2 Drug Disposition and Response

Robert B. Raffa

1. INTRODUCTION

The basis for this book is that a drug–nutrient interaction (DNI) is the result of a physical, chemical, physiologic, or pathophysiologic relationship between a drug and nutrient(s)/food that is considered significant if the therapeutic response is altered adversely or if the nutritional status is compromised. This chapter presents an overview of drug disposition and drug action that forms the basis for understanding such adverse interactions.

Pharmacokinetics is the term used to describe drug disposition, that is the absorption, distribution, metabolism, and excretion of the drug. *Pharmacodynamics* is the term used to describe drug action (i.e., its mechanism and effects).

2. PHARMACOKINETICS

Pharmacokinetics is important for understanding or predicting the magnitude or duration of an effect of a drug or nutrient. A substance can produce an effect only if it can reach its target(s) in adequate concentration. Several factors can affect the absorption and distribution of drugs and nutrients.

2.1. Absorption

The route by which a substance is introduced into the body affects its pharmacokinetics *(1,2)*. Hence, a review of the major characteristics of the more common routes of administration is warranted.

2.1.1. Systemic Routes

Systemic routes of administration are those that deliver the substance with the intent of producing a systemic (on the system) effect, rather than a local effect on, for example, the skin. A subdivision of systemic route of administration is parenteral, which refers to systemic routes other than oral, sublingual, buccal, or rectal, which are termed alimentary routes. Oral 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 drug substance (e.g., hydrophilic, lipophilic), its formulation (e.g., tablet, capsule, liquid,

From: *Handbook of Drug–Nutrient Interactions*
Edited by: J. I. Boullata and V. T. Armenti © Humana Press Inc., Totowa, NJ

slow-release reservoir, or matrix), excipients, physiological environment (e.g., stomach pH), and any metabolism in the gut wall. Alteration of any of these features that occurs, for example, as a result of change in diet, lifestyle, age, or health status, can affect absorption. Nutrients and foodstuffs can affect absorption by direct binding or by altering the physiologic environment (e.g., pH of the stomach contents). The simple act of food ingestion, or even its anticipation, can release digestive enzymes that inactivate certain drugs, such as penicillins. The intravenous route of administration delivers drug substance directly into the bloodstream. With the exception of the portal circulation (see later), the drug is then delivered to the heart and from there to the general circulation. The intravenous 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 later). Intra-arterial drug administration, although much less common clinically than intravenous administration, is advantageous when infusion of a high concentration into a specific target is desired, such as chemotherapeutic agents for treatment of certain cancers and vasodilators for the treatment of Raynaud's syndrome (a condition characterized by excessive vasoconstriction, particularly affecting the digits). Subcutaneous administration involves delivery of the drug into the tissue beneath the skin for subsequent entry into the vasculature. Absorption following subcutaneous administration is generally rapid, depending on the perfusion of a particular site, and the rate of absorption can be accelerated (e.g., by heating or vasodilators) or decelerated (e.g., by cooling, vasoconstrictors, or slow-release formulations). Intramuscular administration is generally rapid because of high vascularity and provides an opportunity for sustained-release formulations such as oil suspensions. Inhalation provides one of the most rapid routes of drug administration due to the large surface area and high vascularity of the lung. 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 due to the warm, moist environment and extensive vascularity of the peritoneum and the transdermal route, because of its convenience and control for extended drug delivery.

Systemic routes of administration provide an opportunity for drug and nutrient/food interactions at several levels, including: the rate at which drug substance or nutrient is available for absorption (e.g., dissolution rate, degree of ionization, adsorption, etc.); the extent of plasma protein binding; and the rate or route of metabolism.

2.1.2. Topical Routes

Topical routes of administration—such as direct application to the skin or mucous membranes—for the purpose of local action are not generally sites of interaction between drugs and nutrients/food. A possible exception is the reduction of ultraviolet light exposure by sunscreen lotions, thereby decreasing activation of vitamin D. However, if the skin is damaged (such as in serious abrasions and 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 interaction.

2.1.3. Other Routes

Direct application of drugs for localized effects to the eye (opthalmic administration), ear (otic administration), nerves (intraneural administration), spinal cord (e.g., epidural or intrathecal administration), or brain (e.g., intracerebroventricular administration) do

not often lead to significant nutrient/food interactions, but any substance that alters the drug's access to specialized compartments (e.g., through the blood–brain barrier [BBB]) will alter the magnitude or duration of the drug effect.

2.1.4. Factors That Affect Absorption

The rate and extent of absorption is influenced by many factors related both to the characteristics of the drug or nutrient substance and the particular characteristics of the recipient at the time of administration *(3)*. For example, the product formulation generally determines the rate of dissolution under specific physiological conditions, but these conditions depend on the person's state of health and other factors, such as diet. The solubility of the administered substance, its dosage, and route of administration also affect absorption.

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

2.2. Distribution

Whether a drug or nutrient is administered directly into the bloodstream, such as intravenously, or indirectly via another route of administration, once in the bloodstream it is subject to binding to plasma proteins, the extent of binding is dependent on the physiochemical properties of the drug. Additionally, the drug or nutrient usually must pass some biological barrier in order to reach its ultimate site of action. Because plasma-protein binding is reversible and competitive, and there is a finite capacity for binding, plasma-protein binding offers a potential site of drug and nutrient/food interaction.

2.2.1. Plasma-Protein Binding

Due to their physicochemical characteristics, drug molecules (D) can form weak, reversible physical and chemical bonds with proteins (P) such as albumin in plasma according to $D + P \Leftrightarrow DP$ *(4)*. These drug–protein complexes (DP) have nothing to do with the drug's ultimate effect, but in some instances, can significantly influence the magnitude or duration of the drug's effect. This is because that protein-bound drug is generally inactive at its site of action and, because of size exclusion, is less likely to transverse the glomerulus into the kidney nephron and be excreted. Each drug binds to plasma proteins to a different extent. Drugs that bind avidly with plasma proteins are susceptible to interaction with other drugs and nutrients that bind to the same sites on plasma proteins. This is because 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. The transfer from the "bound" to the "free" state can result in a significant change in effect magnitude or duration.

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 effects. 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 import because the liver is a site of active biotransforma-

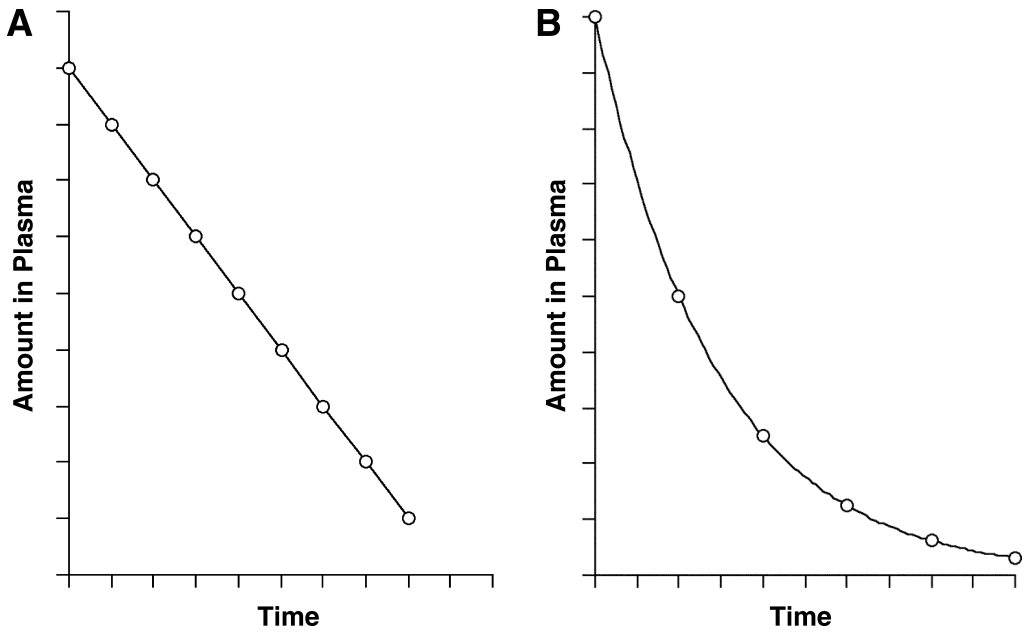

Fig. 1. (**A**) An example of zero-order relationship. (**B**) An example of first-order relationship.

tion (discussed later) and potential for drug interaction. Biotransformation (drug metabolism) in the liver can be extensive, accounting for more than 99% reduction of the parent drug substance for some commonly used drugs. In some cases, this biotransformation results in conversion of an inactive parent substance (prodrug) to its active metabolites. More often, the metabolites are less active than the parent substance. Once through the liver, the drug and metabolites follow the venous drainage to the heart and into the systemic circulation. All subsequent pharmacokinetics is the same as for any other systemically administered substance. Hence, the portal circulation introduces a special influence on drug distribution during the first pass into the circulation *(5)*. Drugs administered intravenously are not subjected to first-pass effect. Oral administration has the highest 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 extent of biotransformation can result in large changes in systemic blood levels. Changes in biotransformation can result from changes in liver function or from the effect of other drugs, nutrients, or food components on hepatic drug metabolizing enzymes.

2.2.3. Blood–Brain Barrier

Many drugs, because of their physicochemical properties, have only limited ability to enter the brain. In general, the BBB restricts passage of macromolecules and substances that are either too hydrophilic (water soluble) or too lipophilic (fat soluble). Nutrients and other necessary substances can be actively transported across the BBB *(6)*. The morphologic basis for the BBB includes tight junctions between the epithelial cells lining the brain capillaries and transport mechanisms that pump substances out of the brain.

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

2.2.4. Biological Membranes

Biological membranes are matrices containing phospholipid bilayers, cholesterol, proteins, and other constituents. Drugs can be transported around or through these membranes, depending on the composition of the particular membrane. Some mechanisms of drug transport are as follow *(7)*:

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 ($HA \Leftrightarrow H^+ + A^-$) and weak bases ($BH^+ \Leftrightarrow H^+ + B$), it is the un-ionized form (HA and B) 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 dependent on a diffusion constant (D), the surface area (A), and the drug concentration (C). This type of diffusion favors molecules in the uncharged form, and hence is a function of the pH of the environment at the membrane and the pK_a of the drug according to relationships termed the Henderson-Hasselbach equations:

$$pK_a = pH + \log\left(\frac{HA}{A^-}\right)$$

for weak acids and

$$pK_a = pH + \log\left(\frac{BH^+}{B}\right)$$

for weak bases. As a consequence, 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 greater surface area. Conversely, an absorption of weak bases is favored in the small intestine (higher pH), and the acidic environment of the kidney nephrons favors (in a pH-dependent manner) excretion of weak bases.

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 does not require energy and is generally selective for molecules having specific structures or other recognized property. If the concentration of drug or nutrient exceeds the number of carriers, the process becomes saturated and 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 adenosine 5'-triphosphate (ATP) to adenosine 3',5'-cyclic monophosphate (catalyzed by Na^+/K^+-ATPase). Active transport is similar to carrier-mediated (facilitated) diffusion (discussed above) in that transport is mediated by a membrane-associated macromolecule (pump), it is saturable, and it is usually selective for certain drugs/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 or nutrients can be transported across biological membranes by becoming entrapped (in "pits") and internalized (in "vesicles") in varying degrees of selectivity. Sucrose and insulin can be internalized in such a manner.

2.2.5. Bioavailability

Because of the multiple barriers to absorption, the amount of drug that enters the systemic circulation is less than the amount administered (with the exception of intravenous administration). The proportion (fraction or percent) of an administered drug dose that reaches the systemic circulation is the drug's bioavailability. Other factors that affect a drug's bioavailability include the first-pass effect, solubility and stability, and the formulation of the drug (including the quality control of its manufacture). Additionally, 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 influence.

2.3. Metabolism

Drug/nutrient substances are often biotransformed (metabolized) to other substances (metabolites) by a variety of biochemical reactions in a variety of locations throughout the body *(8)*. Almost all tissues can metabolize drugs, but the liver, GI tract, and lungs (for gaseous anesthetics) 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 biochemical reactions that are capable of metabolizing foreign substances. 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 or nutrients can conveniently

be categorized into two broad types: reactions that alter the basic chemical structure of the parent molecule—phase 1 reactions—and reactions that result in attachment of some endogenous substance to the parent molecule—phase 2 or conjugation reactions.

2.3.1. Phase 1 Reactions

Phase 1 type reactions often occur in the cytosol, mitochondria, and microsomes (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 removal of hydrogen from the parent molecule) is a common Phase 1 reaction. Microsomal oxidation is a major mechanism of metabolism of many drugs and nutrients because the 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 extensive system are cytochrome P450 (CYP) reductase and the many isozymes of 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 *(9)*. For example, it is estimated that more than 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 CYP-1A2 isozyme. Because the enzymes are saturable, and can be induced or inhibited, the potential for DNIs exist.

2.3.1.2. Reduction. Reduction reactions (e.g., the addition of hydrogen or removal of oxygen from the parent molecule) occur both in microsomal and nonmicrosomal fractions of hepatic and other cells. Metabolism by reduction is less common than by oxidation for presently used drugs. 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 (Conjugation) Reactions

The coupling (conjugation) of an endogenous substance to a drug or 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 drug or nutrient, which decreases the amount that is reabsorbed through kidney tubules, thereby enhancing the fraction that is excreted in the urine. Conjugation with glucose (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 or nutrient 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 or activity) or inhibited by a variety of chemical substances, including themselves and other drugs or nutrients *(10)*. Induction results in an enhanced metabolism of molecules that are biotransformed by affected pathways and results in a decrease in the levels of parent molecule and increase in levels of metabolites. Biological effect will be decreased if parent is more active than metabolites and increased if parent is a prodrug. The opposite occurs with enzyme inhibition.

2.3.5. Factors That Affect Metabolism

Multiple factors can affect metabolism *(11)*, including genetics, typically manifested as polymorphisms; the chemical properties of the drug or nutrient, which determines the susceptibility to the various types of metabolic reactions; the route of administration, which affects 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 still others.

2.4. Elimination

The biological effects of exogenous substances are terminated by the combined processes of redistribution, metabolism, and elimination *(12)*. The major site of drug elimination in humans is the kidney. Several factors affect the rate and extent of elimination, and accumulation occurs if the rate of absorption and distribution of a drug or nutrient exceeds the rate of elimination.

2.4.1. Routes of Elimination

In humans, the kidney is the most common route for elimination of many drugs, partly because the kidney receives about 20–25% of the cardiac output. Other sites include the lungs (particularly for the gaseous anesthetics), and through the feces, and (usually to a lesser, but no less important, extent) sweat, saliva, blood loss, vomit, breast milk, and so on.

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 molecules that pass into the nephron depends on its physicochemical properties. Lipophilic drugs (or the nonionized form of weak acids or bases) are more likely to be reabsorbed through the wall of the nephron back into the circulation. Hydrophilic drugs (or 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 are possible sites of DNIs.

2.4.2. Rate of Elimination

The rate of elimination of most drugs is described by first-order kinetics (i.e., exponential decay) according to $C_t = C_o e^{-kt}$ relating drug concentration (C_t) at time t to the original concentration (C_o). Other drugs are eliminated by zero-order (linear) kinetics. C_o is reduced by one-half in one *half-life* ($t_{1/2}$). In the case of zero-order elimination, equal amounts are eliminated each subsequent half-life. In the case of first-order elimination, equal fractions are eliminated in each subsequent half-life. In either case, the half-life is a function both of the drug and the conditions of the patient.

2.4.3. Clearance

Rate of elimination (mass/time) is equal to the concentration of drug (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 drug due to elimination (e.g., metabolism and/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 or nutrient 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 intravenous dosing of a drug having first-order elimination kinetics, the mean drug concentration (C_m) can be estimated from the dose (D) and fraction of drug remaining (F) by $C_m = -D/\ln F$. The upper (C_{max}) and lower (C_{min}) bounds can be estimated by $D/(1 - F)$ and $FD/(1 - F)$, respectively. The actual clinical results depend on the patient's individual characteristics.

2.4.5. Factors That Affect Elimination

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

3. PHARMACODYNAMICS

The mechanism of a substance's action on biological tissue involves some modification of or interaction with ongoing physiological processes. In some cases, the target is foreign (e.g., bacteria or viruses) or aberrant (cancer cells). In other cases, the target is part of normal physiology (e.g., enzymes or receptors). Mechanisms of action that are shared or opposed by other drugs or nutrients can lead to interactions. Drug actions are quantified and evaluated by dose–response curves.

3.1. Mechanisms of Action

In the broadest sense, drug effects can be categorized into four major mechanisms *(13)*. They can kill invading organisms (e.g., most 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 the 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 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 of the target that are not shared by humans.

3.1.2. Cancer Chemotherapy

Much of 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.

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 mechanisms of action just discussed do not involve overt efforts to communicate with the normal ongoing physiological processes of the host. The chemical nature of cellular function and the communication within and between cells allows for modulation by endogenous chemical substances, drugs or nutrients. The targets of modulation include enzymes, DNA, and a variety of other molecules involved in the synthesis, storage, or metabolism of endogenous substances. Efforts to modulate processes that involve nervous system control directly or indirectly involve interaction with receptors.

3.2. Receptors

Many drugs interact with macromolecular components of cells that then initiate a chain of events which leads to the drug's effect. In a commonly used analogy, the receptor is like a light switch. A better analogy is that a receptor is like a dimmer switch because there is generally tonic activation. A receptor also serves to limit access to the switch to specific molecules (lock and key fit).

3.2.1. Occupation Theory

The most widely supported theory holds that receptors are activated when specific molecules bind (form weak intermolecular chemical bonds) to them and that the magnitude of such a drug's effect is related to the number (or the fraction of the total) receptors

that are occupied *(14)*. 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 equilibrium reaction—according to D + R ⇔ 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 the gas constant, T is temperature (Kelvin) and K_{eq} is the equilibrium constant *(15)*.

3.2.2. Agonists and Antagonists

The vast majority of chemical substances cannot just fit a binding site on any receptor. Chemicals that 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, $1/K_{eq}$ (often designated as K_d). Only a subset of substances that bind to receptors are also capable of eliciting an effect through the receptor (i.e., have intrinsic activity or efficacy). Substances that have affinity and intrinsic activity are termed *agonists*, substances that have affinity, but not intrinsic activity are termed *antagonists*. Antagonists competitively or noncompetitively inhibit the access of agonists to their receptors. In the body, receptors mediate the effects of endogenous agonists such as neurotransmitters, hormones, peptides, and so on. Therefore, antagonist drugs—although lacking intrinsic activity—can produce biological effects by attenuating the signal of the endogenous agonist.

3.2.3. Signal Fidelity

One of the major functions of receptors is to provide the fidelity of the communication between neurons or other cells. The lock and key fit restricts access to molecules of specific three-dimensional shape. The fit is sufficiently flexible, however, that certain molecules (drugs) having three-dimensional shapes similar to the endogenous ligand can bind to their receptors (with greater or lesser affinity and intrinsic activity). In such cases, the fidelity of the normal signal is maintained by the chain of events that occurs post-receptor occupation (i.e., the signal transduction).

3.2.4. Up- and Down-Regulation

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. Additionally, repeated exposure to an agonist or antagonist can alter the number of expressed receptors. The change in receptor number is often interpreted as the body's attempt to counteract the action of the agonist or antagonist in 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 post-receptor electrophysiological or biochemical sequence of events that lead to an agonist's effect. Broadly, transduction mechanisms can be divided into two types: ionotropic, in which activation of the receptor leads directly to influx of ions (such receptors can actually comprise the ion channel); and metabotropic, in which activation of the receptor actuates a series of biochemical second messengers that mediate the response *(16)*.

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 LGICR usually displays selectivity for certain ions (e.g., Na^+, K^+, Ca^{2+}, or Cl^-). The magnitude or the rate of flow of the ions through the membrane is regulated by the binding of ligand to the LGICR. The receptor can be composed of subunits that can be expressed or coupled in different ways in different cells, thus mediating varied effects. Examples of LGICRs are the nicotinic cholinergic, $GABA_A$, glutamate, glycine receptors.

3.3.2. G Protein-Coupled Receptors

The G protein-coupled receptors (GPCRs) often include seven transmembrane (7-TM) regions, an N-terminal extracellular region, and a C-terminal intracellular region *(17)*. A group of guanosine triphosphate (GTP) protein subtypes are coupled to the receptor. Ligand activation of a GPCR induces guanosine 5'-diphosphate (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 *(18)*.

3.3.3. Tyrosine Kinase Receptors

These 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

These intracellular receptors modulate the activity of DNA or other regulatory molecules located within the nucleus and, consequently, the activation or 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 a dose and the corresponding response is a useful measure of drug–nutrient action from both a mechanistic and a practical standpoint. For example, the most commonly observed shape of a dose–response curve is consonant with the occupation theory. Given a reaction scheme of the form $D + R \Leftrightarrow DR$, it follows that the shape of the dose–response curve should be of the form that is actually observed experimentally (hyperbolic) *(19)*. Additionally, certain features of a dose–response curve—or a comparison between them—can yield valuable clinically useful information, such as a measure of relative potency or efficacy.

Several ways of displaying a dose–response curve are described in the following. The type of display can affect certain mathematical (statistical) analyses of the data, but this is beyond the present scope *(20)*.

3.4.1. Quantal

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

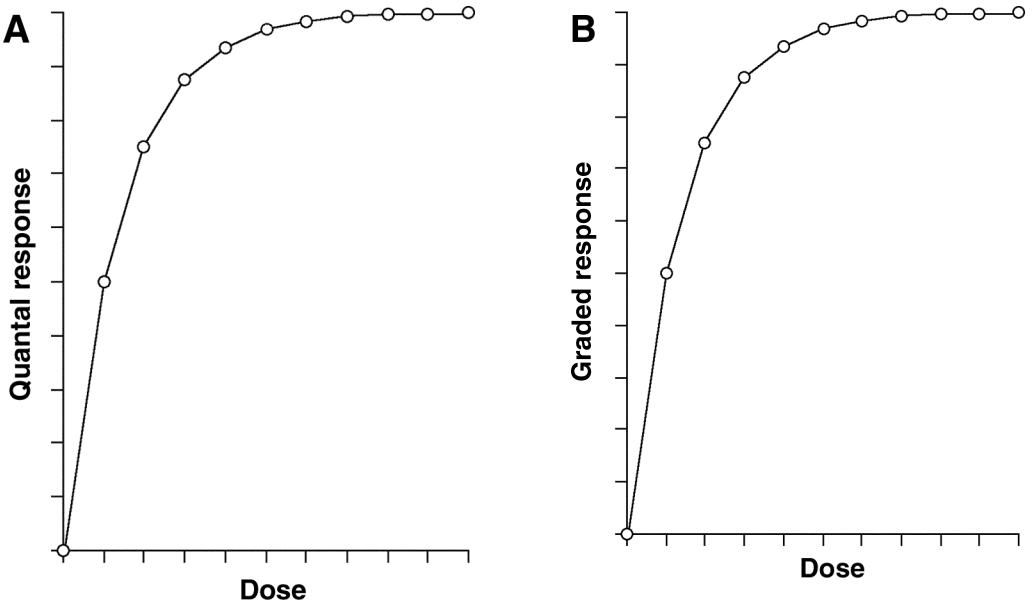

Fig. 2. (**A**) A quantal dose–response curve on rectangular coordinates. (**B**) A graded dose–response curve on rectangular coordinates.

coordinates, the set of points that are derived from plotting response against the administered dose (plotted along an abscissa; the *x*-axis) typically forms a pattern that approximates a rectangular hyperbola (Fig. 2A).

3.4.2. Graded

A graded dose–response curve is one in which the dependent variable (usually plotted along an ordinate; the *y*-axis) is measured using a continuous scale (e.g., systolic blood pressure in mmHg). As with a quantal response, if plotted on rectangular coordinates, the set of points derived from plotting the measured response against the administered dose (plotted along an abscissa; the *x*-axis) typically forms a pattern that approximates a rectangular hyperbola (Fig. 2B).

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. 3). This has become so customary that such a plot is often what is meant by a dose–response curve.

3.4.4. Potency and Efficacy

From a dose–response curve it is possible to estimate the dose that would produce a specified level of effect. The choice of level is arbitrary, but the 50% effect level is convenient and commonly selected. The dose of drug estimated to produce 50% effect is termed the *ED50* (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

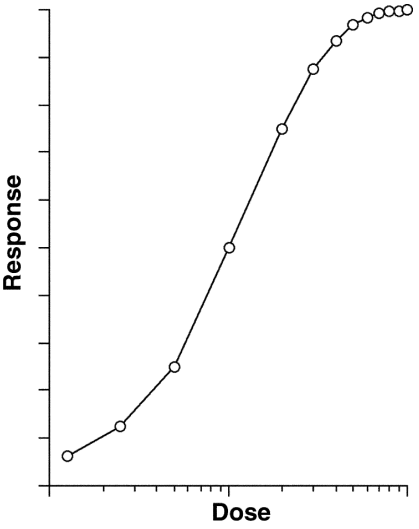

Fig. 3. Quantal or graded dose–response data plotted against $\log_{10}$(dose).

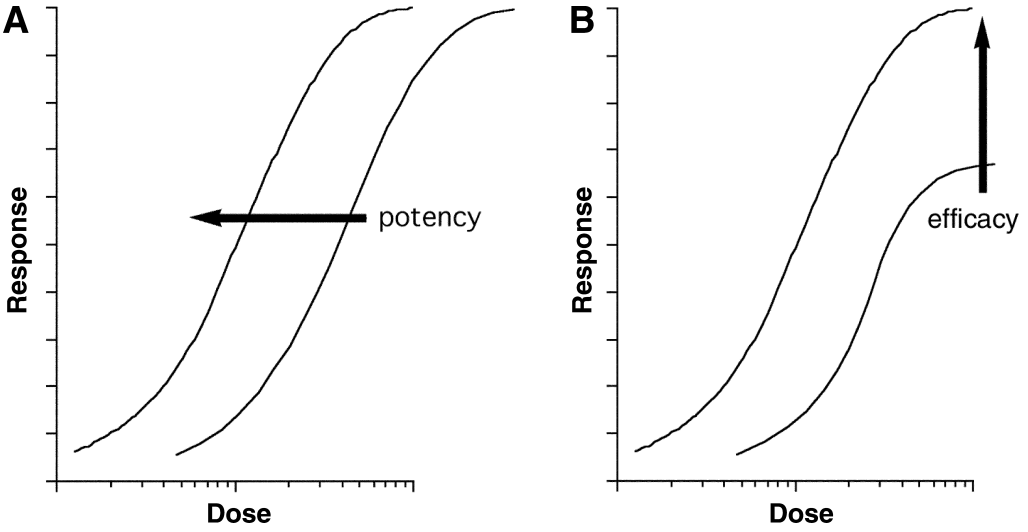

Fig. 4. (**A**) Potency is indicated by the location of a dose–response curve along the *x*-axis. (**B**) Efficacy is indicated by the maximal-attainable level of effect.

to the amount of substance required to produce a specified level of effect (Fig. 4A). Efficacy is a term that refers to a substance's maximal achievable level of effect (Fig. 4B). Potency and efficacy are independent characteristics.

3.4.5. Antagonism

Antagonists, although lacking intrinsic activity, can produce effects when they attenuate the action of an endogenous agonist involved in a pathway that is tonically active and is in opposition to another pathway. For example, antagonists of the muscarinic cholinergic receptor attenuate the parasympathetic influence on heart rate, with consequent increase in heart rate owing to the less opposed influence of the sympathetic subdivision. Hence, such effects of an antagonist can be characterized by dose–response curves.

4. CONCLUSION

The principles of drug disposition and response outlined in this chapter form the basis for understanding DNIs discussed throughout this volume.

REFERENCES

1. Rang HP, Dale MM, Ritter JM, et al. Pharmacology. Churchill Livingstone, New York, NY, 1995, pp. 74–79.
2. Jacob LS. NMS Pharmacology (4th ed.). Williams & Wilkins, Philadelphia, PA, 1996, pp. 3–4.
3. 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.
4. 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.). Churchill Livingstone, New York, NY, 1990, pp. 231–236.
5. Holford NHG, Benet LZ. Pharmacokinetics and pharmacodynamics: dose selection & the time course of drug action. In: Katzung BG, ed. Basic & Clinical Pharmacology (7th ed.). Appleton & Lange, Stamford, CT, 1998, pp. 34–49.
6. 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.
7. Levine RR. Pharmacology: Drug Actions and Reactions (5th ed.). Parthenon, New York, NY, 1996, pp. 51–74.
8. Benet LZ, Kroetz DL, Sheiner LB. Pharmacokinetics: the dynamics of drug absorption, distribution, and elimination. In: Hardman JG, Limbird LE, eds. Goodman & Gilman's the Pharmacological Basis of Therapeutics (9th ed.). McGraw-Hill, New York, NY, 1996, pp. 11–16.
9. Lin JH, Lu AYH. Inhibition and induction of cytochrome P450 and the clinical implications. Clin Pharmacokinet 1998;35:361–390.
10. Park BK, Kitteringham NR, Pirmohamed M, et al. Relevance of induction of human drug-metabolizing enzymes: pharmacological and toxicological implications. Brit J Clin Pharmacol 1996;41:477–491.
11. Lin JH, Lu AYH. Interindividual variability in inhibition and induction of cytochrome P450 enzymes. Annu Rev Pharmacol Toxicol 2001;41:535–567.
12. Shargel L, Yu ABC. Applied Biopharmaceutics and Pharmacokinetics (3rd ed.). Appleton & Lange, Stamford, CT, 1993, pp. 265–292.
13. Raffa RB. Mechanisms of drug action. In: Raffa RB, ed. Quick Look Pharmacology. Fence Creek, Madison, CT, 1999, pp. 14–15.
14. Boeynaems JM, Dumont JE. Outlines of Receptor Theory. Elsevier/North-Holland, Amsterdam, 1980.
15. Raffa RB. Drug-Receptor Thermodynamics: Introduction and Applications. Wiley, Chichester, UK, 2001.
16. Roerig SC. Drug receptors and signaling. In: Raffa RB, ed. Quick Look Pharmacology. Fence Creek, Madison, CT, 1999, pp. 16–17.

17. Strader CD, Fong TM, Tota MR, et al. Structure and function of G protein-coupled receptors. Annu Rev Biochem 1994;63:101–132.
18. Gudermann T, Kalkbrenner F, Schultz G. Diversity and selectivity of receptor-G protein interaction. Annu Rev Pharmacol Toxicol 1996;36:429–459.
19. Tallarida RJ, Jacob LS. The Dose–Response Relation in Pharmacology. Springer-Verlag, New York, NY, 1979.
20. Tallarida RJ. Drug Synergism and Dose-Effect Data Analysis. Chapman & Hall/CRC, Boca Raton, FL, 2000.