plasma protein binding; and the rate or the route of metabolism.

Oral (PO) administration is generally the simplest, most convenient, safest (because of slower onset of drug effect and ability to reverse a mistake), and often most economical route of administration. Most drugs are well absorbed from the gastrointestinal (GI) tract. The rate and extent of absorption is a function of the physiochemical properties of the substance (e.g., water or lipid solubility), its formulation (e.g., tablet, capsule, liquid, slow-release reservoir, matrix), excipients, physiological environment (e.g., high acidity of the stomach), and metabolism in the gut wall. Alteration of any of these features, for example, as a result of change in diet, lifestyle, age, or health status, can affect absorption. Nutrients and foodstuffs can affect the absorption of a drug by binding to it or by altering the physiologic environment (e.g., pH of the stomach). The simple act of food ingestion, or even its anticipation, can release digestive enzymes that inactivate certain drugs (e.g., penicillins).

The *intravenous* (IV) route of administration delivers the drug directly into the bloodstream. The drug is then delivered to the heart and from there to the general circulation. The IV route bypasses problems of absorption from the GI tract, allows for rapid adjustment of dose to effect, can be used even if the patient is unconscious, and avoids the “first-pass effect” (see below). The related *intraarterial* route of administration, although used much less commonly than IV administration, is useful when infusion of a high concentration of drug into a specific target is desired. Examples include chemotherapeutic agents for the treatment of certain cancers and vasodilators for the treatment of Raynaud’s syndrome.

Subcutaneous (SC) administration involves drug delivery into the tissue beneath the skin and its subsequent entry into the blood perfusing the tissue. Absorption following SC administration is generally rapid, depending on blood perfusion of a particular site, and the rate of absorption can be accelerated (e.g., by heating or vasodilators) or slowed (e.g., by cooling, vasoconstrictors, or slow-release formulations).

Intramuscular (IM) administration is generally rapid because of the high vascularity of muscles. It also provides space for drug depots, such as sustained-release formulations, provided a patient has sufficient skeletal muscle.

Inhalation provides one of the most rapid routes of drug administration due to the large surface area and high vascularity of the lungs, provided adequate doses of the active drug reach the distal airway.

Other systemic routes include *intraperitoneal*, which is particularly useful for the administration of drugs to small animals because it provides a rapid, convenient, and reproducible technique, and *transdermal*, because of its convenience and use for extended drug delivery.

2.1.2. TOPICAL ROUTES

Topical routes of administration are generally used for the purpose of local drug action and are generally not sites of drug–nutrient interactions (a possible exception is the reduction of ultraviolet light exposure by sunscreen lotions and the resulting decreased activation of vitamin D). However, if the skin is damaged (such as by abrasions or burns) or if transmucosal passage is significant, the drug does not remain localized to the site of application and administration is akin to systemic administration with the attendant opportunity for a drug–nutrient interaction.

2.1.3. OTHER ROUTES

Direct application of drugs for localized effects to the eye (*ophthalmic* administration), ear (*otic* administration), nerves (*intraneural* administration), spinal cord (e.g., *epidural* or *intrathecal* administration), or brain (e.g., *intracerebroventricular* administration) does not often lead to significant interactions, but any substance that alters the drug's access to specialized compartments particularly via common transporters (e.g., through the blood–brain barrier) can alter the magnitude or the duration of the drug effect.

2.1.4. FACTORS THAT AFFECT ABSORPTION

The rate and extent of absorption of a drug or a nutrient is influenced by the characteristics of the drug or the nutrient and by the characteristics of the patient at the time of administration (4). For example, the rate of dissolution depends on how the product is formulated and also on the person's state of health and other factors, such as diet.

The absorption (and elimination) of substances generally follows either *zero-order* kinetics – i.e., a constant *amount* is absorbed (or eliminated) per unit time (Fig. 1a) – or *first-order* kinetics – i.e., a constant *fraction* is absorbed (or eliminated) per unit time (Fig. 1b). Most currently used drugs follow first-order kinetics.

2.2. Distribution

Once a drug or a nutrient enters the bloodstream, it might bind to a plasma protein (e.g., albumin). In addition, the drug or the nutrient usually must pass some biological barrier in order to reach its site of action.

2.2.1. PLASMA PROTEIN BINDING

Depending on their physicochemical characteristics, drug molecules (D) can form weak, reversible bonds with plasma proteins (P) according to the general equilibrium interaction represented as $D + P \rightleftharpoons DP$ (5). Drug–protein complexes

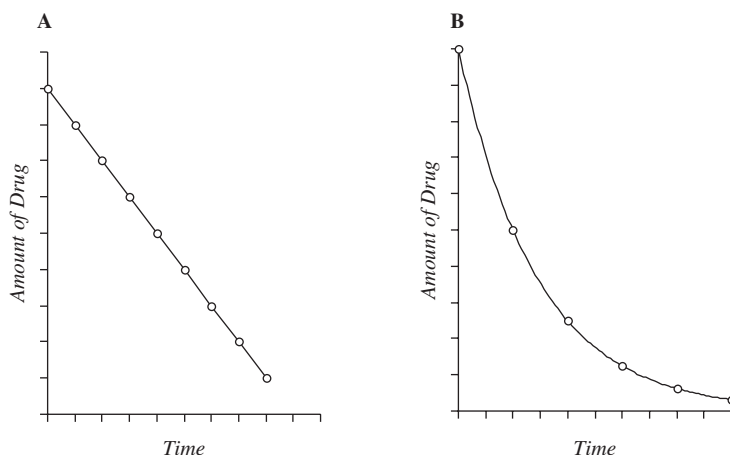


Fig. 1. (A) An example of a zero-order kinetics relationship. (B) An example of a first-order kinetics relationship.

(DP) have nothing to do with the drug's therapeutic effect, but in some instances can significantly influence the magnitude or the duration of the drug's effect. This is because a plasma protein-bound drug is less likely to reach its site of action, is less likely to be active at its site of action, and is less likely to pass into the renal tubules and be excreted. Every drug binds to plasma proteins to a different extent. The extent depends on the physiochemical properties of the drug and on the amount of plasma proteins in the patient's blood. Drugs that bind avidly with plasma proteins are susceptible to interaction with other drugs and nutrients that also bind to the same sites. Plasma protein binding is saturable (i.e., there is a finite number of such sites) and competition occurs among all substances that have affinity for such sites, introducing a new equilibrium between bound and free drug. Transition from the "bound" to the "free" state can result in a significant increase in the magnitude or the duration of effect. Thus, plasma protein binding is a possible site for interactions.

2.2.2. FIRST-PASS EFFECT

The venous drainage system of the stomach and intestines differs from that of most other organs in a way that has implications for drug–nutrient interactions. The venous drainage of most organs goes directly to the heart, but venous drainage of the GI tract sends blood into the *portal circulation*, which delivers blood to the liver. Hepatic venous drainage then goes to the heart. This is of clinical significance because the liver is a site of active biotransformation (drug metabolism) and a potential site for interactions. Biotransformation in the liver can be extensive (>99% for some commonly used drugs). In some cases, this biotransformation results in the conversion of an inactive parent substance (a *prodrug*) to its active metabolite(s). More often, the metabolites are less active than the parent substance. Once through the liver, the drug and its metabolites follow the venous drainage to the heart and into the systemic circulation. All subsequent pharmacokinetic features are the same as for any other systemically administered substance. Hence, the portal

circulation introduces a special influence on distribution during a substance's "first-pass" into the circulation (6). Oral administration of drugs results in the largest first-pass effect. Drugs that are administered IV are not subjected to a first-pass effect.

The extent of first-pass metabolism is an important consideration in drug design, formulation, and dosage regimen. For drugs that undergo high first-pass metabolism, small changes in the rate or the extent of biotransformation (as may occur with interactions) can result in large changes in systemic blood levels. Changes in biotransformation can result from changes in GI and liver function or on hepatic drug-metabolizing enzymes brought about by other drugs, nutrients, or food components.

2.2.3. BLOOD–BRAIN BARRIER

Many drugs have only limited ability to enter the brain because of their physico-chemical properties. The morphologic basis for the blood–brain barrier includes tight junctions between the epithelial cells lining the brain capillaries and transport mechanisms that pump substances out of the brain. In general, the blood–brain barrier restricts the passage of substances that are either too hydrophilic (water soluble) or too lipophilic (fat soluble). Nutritionally required substances can be actively transported across the blood–brain barrier (7).

The permeability of the blood–brain barrier depends on such factors as age, disease, and other influences, including nutritional state. Plasma protein binding is also a factor, since drug molecules highly bound to plasma proteins are less able to traverse the blood–brain barrier. Hence, drug interaction at the level of plasma protein binding can affect blood–brain barrier passage.

2.2.4. BIOLOGICAL MEMBRANES

Biological membranes are bilayer, phospholipid matrices containing cholesterol, proteins, and other constituents. Drugs can be transported around or through these membranes, depending on the properties of the drug and the composition of the particular membrane (*see* Chapter 3). Some mechanisms of drug transport are as follows (8):

Passive diffusion. If a drug is sufficiently lipid soluble, it can diffuse down its concentration gradient (energy is not required, hence the diffusion is "passive"). For weak acids ($\text{HA} \rightleftharpoons \text{H}^+ + \text{A}^-$) and weak bases ($\text{BH}^+ \rightleftharpoons \text{H}^+ + \text{B}$), it is the nonionized form (HA and B respectively) that is more lipid soluble. *Simple diffusion* occurs according to *Fick's law*:

$$\frac{dQ}{dt} = -DA \frac{dC}{dx},$$

where the flux of drug across a membrane is determined by the diffusion constant (D), the surface area (A), and the drug concentration (C). This type of diffusion favors molecules in the uncharged form and is a function of the pH of the environment at the membrane and the $\text{p}K_a$ of the drug according to relationships termed the Henderson–Hasselbach equations:

$$\text{p}K_{\text{a}} = \text{pH} + \log\left(\frac{\text{HA}}{\text{A}^{-}}\right)$$

for weak acids and

$$\text{p}K_{\text{a}} = \text{pH} + \log\left(\frac{\text{BH}^{+}}{\text{B}}\right)$$

for weak bases. As described by these equations, absorption of weak acids (e.g., aspirin) is favored over weak bases in the low pH of the stomach. However, the total amount of absorption is usually greater in the intestines due to the much higher surface area. Conversely, the absorption of weak bases is favored in the small intestine (higher pH). Renal excretion follows the same pattern. Weak acids are usually excreted in alkaline urine; weak bases are excreted faster in acidic urine.

Filtration. Some vascular bed capillaries have pores or channels that allow the passage of low-molecular-weight substances, whether they are polar or nonpolar. Such capillaries serve as molecular sieves (filters) that exclude molecules larger than a certain size.

Carrier-mediated (facilitated) diffusion. Transport of some substances across membranes, although by diffusion down a concentration gradient, is facilitated by membrane-associated molecules (carriers). This type of diffusion is generally selective for molecules having specific structures or another property. If the concentration of drug or nutrient exceeds the number of carriers, the process becomes saturated and any further increase in drug or nutrient concentration will not increase the rate of their passage across the membrane.

Active transport. Some molecules are transported across biological membranes against their concentration gradient. Transport in this direction – “up” a concentration gradient – is not favored thermodynamically and, hence, does not occur spontaneously. It requires input of energy, which is commonly supplied by coupled biochemical reactions that, for example, convert ATP to cAMP (catalyzed by $\text{Na}^{+}/\text{K}^{+}$ -ATPase). Active transport is similar to carrier-mediated (facilitated) diffusion in that transport is mediated by a membrane-associated macromolecule (pump); it is saturable; and it is usually selective for certain drugs or nutrients (based on size, shape, or other characteristic). It differs in its requirement for energy and the ability to pump against a concentration gradient.

Endocytosis. Some drugs and nutrients can be transported across biological membranes by becoming entrapped (in “pits”) and internalized (in “vesicles”) with varying degrees of selectivity. For example, sucrose and insulin can be internalized in this manner.

2.2.5. BIOAVAILABILITY

Due to the multiple barriers to absorption, the amount of a drug that enters the systemic circulation is less than the amount administered (with the exception of IV administration). The proportion (expressed either as fraction or percent) of an administered drug dose that reaches the systemic circulation is referred to as the drug’s *bioavailability*. Factors that affect a drug’s bioavailability include the

first-pass effect, the solubility and stability, and the formulation of the drug product (including the quality control of its manufacture). In addition, a person's dietary patterns, nutritional status, and state of health can affect a drug's bioavailability.

2.2.6. FACTORS THAT AFFECT DISTRIBUTION

Multiple factors affect the distribution of substances in the body. Some are related to the substance itself, such as its physical characteristics (e.g., size, solubility) and its chemical characteristics (e.g., ability to form bonds with plasma proteins or other biochemical substances). Other factors are related to the state of the physiological system, such as concentration of plasma proteins, lipid content of barrier or target tissues, cardiac output, capillary permeability in target or other tissues, and many others. Many of these factors are a function of age, disease, or other influences.

2.3. Metabolism

Drugs and nutrients are often biotransformed (metabolized) to other substances (metabolites) by a variety of biochemical reactions in a variety of locations throughout the body (9). Almost all tissues can metabolize drugs, but the liver, GI tract, and lungs are the major sites of drug metabolism of most drugs in humans. The liver plays a predominant role in drug metabolism for two reasons: first, because of its strategic location relative to the portal circulation and second, because it contains high levels of enzymes capable of metabolizing foreign substances (*see* Chapter 4). In general, but not always, metabolites are less active and more water soluble (which favors excretion in the urine) than the parent substance. In some instances, active metabolites are formed from inactive parent drugs, in which case the parent is termed a *prodrug*. The most common chemical reactions that metabolize drugs and nutrients can be conveniently categorized into two broad types: reactions that alter the basic chemical structure of the parent molecule – *Phase 1 reactions*– and reactions that result in the attachment of some endogenous substance to the parent molecule – *Phase 2* or *conjugation* reactions.

2.3.1. PHASE 1 REACTIONS

Phase 1 reactions often occur in the cytosol, mitochondria, and microsomes (a subcellular component containing membrane-associated enzymes on the smooth endoplasmic reticulum) of cells of the liver and other organs.

2.3.1.1. Oxidation. Oxidation (e.g., the addition of oxygen or the removal of hydrogen from the parent molecule) is a common Phase 1-type reaction. Microsomal oxidation is a common mechanism of metabolism of many drugs and nutrients because these substances typically have chemical structures that make them susceptible to oxidation reactions. There is an extensive system (family) of enzymes that are capable of catalyzing oxidation reactions. Primary components of this system are cytochrome P-450 reductase and the many isozymes of cytochrome P-450 (CYP). Examples of microsomal oxidation reactions are C-oxidation or C-hydroxylation of aliphatic or aromatic groups; N- or O-dealkylation; N-oxidation or N-hydroxylation; sulfoxide formation; deamination; and desulfuration. Examples

of nonmicrosomal enzymes having important roles in the metabolism of endogenous and exogenous substances include alcohol- and aldehyde dehydrogenase; xanthine oxidase; tyrosine hydroxylase; and monoamine oxidase.

The family of CYP enzymes is particularly important in studying metabolism because of the many drugs and nutrients that are metabolized by these enzymes and, in addition, the potential for drug–nutrient interactions (10). For example, it is estimated that over 90% of presently used drugs are metabolized by one or more of the CYP enzymes. Of the most commonly used drugs, about 50% are metabolized by the CYP3A subfamily; about 25% by the CYP2D6 isozyme; about 15% by the CYP2C9 isozyme; and about 5% by the CYP1A2 isozyme. Because the enzymes are saturable, and can be induced or inhibited, there is significant potential for interactions.

2.3.1.2. Reduction. Reduction reactions (e.g., the addition of hydrogen or the removal of oxygen from the parent molecule) occur both in microsomal and non-microsomal fractions of hepatic and other cells. Examples of such reactions include nitro-, azo-, aldehyde-, ketone-, and quinone reduction.

2.3.1.3. Hydrolysis. Hydrolysis-type reactions can occur in multiple locations throughout the body, including the plasma. Examples of some nonmicrosomal hydrolases include esterases, peptidases, and amidases.

2.3.2. PHASE 2 REACTIONS

The coupling (conjugation) of an endogenous substance to a drug or a nutrient molecule typically alters its three-dimensional shape sufficiently to result in a decrease in biological activity. Conjugation also typically results in an increase in water solubility of the substance, which decreases the amount that is reabsorbed through renal tubules and thereby enhances the fraction that is excreted in the urine. Conjugation with glucuronic acid (*glucuronidation*) is the most common conjugation reaction in humans. Other Phase 2 reactions include glycine-, glutamate-, or glutathione-conjugation; *N*-acetylation (acetyl coenzyme A as acetyl donor); *O*-, *S*-, or *N*-methylation (*S*-adenosylmethionine as methyl donor); and sulfate or sulfanilate formation (3'-phosphoadenosine 5'-phosphosulfate as the sulfate donor).

2.3.3. SEQUENCE OF METABOLISM

It is common for a drug to be metabolized through several biotransformation reactions, resulting in the production and the elimination of several or many metabolites, each having its own pharmacokinetic and pharmacodynamic characteristics. It is also common for a substance to undergo a Phase 2-type reaction following a Phase 1-type reaction, but this sequence is not a requirement. It is possible for a Phase 2 reaction to precede a Phase 1 reaction.

2.3.4. INDUCTION OR INHIBITION

Many of the enzymes involved in the biotransformation of drugs and nutrients can be induced (increased in number and activity) or inhibited (reduced in number and activity) by a variety of chemical substances, including themselves and other drugs or nutrients (11). Induction results in an enhanced metabolism of molecules

that are biotransformed by the same pathway and results in a decrease in the level of parent molecule and increase in the level of metabolites. The biological effect will be decreased if the parent is more active than its metabolites and increased if the parent is a prodrug. The opposite occurs with enzyme inhibition.

2.3.5. FACTORS THAT AFFECT METABOLISM

Multiple factors can affect metabolism (12), including genetics (polymorphisms); the chemical properties of the drug or the nutrient (which determines their susceptibility to the various types of metabolic reactions); the route of administration (which affects, for example, the extent of the first-pass effect); dose (which can exceed the capacity of substrates for conjugation reactions); diet (which can also affect the capacity of substrates for conjugation reactions); age and disease (which can affect hepatic function); and others.

2.4. Elimination

The biological effects of exogenous substances are terminated by the combined processes of redistribution, metabolism, and excretion – i.e., elimination (13). Several factors affect the rate and extent of elimination, and accumulation occurs if the rate of absorption and distribution of a drug or a nutrient exceeds the rate of elimination.

2.4.1. ROUTES OF ELIMINATION

In humans, the kidney is the major route for elimination of many drugs, partly due to the fact that the kidneys receive about 20–25% of the cardiac output. Other sites of elimination include the lungs, the feces, and (usually to a lesser, but no less important, extent) sweat, saliva, blood loss, gastric fluid, breast milk, semen, and others.

Size exclusion prevents plasma proteins – and drug molecules that are bound to them – from passing through the glomerulus of a healthy kidney. The fate of a substance that passes into the nephron depends on the substance's physicochemical properties. Lipophilic substances (such as the nonionized form of weak acids or bases) are more likely to be reabsorbed through the wall of the nephron and back into the circulation. Hydrophilic substances (such as the ionized form of weak acids or bases) are more likely to be excreted in the urine. The pH dependence of ionization is exploited clinically by adjusting the urine pH. Some substances are actively transported across the wall of the nephron either into or out of the lumen of the nephron. Such transport processes are generally saturable and, thus, are possible sites of drug–nutrient interactions.

2.4.2. RATE OF ELIMINATION

The elimination of most current drugs follows first-order kinetics (i.e., “exponential decay”) in which the drug concentration at any time t (C_t) is related to the original drug concentration (C_o) by the equation $C_t = C_o e^{-kt}$. In first-order elimination, equal *fractions* of drug are eliminated in equal times and C_o is reduced by 50% in one *half-life* ($t_{1/2}$). Other drugs are eliminated by zero-order (linear) kinetics. In zero-order elimination, equal *amounts* of drug are eliminated in equal times. In both cases, elimination is a function both of the substance and of the condition of the patient.

2.4.3. CLEARANCE

The rate of elimination (mass/time) of a substance is equal to its concentration (mass/volume) times the “clearance” (volume/time). Clearance is the volume of a compartment (e.g., blood) per unit of time that is “cleared” of the substance due to elimination (e.g., metabolism or excretion). The equation that relates renal plasma clearance (Cl), rate of excretion (R_e), drug concentration in plasma (C_p), and drug concentration in urine (C_u) is:

$$ClC_p = C_u R_e.$$

2.4.4. EFFECT OF MULTIPLE DOSING

When a drug is administered according to a fixed-interval schedule, the rate of accumulation is predictable from the dose and half-life. For example, following the repeated IV dosing of a drug having first-order elimination kinetics, the mean drug concentration (C_{av}) can be estimated from the dose (D) and the fraction of drug remaining (F) by the equation

$$C_{av} = -D / \ln F.$$

The upper (C_{max}) and lower (C_{min}) bounds can be estimated by

$$D/(1 - F) \text{ and } FD/(1 - F),$$

respectively (Fig. 2). The actual clinical results depend on the patient’s individual characteristics.

2.4.5. FACTORS THAT AFFECT ELIMINATION

In addition to the factors already cited, elimination can be accelerated by enzyme induction, increases in urine flow, or by change in urine pH and can be slowed by renal impairment, change in pH, or other patient-specific factors.

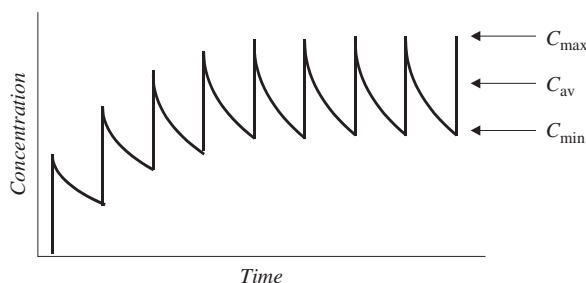


Fig. 2. An example of multiple dosing of a drug having first-order elimination kinetics. C_{max} , C_{av} , and C_{min} are described in the text.

2.5. Pharmacogenetics

Pharmacogenetics (*pharmacogenomics*) is the study of how a person’s genetic makeup (*genotype*) influences the way they respond to a drug (their *phenotype* in this regard) and the role genetic differences play in interindividual variability of

response to drugs. Many genes that encode drug-metabolizing enzymes, transporters, and receptors are now known to be genetically polymorphic – defined as the ability of a gene to assume multiple forms, where the least common allele occurs in >1% of the population. The variation can be in the gene promoter, the coding region (exons), the noncoding region (introns), or an untranslated gene sequence. A polymorphism in any region can lead to faulty protein structure or expression and there are numerous clinical examples of polymorphic enzymes altering a drug's disposition or effect. *Single nucleotide polymorphisms (SNPs)* are defined as mutations that involve a single DNA base substitution. SNPs are the most common variants in the human genome.

Knowledge of a person's phenotype can facilitate better choice of therapeutic approach and the design of more optimal drug regimens, particularly in patients who may not be achieving the expected effect of a drug.

3. PHARMACODYNAMICS

A substance produces a biological effect by modification or interaction with ongoing physiological processes. In some cases the target is foreign (e.g., bacteria or viruses) or aberrant (cancer cells). In most other cases, the target is part of normal physiology (e.g., enzymes or receptors). Drug actions are quantified and evaluated using dose–response curves.

3.1. Mechanisms of Action

In the broadest sense, drug effects can be categorized into four major mechanisms (14). They can kill invading organisms (e.g., antibiotics or antivirals), they can kill aberrant cells (e.g., many cancer chemotherapies), they can neutralize acids (antacids), and they can modify physiological processes.

3.1.1. ANTIBIOTICS/ANTIVIRALS

Antibiotics and antivirals target biochemical processes of invading organisms. For example, penicillins, cephalosporins, carbapenems, and monobactams, which have chemical structures that contain a β -lactam ring, disrupt cell walls or inhibit their synthesis. Sulfonamides and trimethoprim act on enzymatic pathways, resulting in the inhibition of folic acid synthesis. Aminoglycosides, tetracyclines, chloramphenicol, and erythromycin interfere with mechanisms involved in the synthesis of bacterial proteins. Quinolones inhibit bacterial DNA gyrase. Most antivirals work by inhibiting viral replication. In all cases, the clinical utility is significantly increased when the drug exhibits selectivity for biochemical processes essential to the invading organism, but not essential to humans.

3.1.2. CANCER CHEMOTHERAPY

Much current cancer chemotherapy (antineoplastic agents) involves the use of substances that are cytotoxic. In general, current antineoplastic drugs can be divided into four major classes: alkylating agents, antimetabolites, alkaloids, and antibiotics. Alkylating agents bind covalently to DNA, thereby impeding replication and transcription, leading to cell death. Antimetabolite drugs compete with critical precursors of RNA and DNA synthesis, thereby inhibiting cell proliferation.

Alkaloids inhibit microtubular formation and topoisomerase function, thereby blocking cell division and DNA replication. Certain antibiotics inhibit RNA and DNA synthesis. Many patients receive combinations of these drugs.

3.1.3. ANTACIDS

Excess gastric acidity is reduced by treatment with antacids, which are weak bases that convert gastric (hydrochloric) acid to water and a salt. Most antacids in current use contain aluminum hydroxide, magnesium hydroxide, sodium bicarbonate, or a calcium salt.

3.1.4. MODULATION

The chemical nature of cellular function and communication within and between cells allows for modulation by endogenous chemical substances (drugs and nutrients). The targets of such modulation include enzymes, DNA, and a variety of other molecules involved in the synthesis, storage, metabolism, or elimination of endogenous substances.

3.2. *Receptors*

Many drugs interact with macromolecular components of cells that then initiate a chain of events that lead to the drug's effect. In the commonly used analogy, the receptor is like a light switch. A better analogy is that a receptor is like a dimmer switch, since there is generally some basal level of activity. A receptor also serves to limit the access to the switch to only a select number of specific molecules (by “lock-and-key” fit).

3.2.1. OCCUPATION THEORY

Receptors are activated when specific molecules (drugs) form weak intermolecular bonds with them – the magnitude of such a drug's effect is related to the number (or the fraction of the total) of receptors that are “occupied” (15). The formation of drug–receptor complexes is usually reversible such that the reaction between drug molecule (D) and receptor molecule (R) is an equilibrium reaction that can be described and characterized – as any other chemical equilibrium reaction – according to the equation $D + R \rightleftharpoons DR$. The “driving force” for the reaction to proceed in the direction of drug–receptor complex depends on the Gibb's free energy difference (ΔG) according to $\Delta G = -RT \ln K_{eq}$, where R is a constant, T is the temperature (Kelvin), and K_{eq} is the equilibrium constant (16).

3.2.2. AGONISTS AND ANTAGONISTS

The vast majority of chemical substances do not fit a binding site on any receptor. Chemicals that do bind to receptors are said to do so with a certain *affinity*, the magnitude of which is given by the reciprocal of the equilibrium constant and termed the “dissociation constant” (often designated as K_D). Only a subset of substances that bind to receptors are capable of eliciting an effect through the receptor, i.e., have *intrinsic activity*. Substances that have affinity and intrinsic activity are termed *agonists* and substances that have affinity, but not intrinsic activity, are termed *antagonists*. Antagonists competitively or noncompetitively inhibit the access of agonists to their receptors. Since receptors mediate the effects

of endogenous agonists such as neurotransmitters, hormones, and peptides, antagonist drugs – although lacking intrinsic activity *in vitro* – can produce biological effects *in vivo* by attenuating the signal of the endogenous agonist.

3.2.3. SIGNAL FIDELITY

One of the major functions of receptors is to provide the necessary fidelity for accurate and reliable communication between neurons or other cells. The “lock-and-key” requirement restricts access only to molecules of specific three-dimensional shape. The fit is sufficiently flexible, however, that certain molecules (such as drugs) having three-dimensional shapes similar to the endogenous ligand can bind to their receptors (with greater or lesser affinity and intrinsic activity).

3.2.4. “UP-” AND “DOWNREGULATION”

The number of receptors expressed at any given time is the difference between the number synthesized and the number destroyed or internalized and, thus, is a function of the age, health, and other characteristics of the individual. Repeated exposure to an agonist or an antagonist can alter the number of expressed receptors. The change in receptor number is often interpreted as the body’s attempt to counteract excess action of an agonist or an antagonist and an effort to reestablish homeostasis. More permanent change in receptor number can result from drug effects at the level of the gene.

3.3. Signal Transduction

Signal transduction refers to the postreceptor sequence of events that lead to an agonist’s effect. Transduction mechanisms can be divided broadly into two types: *ionotropic*, in which activation of the receptor leads directly to influx of ions, and *metabotropic*, in which activation of the receptor actuates a series of biochemical *second messengers* that mediate the response (17).

3.3.1. LIGAND-GATED ION CHANNELS

Located on the membranes of excitable cells, ligand-gated ion channel receptors (LGICRs) are comprised of segments of transmembrane proteins that form pores of specific size and shape that allow the passage of certain ions. The magnitude or the rate of flow of ions through the membrane is regulated by the binding of ligand to the receptor. LGICRs usually display selectivity for ions (e.g., Na^+ , K^+ , Ca^{2+} , or Cl^-) and can be composed of subunits that can be expressed or coupled in different ways in different cells, thus mediating a variety of effects. Examples of LGICRs are the nicotinic cholinergic, GABA_A , glutamate, and glycine receptors.

3.3.2. GPCRs

The G-protein-coupled receptors (GPCRs) typically include seven transmembrane regions, an *N*-terminal extracellular region, and a *C*-terminal intracellular region (18). A group of guanosine triphosphate (GTP) protein subtypes are coupled to the receptor. Ligand activation of a GPCR induces GDP–GTP exchange and modulation of associated second messengers such as adenylate cyclase, phosphoinositide pathways, and ion channels. Multiple G-protein subtypes allow for selective responses (19).

3.3.3. TYROSINE KINASE RECEPTORS

Tyrosine kinase receptors span the cell membrane and their self-contained catalytic domain functions as an enzyme. Examples include receptors for certain growth factors and insulin.

3.3.4. NUCLEAR RECEPTORS

A large group of intracellular receptors, referred to as the nuclear receptors, are ligand-dependent transcription factors that regulate gene expression. Along with coreceptors and cofactors, the activation or the inhibition of these receptors influences the synthesis and regulation of proteins (e.g., enzymes and receptors) and other cellular components.

3.4. Dose–Response Curves

The relationship between the dose of a drug and its corresponding response is a useful measure of effect from both a mechanistic and a practical standpoint. For example, given a reaction scheme of the form $D + R \rightleftharpoons DR$, it follows that the shape of the dose–response curve should be hyperbolic, something that is observed for many drugs (19). In addition, certain features of a dose–response curve can yield clinically valuable information, such as a measure of relative potency or efficacy (20).

Several ways of displaying a dose–response curve are described in the following sections. The type of display can affect certain mathematical (statistical) analyses of the data (for details, see ref. (21)).

3.4.1. QUANTAL

A “quantal” dose–response curve is one in which the dependent variable, usually plotted on the ordinate (y -axis), is measured as an all-or-none outcome (e.g., the number of patients with systolic blood pressure greater than 140 mm Hg).

3.4.2. GRADED

A “graded” dose–response curve is one in which the dependent variable is measured using a continuous scale (e.g., systolic blood pressure in mm Hg). As with a quantal dose–response curve, the set of points on rectangular coordinates derived from plotting the measured effect against the administered dose typically forms a pattern that approximates a rectangular hyperbola (Fig. 3A).

3.4.3. LOG

For practical, and now partly unnecessary but historical, reasons, dose–response curves are commonly constructed by plotting the response against the logarithm (base 10) of the dose. The shape of such curves becomes sigmoidal or “S shaped” (Fig. 3B). This has become so customary that such a plot is often called a dose–response curve, although log(dose)–response curve is more precise.

3.4.4. POTENCY AND EFFICACY

The dose of the drug estimated to produce 50% effect is termed the ED_{50} (or equivalent) for a quantal dose–response curve and the D_{50} (or equivalent) for a graded dose–response curve. *Potency* is a comparative term that refers to the

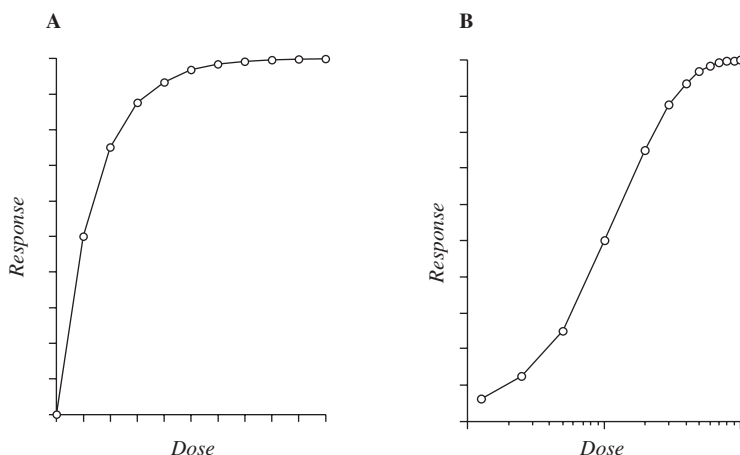


Fig. 3. (A) A dose-response curve on rectangular coordinates. (B) Quantal or graded dose-response data plotted against $\log_{10}(\text{dose})$.

amount of substance that is required to produce a specified level of effect (Fig. 4A). *Efficacy* is a term that refers to a substance's ability to achieve a certain degree of response under specified conditions (Fig. 4B). Potency and efficacy are independent characteristics.

3.4.5. ANTAGONISM

Antagonists, though lacking intrinsic activity, can produce effects when given to a patient because they attenuate the action of an endogenous agonist involved in a pathway that is tonically active. For example, antagonists of the muscarinic cholinergic receptor attenuate the parasympathetic influence on heart rate, with

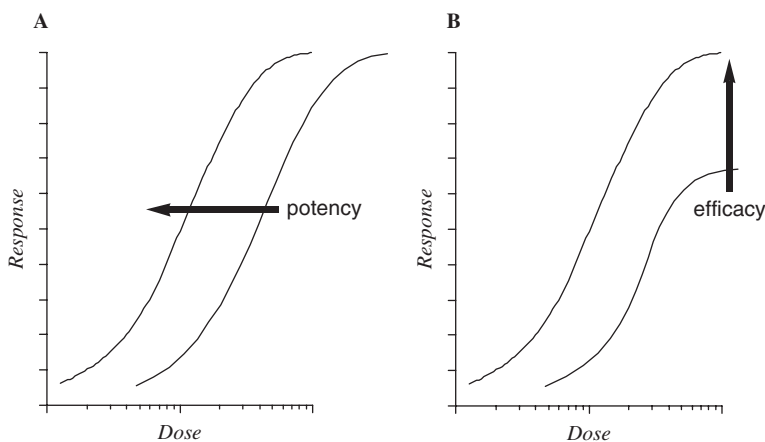


Fig. 4. (A) Potency is indicated by the location of a dose-response curve along the x-axis. (B) Efficacy is indicated by the maximal-attainable level of effect under specified conditions.

consequent increase in heart rate due to the less-opposed influence of the sympathetic subdivision. Such “effects” of an antagonist can also be characterized by a dose–response curve.

4. CONCLUSION

Drugs are substances taken to defend against invading organisms or to correct aberrant physiological processes, while nutrients are substances taken for maintenance of normal physiological processes. Both types of substance are desirable. Both types of substances also have chemical compositions that, by nature or by design, interact with common sites within the body. Therefore, drug–nutrient interactions can occur. The interactions can be deleterious to the intended action of the drug or to the nutritional status of the patient. Either outcome is undesirable. The principles of drug disposition and response outlined in this chapter provide the basis for understanding, or predicting, such interactions. They further provide a foundation for the more detailed treatments of these interactions presented throughout the rest of this book.

Take Home Points

- In the broadest sense, drugs and nutrients share the feature of being chemical substances that – within a proscribed concentration range – produce a beneficial physiological effect.
- Drugs and nutrients share several common sites of transport within the body (absorption, distribution, metabolism, and elimination), each of which represents a potential site of drug–nutrient interaction.
- Drugs and nutrients produce their effects through similar pharmacodynamic mechanisms (e.g., enzymes and receptors), which can be sites of drug–nutrient interaction.
- The clinical significance of a pharmacokinetic or a pharmacodynamic drug–nutrient interaction can be highly dependent on the individual patient – i.e., a function of patient’s general health, nutritional status, age, etc.
- The basic principles of pharmacokinetics and pharmacodynamics provide a basis for understanding the occurrence and treatment of drug–nutrient interactions.

REFERENCES

1. Raffa RB, Rawls SM, Portyansky-Beyzarov E. *Netter’s Illustrated Pharmacology*. Philadelphia, PA: Elsevier, 2005.
2. Rang HP, Dale MM, Ritter JM, et al. *Pharmacology*. New York: Churchill Livingstone, 1995:74–79.
3. Jacob LS. *NMS Pharmacology*. 4th ed. Philadelphia, PA: Williams & Wilkins, 1996:3–4.
4. Xie H-G, Kim RB, Wood AJJ, et al. Molecular basis of ethnic differences in drug disposition and response. *Annu Rev Pharmacol Toxicol* 2001;41:815–850.
5. Pratt WB. The entry, distribution, and elimination of drugs. In: Pratt WB, Taylor P, eds. *Principles of Drug Action: the Basis of Pharmacology*. 3rd ed. New York: Churchill Livingstone, 1990:231–236.

6. Holford NHG, Benet LZ. Pharmacokinetics & pharmacodynamics: dose selection & the time course of drug action. In: Katzung BG, ed. *Basic & Clinical Pharmacology*. 7th ed. Stamford, CT: Appleton & Lange, 1998:34–49.
7. de Boer AG, van der Sandt ICJ, Gaillard PJ. The role of drug transporters at the blood–brain barrier. *Annu Rev Pharmacol Toxicol* 2003;43:629–656.
8. Levine RR. *Pharmacology: Drug Actions and Reactions*. 5th ed. New York: Parthenon, 1996:51–74.
9. Benet LZ, Kroetz DL, Sheiner LB. Pharmacokinetics: the dynamics of drug absorption, distribution, and elimination. In: Hardman JG, Limbird LE, eds-in-chief. *Goodman & Gilman's the Pharmacological Basis of Therapeutics*. 9th ed. New York: McGraw-Hill, 1996:11–16.
10. Lin JH, Lu AYH. Inhibition and induction of cytochrome P450 and the clinical implications. *Clin Pharmacokinet* 1998;35:361–390.
11. Park BK, Kitteringham NR, Pirmohamed M, et al. Relevance of induction of human drug-metabolizing enzymes: pharmacological and toxicological implications. *Br J Clin Pharmacol* 1996;41:477–491.
12. Lin JH, Lu AYH. Interindividual variability in inhibition and induction of cytochrome P450 enzymes. *Annu Rev Pharmacol Toxicol* 2001;41:535–567.
13. Shargel L, Yu ABC. *Applied Biopharmaceutics and Pharmacokinetics*. 3rd ed. Stamford, CT: Appleton & Lange, 1993:265–292.
14. Raffa RB. Mechanisms of drug action. In: Raffa RB, ed. *Quick Look Pharmacology*. Madison, CT: Fence Creek, 1999:14–15.
15. Boeynaems JM, Dumont JE. *Outlines of Receptor Theory*. Amsterdam: Elsevier/North-Holland, 1980:1–226.
16. Raffa RB. *Drug-Receptor Thermodynamics: Introduction and Applications*. Chichester, UK: John Wiley & Sons, 2001:1–781.
17. Roerig SC. Drug receptors and signaling. In: Raffa RB, ed. *Quick Look Pharmacology*. Madison, CT: Fence Creek, 1999:16–17.
18. Strader CD, Fong TM, Tota MR, et al. Structure and function of G protein-coupled receptors. *Annu Rev Biochem* 1994;63:101–132.
19. Gudermann T, Kalkbrenner F, Schultz G. Diversity and selectivity of receptor-G protein interaction. *Annu Rev Pharmacol Toxicol* 1996;36:429–459.
20. Tallarida RJ, Jacob LS. *The dose–response relation in pharmacology*. New York: Springer-Verlag, 1979:1–207.
21. Tallarida RJ. *Drug synergism and dose-effect data analysis*. Boca Raton, FL: Chapman & Hall/CRC, 2000:1–247.



<http://www.springer.com/978-1-60327-363-3>

Handbook of Drug-Nutrient Interactions

Boullata, J.I.; Armenti, V.T. (Eds.)

2010, XXVIII, 824 p. 11 illus., Hardcover

ISBN: 978-1-60327-363-3

A product of Humana Press