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STOELTING'S

Pharmacology & Physiology in Anesthetic Practice

5th Edition

Pamela Flood
James P. Rathmell
Steven Shafer

Wolters Kluwer

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Pamela Flood, MD, MA

Professor of Anesthesiology, Perioperative and Pain Medicine
Stanford University
Palo Alto, California

James P. Rathmell, MD

Executive Vice Chair and Chief, Division of Pain Medicine
Department of Anesthesia, Critical Care and Pain Medicine
Massachusetts General Hospital
Henry Knowles Beecher Professor of Anaesthesia, Harvard Medical School
Boston, Massachusetts

Steven Shafer, MD

Professor of Anesthesiology, Perioperative and Pain Medicine
Stanford University
Palo Alto, California

Wolters Kluwer

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CONTRIBUTORS

Nicholas Anast, MD

Cardiovascular Anesthesia Fellow
Stanford University
Palo Alto, California

Bihua Bie, MD, PhD

Postdoctoral Research Fellow
Anesthesiology Institute
Cleveland Clinic
Cleveland, Ohio

Mark Burbridge, MD

Clinical Instructor
Stanford University
Palo Alto, California

Kenneth Cummings III, MD, MS

Assistant Professor of Anesthesiology
Anesthesiology Institute
Cleveland Clinic
Cleveland, Ohio

Hesham Elsharkawy, MD, MSc

Assistant Professor of Anesthesiology
Cleveland Clinic Lerner College of Medicine
Staff
Department of Outcomes Research
Anesthesiology Institute
Cleveland Clinic
Cleveland, Ohio

Pamela Flood, MD, MA

Professor of Anesthesiology, Perioperative and Pain Medicine
Stanford University
Palo Alto, California

Sumeet Goswami, MD, MPH

Associate Professor of Anesthesiology
Columbia University Medical Center
New York, New York

David A. Grossblatt, MD

Postdoctoral Residency Fellow
Mayo Clinic
Phoenix, Arizona

Jonathan Hastie, MD

Assistant Professor of Anesthesiology
Department of Anesthesiology
Columbia University Medical Center
New York, New York

Maya Jalbout Hastie, MD

Assistant Professor of Anesthesiology
Department of Anesthesiology
Columbia University Medical Center
New York, New York

Bessie Kachulis, MD

Assistant Professor of Anesthesiology
Department of Anesthesiology
Columbia University Medical Center
New York, New York

Mihir M. Kamdar, MD

Instructor, Harvard Medical School
Associate Director, Palliative Care Service
Massachusetts General Hospital
Boston, Massachusetts

Joseph Kwok, MD

Clinical Instructor
Department of Anesthesiology and Pain Medicine
Stanford University School of Medicine
Stanford, California

Barrett Larson, MD

Resident in Anesthesiology
Department of Anesthesiology, Perioperative, and Pain Medicine
Stanford University School of Medicine
Stanford, California

Jerrold H. Levy, MD

Professor of Anesthesiology
Associate Professor of Surgery
Codirector
Cardiothoracic Intensive Care Unit
Duke University School of Medicine
Durham, North Carolina

Sansan S. Lo, MD

Assistant Professor of Anesthesiology
Division of Cardiothoracic Anesthesia
Columbia University
New York, New York

Kamal Maheshwari, MD

Staff Anesthesiologist
Regional Anesthesia and Acute Pain Management
Department of Outcomes Research
Cleveland Clinic
Cleveland, Ohio

Jillian A. Maloney, MD

Department of Anesthesiology
Mayo Clinic
Phoenix, Arizona

Steven Miller, MD

Assistant Professor
Department of Anesthesiology
Columbia University Medical Center
New York-Presbyterian Hospital
New York, New York

Vivek K. Moitra, MD

Associate Professor of Anesthesiology
Department of Anesthesiology
Division of Critical Care
Columbia University Medical Center
New York, New York

Teresa A. Mulaikal, MD

Assistant Professor of Anesthesiology
Columbia University Medical Center
Divisions of Cardiothoracic and Critical Care Medicine,
Department of Anesthesiology
Columbia University Medical Center
New York, New York

Michael J. Murray, MD, PhD

Consultant
Department of Anesthesiology
Mayo Clinic
Phoenix, Arizona
Professor of Anesthesiology
Mayo Medical School
Scottsdale, Arizona

Mohamed A. Naguib, MD, MSc, FFARCSI

Professor of Anesthesiology
Cleveland Clinic Lerner College of Medicine
Faculty
Department of General Anesthesiology
Cleveland Clinic
Cleveland, Ohio

Carter Peatross, MD

Cardiovascular and Thoracic Anesthesiology Fellow
Mayo Clinic
Rochester, Minnesota

James Ramsay, MD

Professor of Anesthesiology
Department of Anesthesia and Perioperative Care
University of California
San Francisco, California

James P. Rathmell, MD

Executive Vice Chair and Chief, Division of Pain Medicine
Department of Anesthesia, Critical Care and Pain Medicine
Massachusetts General Hospital
Henry Knowles Beecher Professor of Anaesthesia,
Harvard Medical School
Boston, Massachusetts

Carl E. Rosow, MD, PhD

Professor
Department of Anesthesia, Critical Care and Pain Medicine
Massachusetts General Hospital
Boston, Massachusetts

Steven Shafer, MD

Professor of Anesthesiology, Perioperative and Pain Medicine
Stanford University
Palo Alto, California

Jack S. Shanewise, MD, FASE

Professor of Anesthesiology
Columbia University Medical Center
New York, New York

Peter Slinger, MD, FRCPC

Professor of Anesthesiology
University of Toronto
Toronto, Canada

Sarah C. Smith, MD

Assistant Professor of Anesthesiology
Division of Cardiothoracic Anesthesiology
Department of Anesthesiology
Columbia University Medical Center
New York, New York

Jessica Spellman, MD

Assistant Professor of Anesthesiology
Department of Anesthesiology
Division of Adult Cardiothoracic Anesthesiology
Columbia University Medical Center
New York, New York

Robert K. Stoelting, MD

Emeritus Professor
Department of Anesthesia
Indiana University School of Medicine
Indianapolis, Indiana

Hui Yang, MD, PhD

Anesthesiology Institute
Cleveland Clinic
Cleveland, Ohio

FOREWORD

My journey with *Pharmacology and Physiology in Anesthetic Practice* began in the early 1980s with what seemed an impossible dream, a single-author anesthesia textbook devoted to the *daily application of principles of pharmacology and physiology in the care of patients*. Many yellow tablets later (my computer skills were in their infancy), an understanding family, residents and faculty in the Department of Anesthesia at Indiana University School of Medicine, and the unwavering support and encouragement of a special friend and publisher, the first edition of *Pharmacology and Physiology in Anesthetic Practice* appeared in the fall of 1986.

The acceptance of the textbook by students, trainees, and practitioners over the years has been incredibly rewarding to me personally and served as the stimulus to create revisions for the next three editions with Simon C. Hillier, MB, ChB joining me as a coeditor for the fourth edition that appeared in 2006.

It is clearly time for a new edition and a new approach if *Pharmacology and Physiology in Anesthetic Practice* is going to continue to meet its original goal of *providing an in-depth but concise and current presentation of those aspects of pharmacology and physiology that are relevant either directly or indirectly to the perioperative anesthetic management of patients*.

In this regard, I could not be more pleased and honored that Drs. James P. Rathmell, Steven Shafer, and Pamela Flood agreed to act as coeditors of a multiauthored fifth edition. Their unique expertise and access to recognized authorities in the wide and expanding areas of pharmacology and physiology that impact the perioperative care of patients is clearly evident in this fifth edition.

On behalf of myself and all our past (and future) readers, I thank the new coeditors and their authors for keeping *Stoelting's Pharmacology and Physiology in Anesthetic Practice* current with the times and fulfilling the dream I had more than 30 years ago.

Robert K. Stoelting, MD

PREFACE TO THE FIFTH EDITION

Robert Stoelting is among the best writers in our specialty. His signature textbook, *Pharmacology and Physiology in Anesthetic Practice*, resonated with residents and young faculty, including us, because it was exceptionally well written. Dr. Stoelting's clear prose succinctly covered the drugs we were using in our daily practice. His explanations of physiology were intuitive and sensible. Every chapter in the earlier editions spoke with the same voice, reflecting the many years he invested in a single-authored textbook. Even though Dr. Hillier joined him as coauthor of the fourth edition, the text always resonated as a single voice.

When first approached about revising the textbook, we turned down the project. It seemed impossible to reproduce the clarity of Dr. Stoelting's work. However, the option for the publisher was to transform *Pharmacology and Physiology in Anesthetic Practice* into a conventional multiauthored textbook. That felt like sacrilege, reducing one of the revered texts in our specialty to a "me too" multiauthored textbook. We agreed to take on the task.

It took a half decade longer than expected. Too much had changed in the 30 years since Dr. Stoelting produced his initial textbook to simply revise the chapters. The textbook required a complete reorganization. Every chapter was nearly completely rewritten.

The job was too much for one person or even three. We chose a hybrid model, in which a small number of authors oversaw major blocks. The final editing was done by two editors, Flood and Rathmell, to approximate the single voice that distinguished the first four editions.

We have to acknowledge the efforts of our publishers Brian Brown and Nicole Dernoski, who never gave up on us during the 7 years it took to produce this textbook. The final book reflects their dedication to Dr. Stoelting's textbook. They knew he had created a gem. They were determined to keep it polished.

We are proud to bring the fifth edition of Dr. Stoelting's textbook to anesthesiology residents, clinicians, and investigators. The name has been changed, forever, to reflect where this started. It is now *Stoelting's Pharmacology and Physiology in Anesthetic Practice*. Making no pretense of reproducing the elegant writing of Dr. Stoelting's original textbook, we have tried to capture the current state-of-the-art in anesthetic pharmacology and physiology.

Is everything in this book correct? No. The authors of each chapter have imperfect understanding; knowledge changes and mistakes happen. Wikipedia brilliantly addresses this by allowing readers who catch errors to fix them. We can't implement the Wikipedia approach in a textbook, but we can come close by inviting you, the reader compulsive enough to read the Preface, to bring any errors, corrections, or suggestions to our attention. The e-mail address is StoeltingSuggestions@gmail.com. We invite our readers to become "peer reviewers," pointing out errors, out-of-date references, drugs no longer used, or missing content relevant to pharmacology and physiology in anesthesia practice. In this manner, readers will become collaborators for all future editions.

This fifth edition is our tribute to the profound contribution to education and clinical practice made by Dr. Stoelting with his now eponymous textbook.

Pamela Flood, MD
James P. Rathmell, MD
Steven Shafer, MD

CONTENTS

CHAPTER 1

Basic Principles of Physiology

Pamela Flood • Steven Shafer

This chapter will review the basic principles of the composition of the body and the structure of cells. Although very basic, these principles are essential for everything that follows.

Body Composition

Water is the most abundant single constituent of the body and is the medium in which all metabolic reactions occur. Water accounts for about 60% of the weight in an adult man and about 50% of the body weight in an adult woman (Fig. 1-1)[1]; the difference is due to increased body fat in women. In a neonate, total body water may represent 70% of body weight. Total body water is less in obese individuals, reflecting the decreased water content of adipose tissue. Advanced age is also associated with increased fat content and decreased total body water (Table 1-1).

Body fluids can be divided into intracellular and extracellular fluid, depending on their location relative to the cell membrane (see Fig. 1-1).[1] Approximately two-thirds of the total body fluid in an adult are contained inside the estimated 100 trillion cells of the body. The fluid in these cells, despite individual differences in constituents, is collectively designated ***intracellular flu d***. The one-third of fluid outside the cells is referred to as ***extracellular fluid***. Extracellular fluid is divided into interstitial fluid and plasma (intravascular fluid) by the capillary membrane (see Fig. 1-1).[1]

Interstitial fluid is present in the spaces between cells. An estimated 99% of this fluid is held in the gel structure of the interstitial space. Plasma is the noncellular portion of blood. The average plasma volume is 3 L, a little over half of the blood volume of 5 L. Plasma is in dynamic equilibrium with the interstitial fluid through pores in the capillaries; the interstitial fluid serving as a reservoir from which water and electrolytes can be mobilized into the circulation. Loss of plasma volume from the intravascular space is minimized by colloid osmotic pressure exerted by the plasma proteins.

Other extracellular fluid that may be considered as part of the interstitial fluid includes cerebrospinal fluid, gastrointestinal fluid (because it is mostly resorbed), and fluid in potential spaces (pleural space, pericardial space, peritoneal cavity, synovial cavities). Excess amounts of fluid in the interstitial space manifest as peripheral edema.

The normal daily intake of water (drink and internal product of food metabolism) by an adult averages 2.5 L, of which about 1.5 L is excreted as urine, 100 mL is lost in sweat, and 100 mL is present in feces. All gases that are inhaled become saturated with water vapor (47 mm Hg at 37°C). This water vapor is subsequently exhaled, accounting for an average daily water loss through the lungs of 300 to 400 mL. The water content of inhaled gases decreases with decreases in ambient air temperature such that more endogenous water is required to achieve a saturated water vapor pressure at body temperature. As a result, insensible water loss from the lungs is greatest in cold environments and least in warm temperatures. The remaining 400 mL i s lost by diffusion through the skin. This is insensible water loss, not perceived as sweat. Insensible water loss is limited by the mostly impermeable layer of the skin (cornified squamous epithelium). When the cornified layer is removed or interrupted, as after burn injury, the loss of water through the skin is greatly increased.

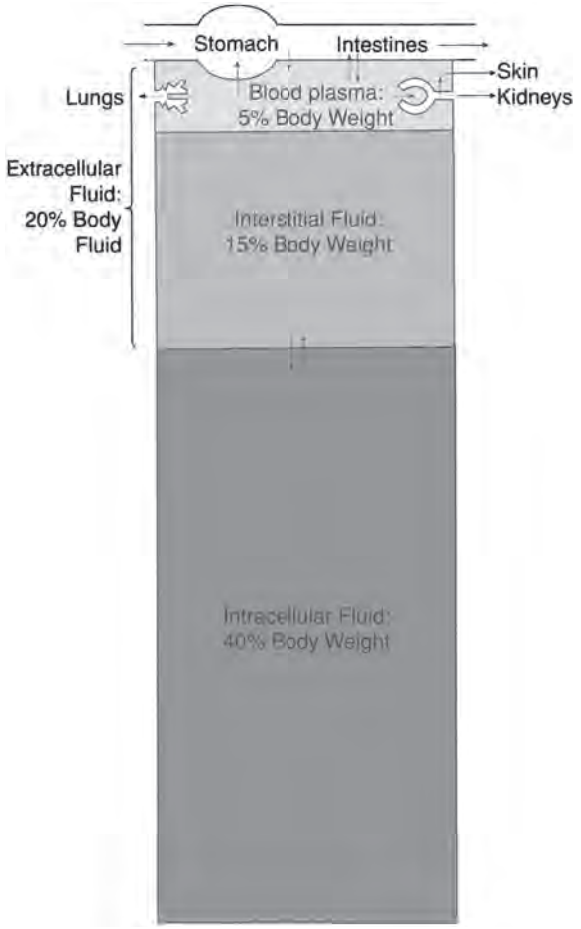

FIGURE 1-1 Body fluid compartments and the percentage of body weight represented by each compartment. The location relative to the capillary membrane divides extracellular fluid into plasma or interstitial fluid. *Arrows* represent fluid movement between compartments. (From Gamble JL. *Chemical Anatomy, Physiology, and Pathology of Extracellular Fluid*. 6th ed. Boston, MA: Harvard University Press; 1954, with permission.)

Blood Volume

Blood contains extracellular fluid, the plasma, and intracellular fluid, mostly held in erythrocytes. The body has multiple systems to maintain intravascular fluid volume, including renin-angiotensin system, and arginine vasopressin (antidiuretic hormone) that increase fluid reabsorption in the kidney and evoke changes in the renal tubules that lead to restoration of intravascular fluid volume (see Chapter 17).

The average blood volume of an adult is 5 L, comprising about 3 L of plasma and 2 L of erythrocytes. These volumes vary with age, weight, and gender. For example, in nonobese individuals, the blood volume varies in direct proportion to the body weight, averaging 70 mL/kg for lean men and women. The greater the ratio of fat to body weight, however, the less is the blood volume in milliliter per kilogram because adipose tissue has a decreased vascular supply. The hematocrit or packed cell volume is approximately the erythrocyte fraction of blood volume. The normal hematocrit is about 45% for men and postmenopausal women and about 38% for menstruating women, with a range of approximately ± 5%.

Table 1-1

Total Body Water by Age and Gender

	Total Body Water	
Age (yrs)	Men (%)	Women (%)
18–40	61	51
40–60	55	47
>60	52	46

Constituents of Body Fluid Compartments

The constituents of plasma, interstitial fluid, and intracellular fluid are identical, but the quantity of each substance varies among the compartments (Fig. 1-2).[2] The most striking differences are the low protein content in interstitial fluid compared with intracellular fluid and plasma and the fact that sodium and chloride ions are largely extracellular, whereas most of the potassium ions (approximately 90%) are intracellular. This unequal distribution of ions results in establishment of a potential (voltage) difference across cell membranes.

The constituents of extracellular fluid are carefully regulated by the kidneys so that cells are bathed in a fluid containing the proper concentrations of electrolytes and nutrients. The normal amount of sodium and potassium in the body is about 58 mEq/kg and 45mEq/kg, respectively (note that normal serum level of sodium is 137 to 142 mEq/L and potassium is 3.5 to 5.5 mEq/L, reflecting the intracellular and extracellular predominance of each electrolyte). Trauma is associated with progressive loss of potassium through the kidneys due in large part to the increased secretion of vasopressin and in variable part (depending on the type of surgery) to the role of nasogastric suctioning and direct potassium loss. For example, a patient undergoing surgery excretes about 100 mEq of potassium in the first 48 hours postoperatively and, after this period, about 25 mEq daily. Plasma potassium concentrations are not good indicators of total body potassium content because most potassium is intracellular. There is a correlation, however, between the potassium and hydrogen ion content of plasma; the two are increasing and decreasing together.

Osmosis

Osmosis is the movement of water (solvent molecules) across a semipermeable membrane from a compartment in which the nondiffusible solute (ion) concentration is

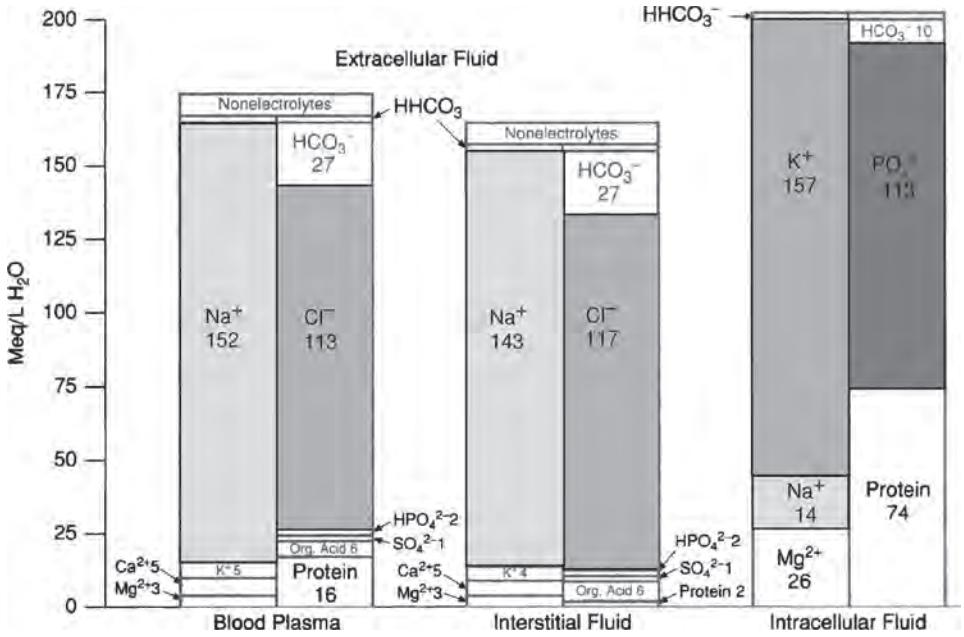

FIGURE 1-2 Electrolyte composition of body fluid compartments. (From Leaf A, Newburgh LH. *Significance of the Body Fluids in Chemical Medicine*. 2nd ed. Springfield, IL: Thomas; 1955, with permission.)

lower to a compartment in which the solute concentration is higher (Fig. 1-3).[3] The lipid bilayer that surrounds all cells is freely permeable to water but is impermeable to ions. As a result, water rapidly moves across the cell membrane to establish osmotic equilibration, which happens almost instantly.

Cells control their size by controlling intracellular osmotic pressure. The maintenance of a normal cell volume and pressure depends on sodium–potassium adenosine triphosphatase (ATPase) (sodium–potassium exchange pump), which maintains the intracellular–extracellular ionic balance by removing three sodium ions from the cell for every two potassium ions brought into the cell. The sodium–potassium pump also maintains the transmembrane electrical potential and the sodium and potassium concentration gradients that power many cellular processes, including neural conduction.

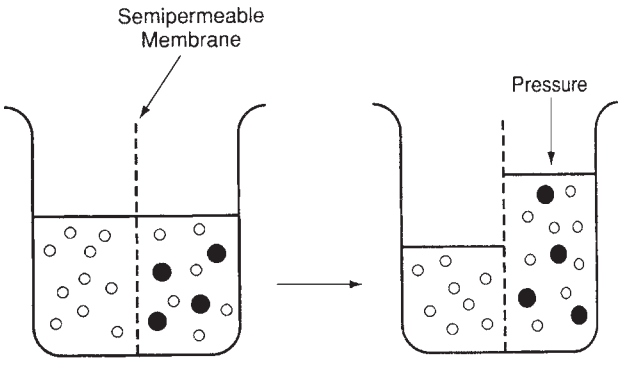

FIGURE 1-3 Diagrammatic representation of osmosis depicting water molecules *(open circles)* and solute molecules *(solid circles)* separated by a semipermeable membrane. Water molecules move across the semipermeable membrane to the area of higher concentration of solute molecules. Osmotic pressure is the pressure that would have to be applied to prevent continued movement of water molecules. (From Ganong WF. *Review of Medical Physiology*. 21st ed. New York, NY: Lange Medical Books/McGraw-Hill; 2003.)

The osmotic pressure exerted by nondiffusible particles in a solution is determined by the number of particles in the solution (degree of ionization) and not the type of particles (molecular weight) (see Fig. 1-3).[3] Thus a 1-mol solution of glucose or albumin and 0.5-mol solution of sodium chloride exert the same osmotic pressure, because the sodium chloride exists as independent sodium and chloride ions, each having a concentration of 0.5 mol. Osmole is the unit used to express osmotic pressure in solutes, but the denominator for osmolality is kilogram of *water*. ***Osmolarity*** is the correct terminology when osmole concentrations are expressed in liters of body fluid (e.g., plasma) rather than kilogram of water (***osmolality***). Because it is much easier to express body fluids in liters of fluid rather than kilograms of free water, almost all physiology calculations are based on osmolarity. Plasma osmolarity is important in evaluating dehydration, overhydration, and electrolyte abnormalities.

Normal plasma has an osmolarity of about 290 mOsm/L. All but about 20 mOsm of the 290 mOsm in each liter of plasma are contributed by sodium ions and their accompanying anions, principally chloride and bicarbonate. Proteins normally contribute <1 mOsm/L. The major nonelectrolytes of plasma are glucose and urea, and these substances can contribute significantly to plasma osmolarity when hyperglycemia or uremia is present, as suggested by the standard calculation of plasma osmolarity:

$$\text{Plasma osmolarity} = 2\,(Na^+) + 0.055\,(\text{glucose}) + 0.36\,(\text{blood urea nitrogen}).$$

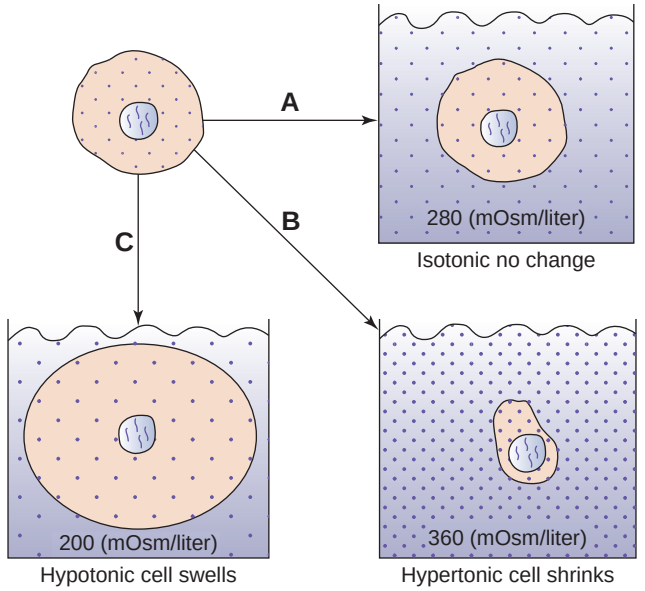

FIGURE 1-4 Effects of isotonic *(A)*, hypertonic *(B)*, and hypotonic *(C)* solutions on cell volume. (Modified from Guyton AC, Hall JE. *Textbook of Medical Physiology*. 10th ed. Philadelphia, PA: W.B. Saunders; 2000.)

Tonicity of Fluids

Packed erythrocytes must be suspended in ***isotonic*** solutions to avoid damaging the cells (e.g., Fig. 1-4).[4] A 0.9% solution of sodium chloride is isotonic and remains so because there is no net movement of the osmotically active particles in the solution into cells, and the particles are not metabolized. A solution of 5% glucose in water is initially isotonic when infused, but glucose is metabolized, so the net effect is that of infusing a hypotonic solution. Lactated Ringer solution plus 5% glucose is initially hypertonic (about 560 mOsm/L), but as glucose is metabolized, the solution becomes less hypertonic.

Fluid Management

The goal of fluid management is to maintain normovolemia and thus hemodynamic stability. Crystalloids consist of water; electrolytes; and, occasionally, glucose that freely distribute along a concentration gradient between the two extracellular spaces. After 20 to 30 minutes, an estimated 75% to 80% of an isotonic saline or a lactate-containing solution will have distributed outside the confines of the circulation, thus limiting the efficacy of these solutions in treating hypovolemia. Indeed, the ability of crystalloids to restore perfusion in the microcirculation is doubtful.[5]

Hypotonic intravenous fluids equilibrate with extracellular fluid, causing it to become hypotonic with respect to intracellular fluid. When this occurs, osmosis rapidly increases intracellular water, causing cellular swelling. Increased intracellular fluid volume is particularly undesirable in patients with intracranial mass lesions or increased intracranial pressure. Protection from excessive fluid accumulation in the interstitium (extravascular lung water) is mediated by lymphatic flow, which can increase as much as 10-fold.

Hypertonic saline solutions (7.5% sodium chloride) have been useful for rapid intravascular fluid repletion during resuscitation as during hemorrhagic and septic shock. Hypertonic saline solutions compare favorably with mannitol for lowering intracranial pressure.[6] The primary effect of hypertonic saline solutions (increase systemic blood pressure and decrease intracranial pressure) most likely reflects increased intravascular fluid volume because of fluid shifts and movement of water away from uninjured regions of the brain. The use of hypertonic saline solutions is viewed as short-term treatment as hypertonicity and hypernatremia are likely with sustained administration. Furthermore, patients with hypotension due to traumatic brain injury who received prehospital resuscitation with hypertonic saline solutions have similar neurologic outcomes to those treated with conventional fluids when assessed 6 months after the initial injury.[7]

Dehydration

Loss of water by gastrointestinal or renal routes or by diaphoresis (excessive sweating) is associated with an initial deficit in extracellular fluid volume. At the same instant, intracellular water passes to the extracellular fluid compartment by osmosis, thus keeping the osmolarity in both compartments equal despite decreased absolute volume (dehydration) of both compartments. The ratio of extracellular fluid to intracellular fluid is greater in infants than adults, but the absolute volume of extracellular fluid is obviously less, explaining why dehydration develops more rapidly and is often more severe in the very young. Clinical signs of dehydration are likely when about 5% to 10% (severe dehydration) of total body fluids have been lost in a brief period of time. Physiologic mechanisms can usually compensate for acute loss of 15% to 25% of the intravascular fluid volume, whereas a greater loss places the patient at risk for hemodynamic decompensation.

Cell Structure and Function

The basic living unit of the body is the cell. It is estimated that the entire body consists of 100 trillion or more cells, of which (amazingly) about 25 trillion are red blood cells.[4] Each organ is a mass of cells held together by intracellular supporting structures. A common characteristic of all cells is dependence on oxygen to combine with nutrients (carbohydrates, lipids, proteins) to release energy necessary for cellular function. Almost every cell is within 25 to 50 μm of a capillary, assuring prompt diffusion of oxygen to cells. All cells exist in nearly the same composition of extracellular fluid (***milieu interieur*** or interior milieu, the extracellular fluid environment), and the organs of the body (lungs, kidneys, gastrointestinal tract) function to

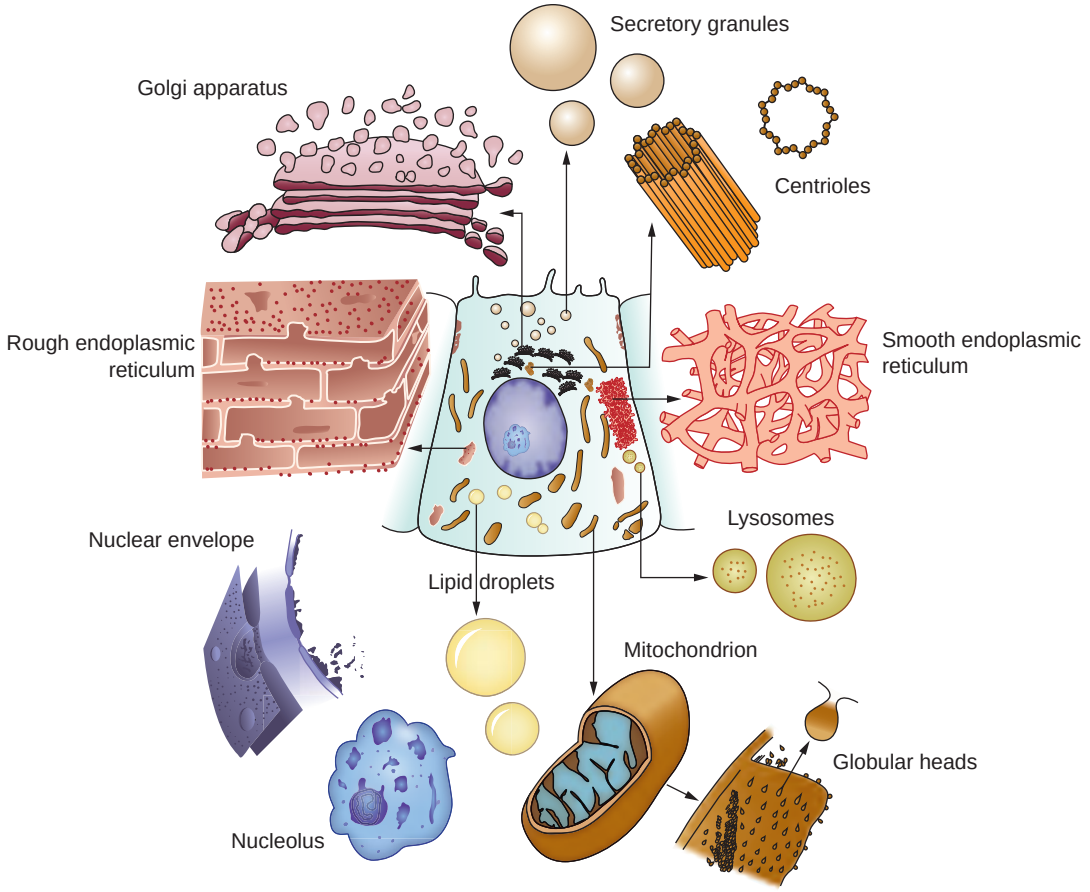

FIGURE 1-5 Schematic diagram of a hypothetical cell *(center)* and its organelles.

maintain a constant composition (homeostasis) of extracellular fl id.

Cell Anatomy

The principal components of cells include the nucleus (except for mature red blood cells), and the cytoplasm, which contains structures known as ***organelles*** (Fig. 1-5).[8] The nucleus is separated from the cytoplasm by a nuclear membrane, and the cytoplasm is separated from surrounding fluids by a cell (plasma) membrane. The membranes around the cell, the nucleus, and organelles are lipid bilayers.

Cell Membrane

Each cell is surrounded by a lipid bilayer that acts as a permeability barrier, allowing the cell to maintain a cytoplasmic composition different from the extracellular fluid. Proteins and phospholipids are the most abundant constituents of cell membranes (Table 1-2). The lipid bilayer is interspersed with large globular proteins (Fig. 1-6).[9] The lipid bilayer of cell membranes is readily permeable to water, both through passive diffusion and through aquaporins, specialized proteins in the membrane that function as water channels (described in the following text). Lipid bilayers are nearly impermeable to water-soluble substances, such as ions and glucose. Conversely, fat-soluble substances (e.g., steroids) and gases readily cross cell membranes.

There are several types of proteins in the cell membrane (see Table 1-2). In addition to structural proteins

Table 1-2

Cell Membrane Composition

Phospholipids
Lecithins (phosphatidylcholines)
Sphingomyelins
Amino phospholipids (phosphatidylethanolamine)
Proteins
Structural proteins (microtubules)
Transport proteins (sodium–potassium ATPase)
Ion channels
Receptors
Enzymes (adenylate cyclase)

ATPase, adenosine triphosphatase.

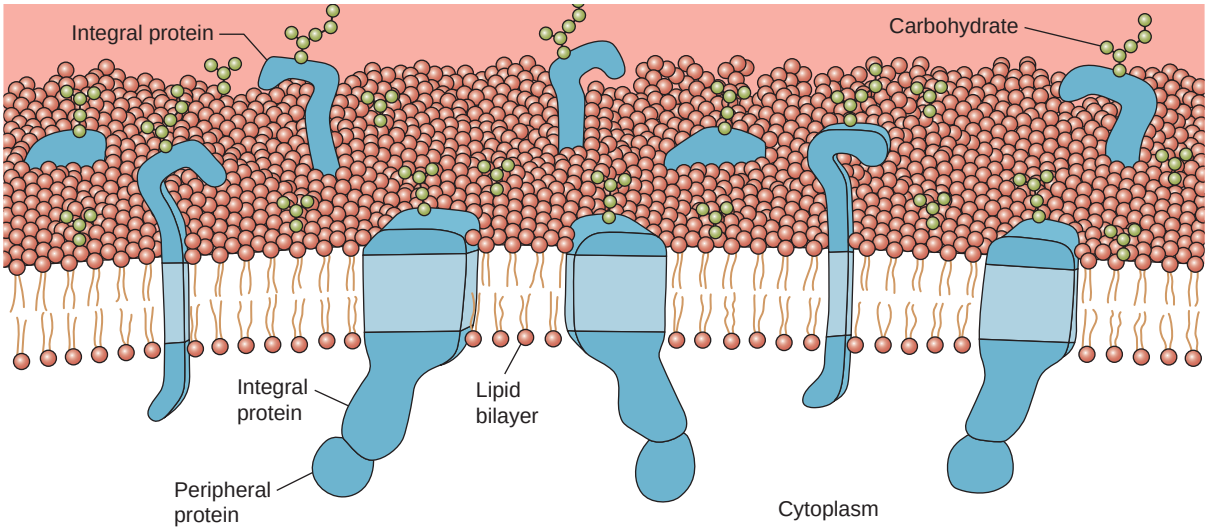

FIGURE 1-6 The cell membrane is a two molecule–thick lipid bilayer containing protein molecules that extend through the bilayer.

(microtubules), there are transport proteins (sodium–potassium adenosine ATPase) that function as pumps, actively transporting ions across cell membranes. Other proteins function as passive channels for ions that can be opened or closed by changes in the conformation of the protein. There are proteins that function as receptors to bind ligands (hormones or neurotransmitters), thus initiating physiologic changes inside cells. Another group of proteins functions as enzymes (adenylate cyclase) catalyzing reactions at the surface of cell membranes. The protein structure of cell membranes, especially the enzyme content, varies from cell to cell.

Transfer of Molecules through Cell Membranes

Diffusion

Oxygen, carbon dioxide, and nitrogen move through cell membranes by simple diffusion through the lipid bilayer. Because of the slowness of diffusion over macroscopic distances, organisms have developed circulatory systems to deliver nutrients within reasonable diffusion ranges of cells (Table 1-3). Water is also able to diffuse through cells, although not as freely as gases. Lipids generally diffuse readily through the lipid bilayer. However, cell membranes are virtually impermeable to ions and charged water-soluble molecules, especially those with molecular weights of greater than 200 daltons.

Poorly lipid-soluble substances, such as glucose and amino acids, may pass through lipid bilayers by facilitated diffusion. For example, glucose combines with a carrier to form a complex that is lipid soluble. This lipid-soluble complex can diffuse to the interior of the cell membrane where glucose is released into the cytoplasm, and the carrier moves back to the exterior of the cell membrane, where it becomes available to transport more glucose from the extracellular fluid (Fig. 1-7).[4] As such, the carrier renders glucose soluble in cell membranes that otherwise would prevent its passage. Insulin greatly speeds facilitated diffusion of glucose and some amino acids across cell membranes.

Table 1-3

Predicted Relationship between Diffusion Distance and Time

Diffusion Distance (mm)	Time Required for Diffusion
0.001	0.5 ms
0.01	50 ms
0.1	5 s
1	498 s
10	14 h

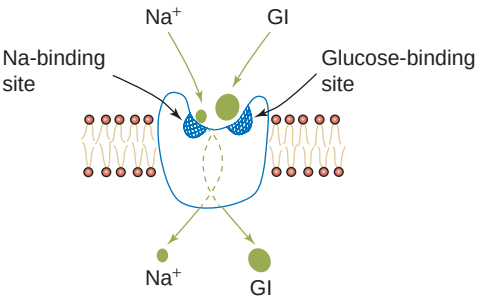

FIGURE 1-7 Glucose (Gl) can combine with a sodium cotransport carrier system at the outside surface of the cell membrane to facilitate diffusion (carrier-mediated diffusion) of Gl across the cell membrane. At the inside surface of the cell membrane, Gl is released to the interior of the cell and the carrier again becomes available for reuse.

Endocytosis and Exocytosis

Endocytosis and exocytosis transfer molecules such as nutrients across cell membranes without the molecule actually passing through the cell membrane. The uptake of particulate matter (bacteria, damaged cells) by cells is termed phagocytosis, whereas uptake of materials in solution in the extracellular fluid is termed pinocytosis (Fig. 1-8).[10] The process of phagocytosis is initiated when antibodies attach to damaged tissue and foreign substances (opsonization), facilitating binding to specialized proteins on the cell surface and endocytosis. Fusion of phagocytic or pinocytic vesicles with lysosomes allows intracellular digestion of materials to proceed. Neurotransmitters are ejected from cells by exocytosis, a process that requires calcium ions and resembles endocytosis in reverse.

Sodium–Potassium Adenosine Triphosphatase

As mentioned previously, sodium–potassium ATPase, also known as the sodium–potassium pump, is an ATP-dependent sodium and potassium transporter on the cell membrane that ejects three sodium ions from the cell in exchange for the import of two potassium ions (Fig. 1-9).[4] This action maintains oncotic equilibration across the cell membrane, reducing the number of intracellular ions to balance the large number of protein and other intracellular constituents. It also is responsible for the transmembrane electrical potential, creating a net positive charge on the outside of the cell from the excess of positive sodium ions outside compared to number of positive potassium ions inside of the cell. Lastly, it creates the sodium gradients responsible for propagation of the action potential and the potassium gradient that rapidly restores the resting membrane potential after conduction of an action potential. In the brain, the sodium–potassium pump accounts for nearly 50% of energy consumption.[11]

Other ion transporters include hydrogen–potassium ATPases in the gastric mucosa and renal tubules, the transporter that exchanges protons for potassium ions. Calcium ATPases are responsible for maintaining very low cytoplasmic concentrations of calcium either by ejecting calcium from the cell (plasma membrane calcium ATPase) or sequestering calcium in the endoplasmic reticulum via the sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA ATPase).[12]

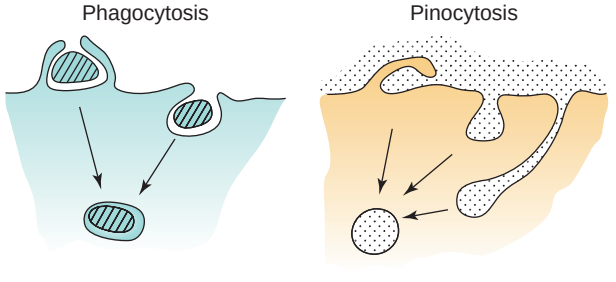

FIGURE 1-8 Schematic depiction of phagocytosis (ingestion of solid particles) and pinocytosis (ingestion of dissolved particles).

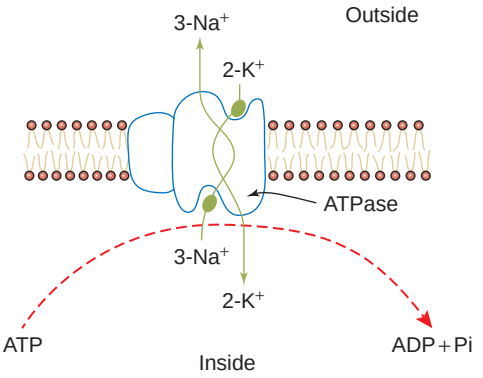

FIGURE 1-9 Sodium–potassium adenosine triphosphatase is an enzyme present in all cells that catalyzes the conversion of adenosine triphosphate (ATP) to adenosine diphosphate (ADP). The resulting energy is used by the active transport carrier system (sodium–potassium pump) that is responsible for the outward movement of three sodium ions across the cell membrane for every two potassium ions that pass inward. (From Guyton AC, Hall JE. *Textbook of Medical Physiology*. 10th ed. Philadelphia, PA: Saunders; 2000, with permission.)

Ion Channels

Ion channels are transmembrane proteins that generate electrical signals in the brain, nerves, heart, and skeletal muscles (Fig. 1-10).[13] Ion channels use the energy stored in the chemical and electrical gradients created by sodium–potassium ATPase to rapidly initiate changes in transmembrane potential, causing conduction of an action potential.

Because of their charge, most ions are relatively insoluble in cell membranes such that their passage across these membranes is thought to occur through protein channels. These channels are likely to be intermolecular spaces in proteins that extend through the entire cell membrane. Some channels are highly specific with respect to ions allowed to pass (sodium, potassium), whereas other channels allow all ions below a certain size to pass (Table 1-4). Tetrodotoxin is a specific blocker of sodium ion channels as a result of binding to the extracellular side of the channel, whereas tetraethylammonium blocks potassium ion channels by attaching to the inside surface of the membrane.

Genes encoding the protein ion channels may be defective, leading to diseases such as cystic fibrosis (chloride channel defects), long Q-T interval syndrome (mutant potassium or, less commonly, sodium channels), hereditary nephrolithiasis (chloride channel), hereditary myopathies including myotonia congenital (chloride channel), and malignant hyperthermia (calcium channel defects).[13] Many drugs target ion channels, including common intravenous anesthetics and, perhaps, inhalational anesthetics. Ion channels are discussed in detail in Chapter 3.

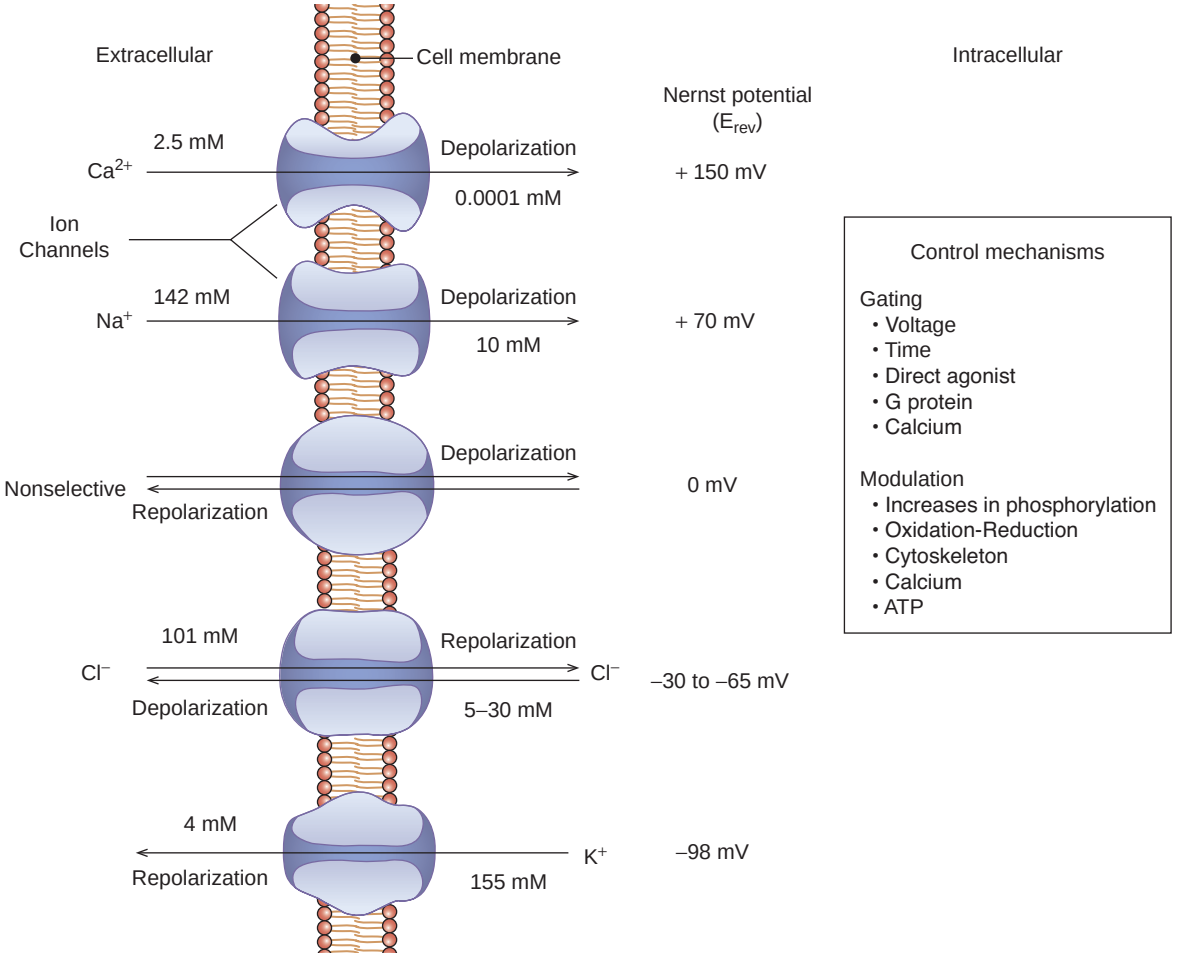

FIGURE 1-10 The five major types of protein ion channels are calcium, sodium, nonselective, chloride, and potassium. Flow of ions through these channels (calcium and sodium into cells and potassium outward) determines the transmembrane potential of cells. (Modified from Ackerman MJ, Clapham DE. Ion channels—basic science and clinical disease. *N Engl J Med.* 1997;336:1575–1586, with permission.)

Protein-Mediated Transport

Protein-mediated transport is responsible for movement of specific substrates across cell membranes. P glycoprotein is responsible for the movement of many drugs across the cell membrane, notably including the transport of morphine out of the central nervous system (CNS), slowing the rate of rise of morphine in the CNS. Virtually all transport of molecules against concentration gradients requires proteins, which use energy provided by ATP to pump the molecule against the concentration gradient.

Active transport via proteins requires energy that is most often provided by hydrolysis of ATP. Indeed, carrier molecules are enzymes known as ATPases that catalyze the hydrolysis of ATP. The most important of the ATPases is sodium–potassium ATPase, which is also known as the sodium–potassium pump. Substances that are actively transported through cell membranes against a c oncentration gradient include sodium, potassium, calcium, hydrogen, chloride, and magnesium ions; iodide (thyroid gland); carbohydrates; and amino acids.

Table 1-4
Diameters of Ions, Molecules, and Channels

	Diameter (nm)[a]
Channel (average)	0.80
Water	0.30
Sodium (hydrated)	0.51
Potassium (hydrated)	0.40
Chloride (hydrated)	0.39
Glucose	0.86

[a]1 nm = 10 Å.

Sodium Ion Cotransport

Despite the widespread presence of sodium–potassium ATPase, the active transport of sodium ions in some tissues is coupled to the transport of other substances. For example, a carrier system present in the gastrointestinal tract and renal tubules will transport sodium ions only in

combination with a glucose molecule. As such, glucose is returned to the circulation, thus preventing its excretion. Sodium ion cotransport of amino acids is an active transport mechanism that supplements facilitated diffusion of amino acids into cells. Epithelial cells lining the gastrointestinal tract and renal tubules are able to reabsorb amino acids into the circulation by this mechanism, thus preventing their excretion.

Other substances, including insulin, steroids, and growth hormone, influence amino acid transport by the sodium ion cotransport mechanism. For example, estradiol facilitates transport of amino acids into the musculature of the uterus, which promotes development of this organ.

Aquaporins

Aquaporins are protein channels that permit the free flux of water across cell membranes.[14] In the absence of aquaporins, diffusion of water might not be sufficiently rapid for some physiologic processes. Genetic defects in aquaporins are responsible for several clinical diseases, including some cases of congenital cataracts[15] and nephrogenic diabetes insipidus.[16]

Nucleus

The nucleus is primarily made up of the 46 chromosomes, except the nucleus of the egg cell, which contains 23. Each chromosome consists of a molecule of DNA covered with proteins. The nucleus is surrounded by a membrane that separates its contents from the cytoplasm, through which substances, including RNA, pass from the nucleus to the cytoplasm.

The nucleolus is a non–membrane-bound structure within the nucleus responsible for the synthesis of ribosomes. Centrioles are present in the cytoplasm near the nucleus and are concerned with the movement of chromosomes during cell division.

Structure and Function of DNA and RNA

DNA consists of two complementary nucleotide chains composed of adenine, guanine, thymine, and cytosine (Fig. 1-11).[17] The genetic message is determined by the sequence of nucleotides. DNA is transcribed to RNA, which transfers the genetic message to the site of protein synthesis (ribosomes) in cytoplasm. Cell reproduction (mitosis) is determined by the DNA genetic system. The human genome has now been 99% sequenced and is composed of just 20,000 to 25,000 genes.[18] The protein encoding genes account for only 1% to 2% of our DNA, the rest being regulatory sequences, non–protein-encoding RNA sequences, introns, and a considerable amount of DNA termed "junk" because it has no known function. Our genome differs from that of chimpanzees by just 1%.[19]

Genes are regulated by specific regulatory proteins and RNA molecules. Regulatory proteins are the target of many hormones, such as steroids, and drugs (antineoplastic drugs).

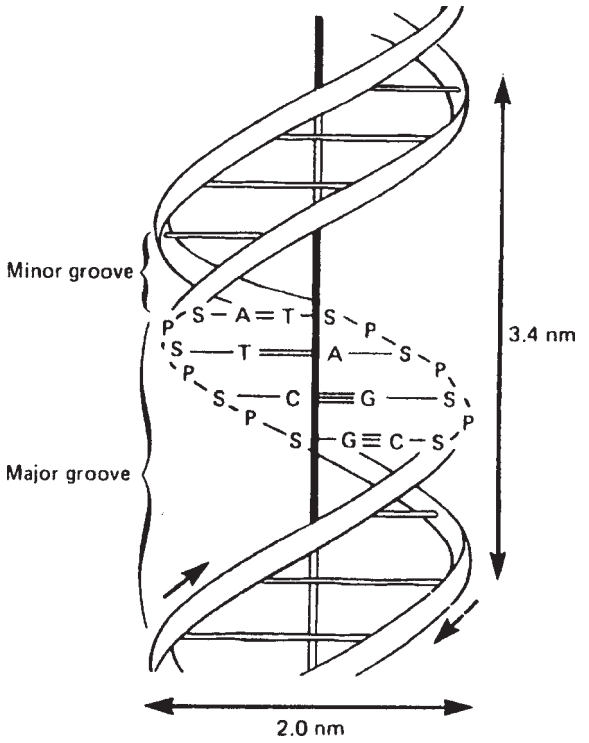

FIGURE 1-11 Double helical structure of DNA with adenine (A) bonding to thymine (T) and cytosine (C) to guanine (G). (From Murray RK, Granner DK, Mayes PA, et al. *Harper's Biochemistry*. 21st ed. Norwalk, CT: Appleton & Lange; 1988, with permission.)

Cytoplasm

The cytoplasm consists of water; electrolytes; and proteins including enzymes, lipids, and carbohydrates. About 70% to 80% of the cell volume is water. Cellular chemicals are dissolved in the water, and these substances can diffuse to all parts of the cell in this fluid medium. Proteins are, next to water, the most abundant substance in most cells, accounting for 10% to 20% of the cell mass.

The cytoplasm contains numerous organelles with specific roles in cellular function.

Mitochondria

Mitochondria are the power-generating units of cells containing both the enzymes and substrates of the tricarboxylic acid cycle (Krebs cycle) and the electron transport chain. As a result, oxidative phosphorylation and synthesis of adenosine triphosphate (ATP) are localized to mitochondria. ATP leaves the mitochondria and diffuses throughout the cell, providing energy for cellular functions. Mitochondria consist of two lipid bilayers, the outer bilayer in contact with the cytoplasm, and the inner layer that houses most of the biochemical machinery and the mitochondrial DNA. The space between these two membranes functions as a reservoir for protons created during electron transport. It is the movement of these protons back to the matrix, through the inner membrane, that drives most of the conversion of ADP to ATP, the primary form of intercellular energy, by ATP synthase.[20]

Increased need for ATP in the cell leads to an increase in the number of mitochondria. A number of diseases are known to be based on aberrant mitochondrial function.[21] The common element of mitochondrial diseases is aberrant cellular energetics. There are approximately 1,500 proteins responsible for mitochondrial function. Of these, only 13 are encoded by mitochondrial DNA, the balance being encoded by nuclear DNA. Thus, the vast majority of mitochondrial diseases follow standard models of genetic inheritance.

Endoplasmic Reticulum

The endoplasmic reticulum is a complex lipid bilayer that wraps and folds, creating tubules and vesicles in the cytoplasm. Ribosomes, composed mainly of RNA, attach to the outer portions of many parts of the endoplasmic reticulum membranes, serving as the sites for protein synthesis (hormones, hemoglobin). Th portion of the membrane containing these ribosomes is known as the ***rough endoplasmic reticulum***. The part of the membrane that lacks ribosomes is the ***smooth endoplasmic reticulum***. Th s smooth portion of the endoplasmic reticulum membrane functions in the synthesis of lipids, metabolism of carbohydrates, and other enzymatic processes. The sarcoplasmic reticulum is found in muscle cells, where it serves as a reservoir for calcium.

Lysosomes

Lysosomes are lipid membrane–enclosed globules scattered throughout the cytoplasm, providing an intracellular digestive system. Lysosomes are filled with digestive (hydrolytic) enzymes. When cells are damaged or die, these digestive enzymes cause autolysis of the remnants. Bactericidal substances in the lysosome kill phagocytized bacteria before they can cause cellular damage. These bactericidal substances include (a) lysozyme, which dissolves the cell membranes of bacteria; (b) l ysoferrin, which binds iron and other metals that are essential for bacterial growth; (c) acid that has a pH of <4; and (d) hydrogen peroxide, which can disrupt some bacterial metabolic systems.

Lysosomal storage diseases are genetic disorders caused by inherited genetic defect in lysosomal function, resulting in accumulation of incompletely degraded macromolecules. There are about 50 known lysosomal storage diseases, including Tay-Sachs, Gaucher, Fabry, and Niemann-Pick disease.[22]

Golgi Apparatus

The Golgi apparatus is a collection of membrane-enclosed sacs that are responsible for storing proteins and lipids as well as performing postsynthetic modifications including glycosylation and phosphorylation. Proteins synthesized in the rough endoplasmic reticulum are transported to the Golgi apparatus, where they are stored in highly concentrated packets (secretory vesicles) for subsequent release into the cell's cytoplasm, or transport to the surface for extracellular release via exocytosis. Exocytotic vesicles continuously release their contents, whereas secretory vesicles store the packaged material until a triggering signal is received. Neurotransmitter release is a highly relevant (to anesthesia) example of regulated secretion. The Golgi apparatus is also responsible for creating lysosomes.

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CHAPTER 2

Basic Principles of Pharmacology

Pamela Flood • Steven Shafer

This chapter combines Dr. Stoelting's elegant description of pharmacology with a mathematical approach first presented by Dr. Shafer[1] in 1997, and most recently in *Miller's Anesthesia* textbook.[2,3] The combination of approaches sets a foundation for the pharmacology presented in the subsequent chapters. It also explains the fundamental principles of drug behavior and drug interaction that govern our daily practice of anesthesia.

Receptor Theory

A drug that activates a receptor by binding to that receptor is called an ***agonist***. Most agonists bind through a combination of ionic, hydrogen, and van der Waals interactions (the sum of the attractive or repulsive forces between molecules), making them reversible. Rarely, an agonist will bind covalently to the receptor, rendering the interaction irreversible. Receptors are often envisioned as proteins that are either unbound or are bound to the agonist ligand. When the receptor is bound to the agonist ligand, the effect of the drug is produced. When the receptor is not bound, there is no effect. The receptor state is seen as binary: It is either unbound, resulting in one conformation, or it is bound, resulting in another conformation. Agonists are often portrayed as simply activating a receptor (Fig. 2-1). In this view, the magnitude of the drug effect reflects the total number of receptors that are bound. In this simplistic view, the "most" drug effect occurs when every receptor is bound.

This simple view helps to understand the action of an antagonist (Fig. 2-2). An ***antagonist*** is a drug that binds to the receptor without activating the receptor. Antagonists typically bind with ionic, hydrogen, and van der Waals interactions, rendering them reversible. Antagonists block the action of agonists simply by getting in the way of the agonist, preventing the agonist from binding to the receptor and producing the drug effect. ***Competitive antagonism*** is present when increasing concentrations of the antagonist progressively inhibit the response to the agonist. This causes a rightward displacement of the agonist dose-response (or concentration-response) relationship. ***Noncompetitive antagonism*** is present when, after administration of an antagonist, even high concentrations of agonist cannot completely overcome the antagonism. In this instance, either the agonist is bound irreversibly (and probably covalently) to the receptor site, or it binds to a different site on the molecule and the interaction is allosteric (based on a change in shape and thereby the activity of the receptor). Noncompetitive antagonism causes both a rightward shift of the dose-response relationship as well as a decreased maximum efficacy of the concentration versus response.

Although this simple view of activated and inactivated receptors explains agonists and antagonists, it has a more difficult time with ***partial agonists*** and ***inverse agonists*** (Fig. 2-3). A partial agonist is a drug that binds to a receptor (usually at the agonist site) where it activates the receptor but not as much as a full agonist. Even at supramaximal doses, a partial agonist cannot cause the full drug effect. Partial agonists may also have antagonist activity in which case they are also called ***agonist-antagonists***. When a partial agonist is administered with a full agonist, it decreases the effect of the full agonist. For example, butorphanol acts as a partial agonist at the μ opioid receptor. Given alone, butorphanol is a modestly efficacious analgesic. Given along with fentanyl, it will partly reverse the fentanyl analgesia, and in individuals using opioids chronically, may precipitate withdrawal. Inverse agonists bind at the same site as the agonist (and likely compete with it), but they produce the opposite effect of the agonist. Inverse agonists "turn off" the constitutive activity of the receptor. The simple view of receptors as bound or unbound does not explain partial agonists or inverse agonists.

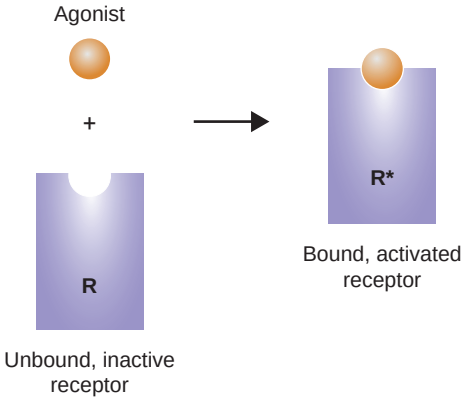

FIGURE 2-1 The interaction of a receptor with an agonist may be portrayed as a binary bound versus unbound receptor. The unbound receptor is portrayed as inactive. When the receptor is bound to the agonist ligand, it becomes the activated, *R**, and mediates the drug effect. This view is too simplistic, but it permits understanding of basic agonist behavior.

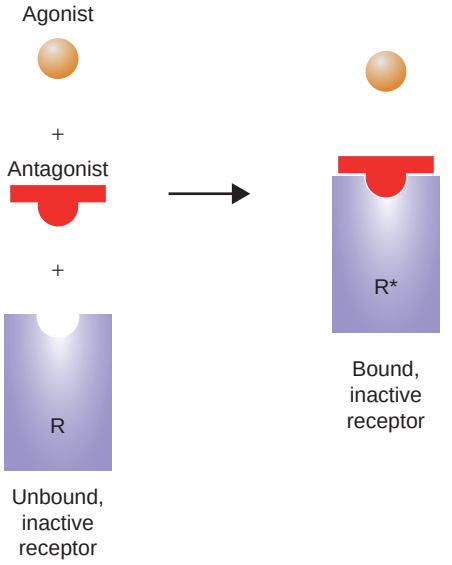

FIGURE 2-2 The simple view of receptor activation also explains the action of antagonist. In this case, the antagonist *(red)* binds to the receptor, but the binding does not cause activation. However, the binding of the antagonist blocks the agonist from binding, and thus blocks agonist drug effect. If the binding is reversible, this is competitive antagonism. If it is not reversible, then it is noncompetitive antagonism.

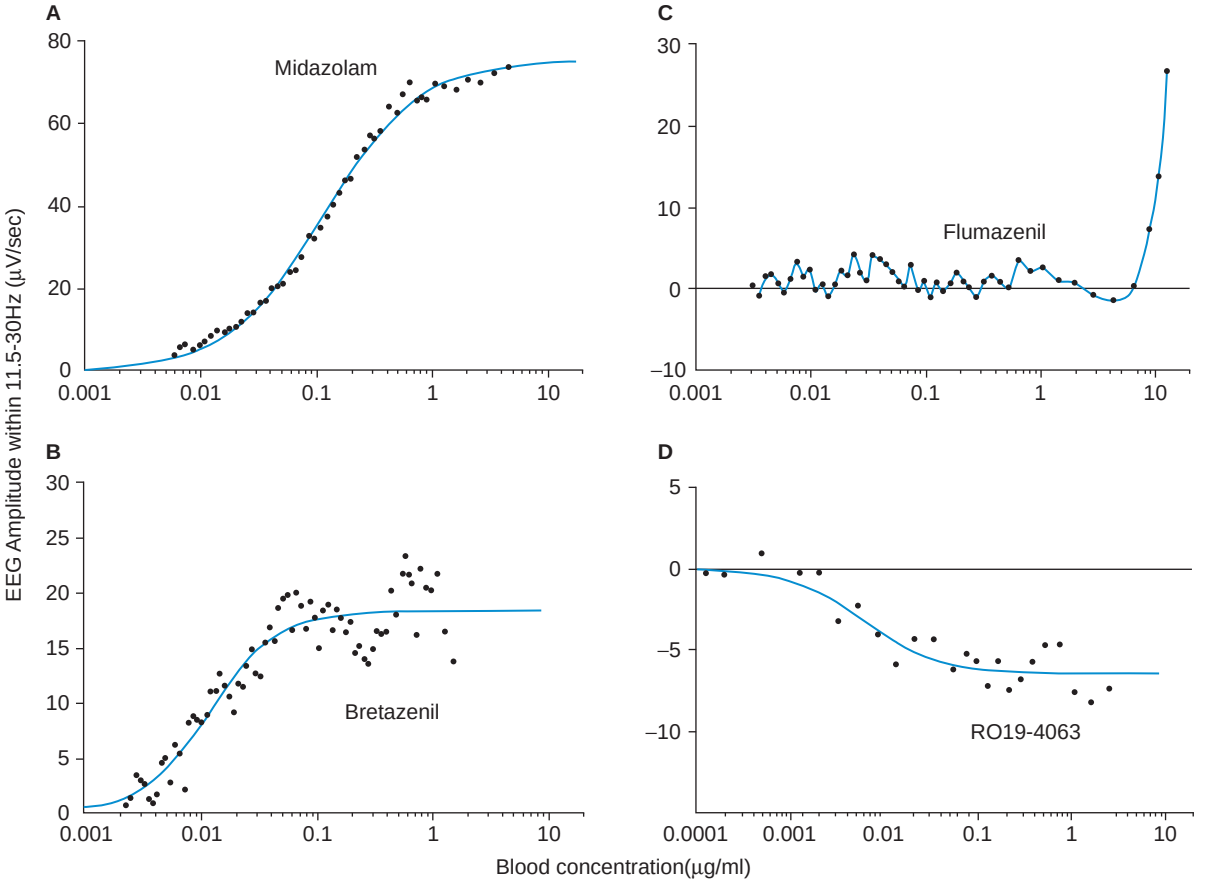

FIGURE 2-3 The concentration versus EEG response relationship for four benzodiazepine ligands: midazolam (full agonist), bretazenil (partial agonist), flumazenil (competitive antagonist), and RO 19-4063 (inverse agonist). (From Shafer S. Principles of pharmacokinetics and pharmacodynamics. In: Longnecker DE, Tinker JH, Morgan GE, eds. *Principles and Practice of Anesthesiology*. 2nd ed. St. Louis, MO: Mosby-Year Book; 1997:1159, based on Mandema JW, Kuck MT, Danhof M. In vivo modeling of the pharmacodynamic interaction between benzodiazepines which differ in intrinsic efficacy. *J Pharmacol Exp Ther*. 1992;261[1]:56–61.)

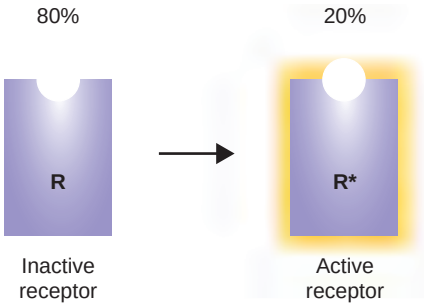

FIGURE 2-4 Receptors have multiple states, and they switch spontaneously between them. In this case, the receptor has just two states. It spends 80% of the time in the inactive state and 20% of the time in the active state in the absence of any ligand.

It turns out that receptors have many natural conformations, and they naturally fluctuate between these different conformations (Fig. 2-4). Some of the conformations are associated with the pharmacologic effect, and some are not. In the example shown, the receptor only has two states: an inactive state and an active state that produces the same effect as if an agonist were bound to the receptor, although at a reduced level because the receptor only spends 20% of its time in this activated state.

In this view, ligands do not cause the receptor shape to change. That happens spontaneously. However, ligands change the ratio of active to inactive states by (thermodynamically) favoring one of the states. Figure 2-5 shows the receptor as seen in Figure 2-4 in the presence of an agonist, a partial agonist, an antagonist, and an inverse agonist. Presence of the full agonist causes the conformation of the active state to be strongly favored, causing the receptors to be in this state nearly 100% of the time. The partial agonist is not as effective in stabilizing the receptor in the active state, so the bound receptor only spends 50% of its time in this state. The antagonist does not favor either state; it just gets in the way of binding (as before; see Fig. 2-2). The inverse agonist favors the inactive state, reversing the baseline receptor activity.

Using this information, we can now interpret the action of several ligands for the benzodiazepine receptor (see Fig. 2-3). The actions include full agonism (midazolam), partial agonism (bretazenil), competitive antagonism (flumazenil), and inverse agonism (RO 19-4063). This range of actions can be explained by considering receptor states. Assume that the γ-aminobutyric acid (GABA) receptor has several conformations, one of which is particularly sensitive to endogenous GABA. Typically, there are some GABA receptors in this more sensitive conformation. As a full agonist, midazolam causes nearly all of the GABA receptors to be in the confirmation with increased sensitivity to GABA. Bretazenil does the same thing but not as well. Even when every benzodiazepine receptor is occupied by bretazenil, fewer GABA receptors are in the more sensitive confirmation. Bretazenil simply does not favor

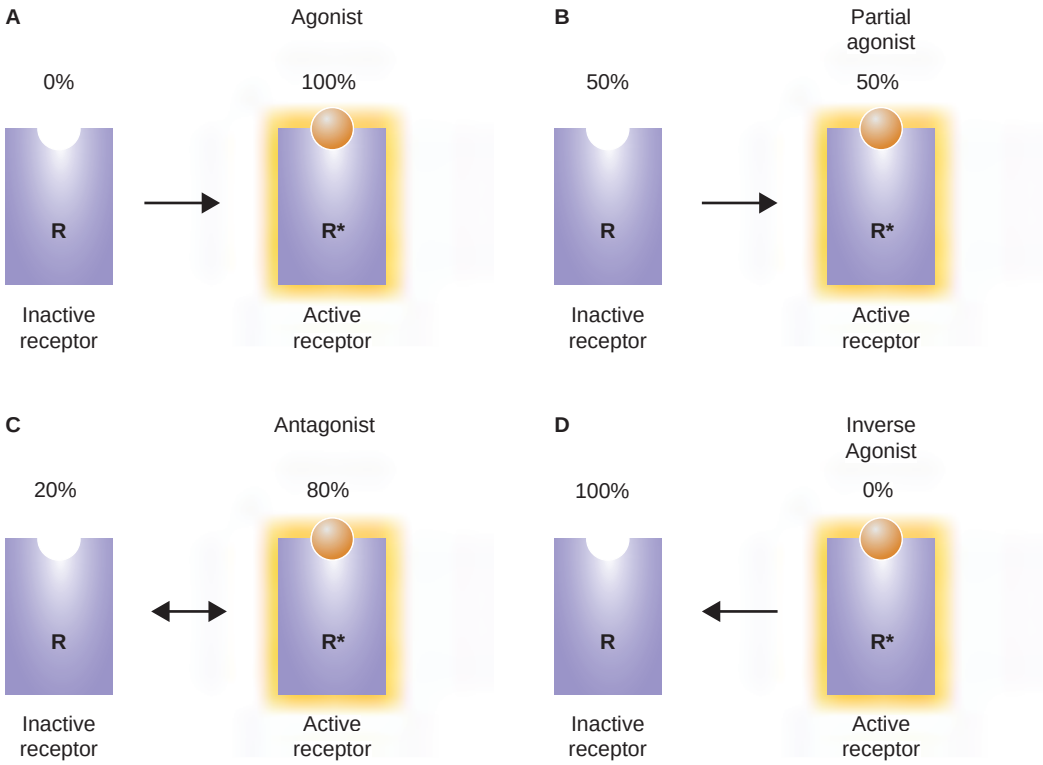

FIGURE 2-5 The action of agonists **(A)**, partial agonists **(B)**, antagonists **(C)**, and inverse agonists **(D)** can be interpreted as changing the balance between the active and inactive forms of the receptor. In this case, in the absence of agonist, the receptor is in the activated state 20% of the time. This percentage changes based on nature of the ligand bound to the receptor.

that conformation as well as midazolam. When flumazenil is in the binding pocket, it does not change the relative probabilities of the receptor being in any conformation. Flumazenil just gets in the way of other drugs that would otherwise bind to the pocket. RO 19-4063 actually decreases the number of GABA receptors in the more sensitive conformation. Usually, some of them are in this more sensitive conformation, but that number is decreased by the inverse agonist RO 19-4063 (which was never developed as a drug because endogenous benzodiazepines, although anticipated, have not been described). The notion of the drugs having multiple conformations, and drugs acting through favoring particular conformations, helps to understand the action of agonists, partial agonists, antagonists, and inverse agonists.

Receptor Action

The number for receptors in cell membranes is dynamic and increases (upregulates) or decreases (downregulates) in response to specific stimuli. For example, a patient with pheochromocytoma has an excess of circulating catecholamines. In response, there is a decrease in the numbers of β-adrenergic receptors in cell membranes in an attempt to maintain homeostasis. Likewise, prolonged treatment of asthma with a β agonist may result in tachyphylaxis (decreased response to the same dose of β agonist, also called ***tolerance***) because of the decrease in β adrenergic receptors. Conversely, lower motor neuron injury causes an increase in the number of nicotinic acetylcholine receptors in the neuromuscular junction, leading to an exaggerated response to succinylcholine. Changing receptor numbers is one of many mechanisms that contribute to variability in response to drugs.

Receptor Types

Receptors for drug action can be classified by location. Many of the receptors thought to be the most critical for anesthetic interaction are located in the lipid bilayer of cell membranes. For example, opioids, intravenous sedative hypnotics, benzodiazepines, β blockers, catecholamines, and muscle relaxants (most of which are actually antagonists) all interact with membrane-bound receptors. Other receptors are intracellular proteins. Drugs such as caffeine, insulin, steroids, theophylline, and milrinone interact with intracellular proteins. Circulating proteins can also be drug targets; for example, the many drugs that affect components of the coagulation cascade.

There are also drugs that do not interact with proteins at all. Stomach antacids such as sodium citrate simply work by changing gastric pH. Chelating drugs work by binding divalent cations. Iodine kills bacteria by osmotic pressure (intracellular desiccation), and intravenous sodium bicarbonate changes plasma pH. The mechanism of action of these drugs does not involve receptors per se, and hence these drugs will not be further considered in this section.

Proteins function in the body as small machines, catalyzing enzymatic reactions and acting as ion channels among other functions. When a drug binds to a receptor, it changes the activity of the machine, typically by enhancing its activity (e.g., propofol increases the sensitivity of the GABA-A receptor to GABA, the endogenous ligand), decreasing its activity (ketamine decreases the activity of the *N*-methyl-d-aspartate [NMDA] receptor), or triggering a chain reaction (opioid binding to the μ opioid receptor activates an inhibitory G protein that decreases adenylyl cyclase activity). The protein's response to binding of the drug is responsible for the drug effect.

Pharmacokinetics

Pharmacokinetics is the quantitative study of the absorption, distribution, metabolism, and excretion of injected and inhaled drugs and their metabolites. Thus, pharmacokinetics describes what the body does to a drug. Pharmacodynamics is the quantitative study of the body's response to a drug. Thus, pharmacodynamics describes what the drug does to the body. This section will introduce the basic principles of pharmacokinetics. The next section discusses the basic principles of pharmacodynamics.

Pharmacokinetics determines the concentration of a drug in the plasma or at the site of drug effect. Pharmacokinetic variability is a significant component of patient-to-patient variability in drug response and may result from genetic modifications in metabolism; interactions with other drugs; or disease in the liver, kidneys, or other organs of metabolism.[4]

The basic principles of pharmacokinetics are absorption, metabolism, distribution, and elimination. These processes are fundamental to all drugs. They can be described in basic physiologic terms or using mathematical models. Each serves a purpose. Physiology can be used to predict how changes in organ function will affect the disposition of drugs. Mathematical models can be used to calculate the concentration of drug in the blood or tissue following any arbitrary dose, at any arbitrary time. We will initially tackle the physiologic principles that govern distribution, metabolism, elimination, and absorption, in that order. We will then turn to the mathematical models.

Distribution

When drugs are administered, they mix with body tissues and are immediately diluted from the concentrated injectate in the syringe to the more dilute concentration measured in the plasma or tissue. This initial distribution (within 1 minute) after bolus injection is considered mixing within the "central compartment" (Fig. 2-6). The

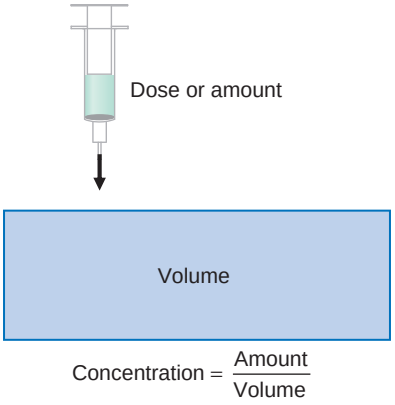

FIGURE 2-6 The central volume is the volume that intravenously injected drug initially mixes into. (From Shafer S, Flood P, Schwinn D. Basic principles of pharmacology. In: Miller RD, Eriksson LI, Fleisher LA, et al, eds. *Miller's Anesthesia*. Vol 1. 7th ed. Philadelphia, PA: Churchill Livingstone; 2010:479–514, with permission.)

central compartment is physically composed of those elements of the body that dilute the drug within the first minute after injection: the venous blood volume of the arm, the volume of the great vessels, the heart, the lung, and the upper aorta, and whatever uptake of drug occurs in the first passage through the lungs. Many of these volumes are fi ed, but drugs that are highly fat soluble may be avidly taken up in the first passage through the lung, reducing the concentration measured in the arterial blood and increasing the apparent size of the central compartment. For example, first-pass pulmonary uptake of the initial dose of lidocaine, propranolol, meperidine, fentanyl, sufentanil, and alfentanil exceeds 65% of the dose.[5]

The body is a complex space, and mixing is an ongoing process. Almost by definition, the central compartment is the mixing with a small portion of the blood volume and the lung tissue. Several minutes later, the drug will fully mix with the entire blood volume. However, it may take hours or even days for the drug to fully mix with all bodily tissues because some tissues have very low perfusion.

In the process of mixing, molecules are drawn to other molecules, some with specific binding sites. A drug that is polar will be drawn to water, where the polar water molecules find a low energy state by associating with the charged aspects of the molecule. A drug that is nonpolar has a higher affinity for fat, where van der Waals binding provides numerous weak binding sites. Many anesthetic drugs are highly fat soluble and poorly soluble in water. High fat solubility means that the molecule will have a large volume of distribution because it will be preferentially taken up by fat, diluting the concentration in the plasma. The extreme example of this is propofol, which is almost inseparable from fat. The capacity of body fat to hold propofol is so vast that in some studies the total volume of distribution of propofol has been reported as exceeding 5,000 L. Of course, nobody has a total volume of 5,000 L. It is important to understand that those 5,000 L refer to imaginary aqueous liters or the amount of plasma that would be required to dissolve the initial dose of propofol. Because propofol is so fat soluble, a large amount of propofol is dissolved in the body's fatty tissues and the concentration measured in the plasma will be low.

Following bolus injection, the drug primarily goes to the tissues that receive the bulk of arterial blood flow: the brain, heart, kidneys, and liver. These tissues are often called ***the vessel rich group***. The rapid blood flow ensures that the concentration in these highly perfused tissues rises rapidly to equilibrate with arterial blood. However, for highly fat soluble drugs, the capacity of the fat to hold the drug greatly exceeds the capacity of highly perfused tissues. Initially, the fat compartment is almost invisible because the blood supply to fat is quite limited. However, with time, the fat gradually absorbs more and more drug, sequestering it away from the highly perfused tissues. This redistribution of drug from the highly perfused tissue to the fat accounts for a substantial part of the offset of drug effect following a bolus of an intravenous anesthetic or fat-soluble opioid (e.g., fentanyl). Muscles play an intermediate role in this process, having (at rest) blood flow that is intermediate between highly perfused tissues and fat.

Protein Binding

Most drugs are bound to some extent to plasma proteins, primarily albumin, α_1-acid glycoprotein, and lipoproteins.[6] Most acidic drugs bind to albumin, whereas basic drugs bind to α_1-acid glycoprotein. Protein binding effects both the distribution of drugs (because only the free or unbound fraction can readily cross cell membranes) and the apparent potency of drugs, again because it is the free fraction that determines the concentration of bound drug on the receptor.

The extent of protein binding parallels the lipid solubility of the drug. This is because drugs that are hydrophobic are more likely to bind to proteins in the plasma and to lipids in the fat. For intravenous anesthetic drugs, which tend to be quite potent, the number of available protein binding sites in the plasma vastly exceeds the number of sites actually bound. As a result, the fraction bound is not dependent on the concentration of the anesthetic and only dependent on the protein concentration.

Binding of drugs to plasma albumin is nonselective, and drugs with similar physicochemical characteristics may compete with each other and with endogenous substances for the same protein binding sites. For example, sulfonamides can displace unconjugated bilirubin from binding sites on albumin, leading to the risk of bilirubin encephalopathy in the neonate.

Age, hepatic disease, renal failure, and pregnancy can all result in decreased plasma protein concentration. Alterations in protein binding are important only for drugs that are highly protein bound (e.g., >90%). For such drugs, the free fraction changes as an inverse proportion

with a change in protein concentration. If the free fraction is 2% in the normal state, then in a patient with 50% decrease in plasma proteins, the free fraction will increase to 4%, a 100% increase.

Theoretically, an increase in free fraction of a drug may increase the pharmacologic effect of the drug, but in practice, it is far from certain that there will be any change in pharmacologic effect at all. The reason is that it is the unbound fraction that equilibrates throughout the body, including with the receptor. Plasma proteins only account for a small portion of the total binding sites for drug in the body. Because the free drug ***concentration*** in the plasma and tissues represents partitioning with all binding sites, not just the plasma binding sites, the actual free drug concentration that drives drug on and off receptors may change fairly little with changes in plasma protein concentration.

Metabolism

Metabolism converts pharmacologically active, lipid-soluble drugs into water-soluble and usually pharmacologically inactive metabolites. However, this is not always the case. For example, diazepam and propranolol may be metabolized to active compounds. Morphine-6-glucuronide, a metabolite of morphine, is a more potent opioid than morphine itself. In some instances, an inactive parent compound (prodrug) metabolized to an active drug. This is the case with codeine, which is an exceedingly weak opioid. Codeine is metabolized to morphine, which is responsible for the analgesic effects of codeine.

Pathways of Metabolism

The four basic pathways of metabolism are (a) oxidation, (b) reduction, (c) hydrolysis, and (d) conjugation. Traditionally, metabolism has been divided into phase I and phase II reactions. Phase I reactions include oxidation, reduction, and hydrolysis, which increase the drug's polarity and prepare it for phase II reactions. Phase II reactions are conjugation reactions that covalently link the drug or metabolites with a highly polar molecule (carbohydrate or an amino acid) that renders the conjugate more water soluble for subsequent excretion. Hepatic microsomal enzymes are responsible for the metabolism of most drugs. Other sites of drug metabolism include the plasma (Hofmann elimination, ester hydrolysis), lungs, kidneys, and gastrointestinal tract and placenta (tissue esterases).

Hepatic microsomal enzymes, which participate in the metabolism of many drugs, are located principally in hepatic smooth endoplasmic reticulum. These microsomal enzymes are also present in the kidneys, gastrointestinal tract, and adrenal cortex. Microsomes are vesicle-like artifacts re-formed from pieces of the endoplasmic reticulum when cells are homogenized; microsomal enzymes are those enzymes that are concentrated in these vesicle-like artifacts.

Phase I Enzymes

Enzymes responsible for phase I reactions include cytochrome P450 enzymes, non–cytochrome P450 enzymes, and flavin-containing monooxygenase enzymes. The cytochrome P450 enzyme (CYP) system is a large family of membrane-bound proteins containing a heme cofactor that catalyze the metabolism of endogenous compounds. P450 enzymes are predominantly hepatic microsomal enzymes although there are also mitochondrial P450 enzymes. The designation cytochrome P450 emphasizes this substance's absorption peak at 450 nm when it is combined with carbon monoxide. The cytochrome P450 system is also known as the mixed function oxidase system because it involves both oxidation and reduction steps; the most common reaction catalyzed by cytochrome P450 is the monooxygenase reaction, for example, insertion of one atom of oxygen into an organic substrate while the other oxygen atom is reduced to water. Cytochrome P450 functions as the terminal oxidase in the electron transport chain.

Individual cytochrome P450 enzymes have evolved from a common protein.[7] Cytochrome P450 enzymes, often called ***CYPs***, that share more than 40% sequence homology are grouped in a family designated by a number (e.g., "CYP2"), those that share more than 55% homology are grouped in a subfamily designated by a letter (e.g., "CYP2A"), and individual CYP enzymes are identified by a third number (e.g., "CYP2A6"). Ten isoforms of cytochrome P450 are responsible for the oxidative metabolism of most drugs. The preponderance of CYP activity for anesthetic drugs is generated by CYP3A4, which is the most abundantly expressed P450 isoform, comprising 20% to 60% of total P450 activity. P450 3A4 metabolizes more than one-half of all currently available drugs, including opioids (alfentanil, sufentanil, fentanyl), benzodiazepines, local anesthetics (lidocaine, ropivacaine), immunosuppressants (cyclosporine), and antihistamines (terfenadine).

Drugs can alter the activity of these enzymes through induction and inhibition. Induction occurs through increased expression of the enzymes. For example, phenobarbital induces microsomal enzymes and thus can render drugs less effective through increased metabolism. Conversely, other drugs directly inhibit enzymes, increasing the exposure to their substrates. Famously, grapefruit juice (not exactly a drug) inhibits CYP 3A4, possibly increasing the concentration of anesthetics and other drugs.

Oxidation

Cytochrome P450 enzymes are crucial for oxidation reactions. These enzymes require an electron donor in the form of reduced nicotinamide adenine dinucleotide (NAD) and molecular oxygen for their activity. The molecule of oxygen is split, with one atom of oxygen oxidizing each molecule of drug and the other oxygen atom being incorporated into a molecule of water. Examples of oxidative metabolism of drugs catalyzed by cytochrome P450 enzymes include hydroxylation, deamination, desulfuration, dealkylation,

and dehalogenation. Demethylation of morphine to normorphine is an example of oxidative dealkylation. Dehalogenation involves oxidation of a carbon-hydrogen bond to form an intermediate metabolite that is unstable and spontaneously loses a halogen atom. Halogenated volatile anesthetics are susceptible to dehalogenation, leading to release of bromide, chloride, and fluoride ions. Aliphatic oxidation is oxidation of a side chain. For example, oxidation of the side chain of thiopental converts the highly lipid-soluble parent drug to the more water-soluble carboxylic acid derivative. Thi pental also undergoes desulfuration to pentobarbital by an oxidative step.

Epoxide intermediates in the oxidative metabolism of drugs are capable of covalent binding with macromolecules and may be responsible for some drug-induced organ toxicity, such as hepatic dysfunction. Normally, these highly reactive intermediates have such a transient existence that they exert no biologic action. When enzyme induction occurs, however, large amounts of reactive intermediates may be produced, leading to organ damage. This is especially likely to occur if the antioxidant glutathione, which is in limited supply in the liver, is depleted by the reactive intermediates.

Reduction

Cytochrome P450 enzymes are also essential for reduction reactions. Under conditions of low oxygen partial pressures, cytochrome P450 enzymes transfer electrons directly to a substrate such as halothane rather than to oxygen. This electron gain imparted to the substrate occurs only when insufficient amounts of oxygen are present to compete for electrons.

Conjugation

Conjugation with glucuronic acid involves cytochrome P450 enzymes. Glucuronic acid is synthesized from glucose and added to lipid-soluble drugs to render them water soluble. The resulting water-soluble glucuronide conjugates are then excreted in bile and urine. In premature infants, reduced microsomal enzyme activity interferes with conjugation, leading to neonatal hyperbilirubinemia and the risk of bilirubin encephalopathy. The reduced conjugation ability of the neonate increases the effect and potential toxicity of drugs that are normally inactivated by conjugation with glucuronic acid.

Hydrolysis

Enzymes responsible for hydrolysis of drugs, usually at an ester bond, do not involve the cytochrome P450 enzyme system. Hydrolysis often occurs outside of the liver. For example, remifentanil, succinylcholine, esmolol, and the ester local anesthetics are cleared in the plasma and tissues via ester hydrolysis.

Phase II Enzymes

Phase II enzymes include glucuronosyltrasferases, glutathione-S-transferases, N-acetyl-transferases, and sulfotransferases. Uridine diphosphate glucuronosyltransferase catalyzes the covalent addition of glucuronic acid to a variety of endogenous and exogenous compounds, rendering them more water soluble. Glucuronidation is an important metabolic pathway for several drugs used during anesthesia, including propofol, morphine (yielding morphine-3-glucuronide and the pharmacologically active morphine-6-glucuronide), and midazolam (yielding the pharmacologically active 1-hydroxymidazolam). Glutathione-S-transferase (GST) enzymes are primarily a defensive system for detoxification and protection against oxidative stress. N-acetylation catalyzed by *N*-acetyltransferase (NAT) is a common phase II reaction for metabolism of heterocyclic aromatic amines (particularly serotonin) and arylamines, including the inactivation of isoniazid.

Hepatic Clearance

The rate of metabolism for most anesthetic drugs is proportional to drug concentration, rending the clearance of the drug constant (i.e., independent of dose). This is a fundamental assumption for anesthetic pharmacokinetics. Exploring this assumption will provide insight into what clearance actually is and how it relates to the metabolism of drugs.

Although the metabolic capacity of the body is large, it is not possible that metabolism is *always* proportional to drug concentration because the liver does not have infinite metabolic capacity. At some rate of drug flow into the liver, the organ will be metabolizing drug as fast as the metabolic enzymes in the organ allow. At this point, metabolism can no longer be proportional to concentration because the metabolic capacity of the organ has been exceeded.

Understanding metabolism starts with a simple mass balance: the rate at which drug flows *out* of the liver must be the rate at which drug flows *into* the liver, minus the rate at which the liver metabolizes drug. The rate at which drug flows into the liver is liver blood flow, Q, times the concentration of drug flowing in, C_{inflow}. The rate at which drug flows out of the liver is liver blood flow, Q, times the concentration of drug flowing out, $C_{outflow}$. The rate of hepatic metabolism by the liver, R, is the difference between the drug concentration flowing into the liver and the drug concentration flowing out of the liver, times the rate of liver blood flow:

$$\text{Rate of drug metabolism} = R = Q(C_{inflow} - C_{outflow}) \qquad \text{Equation 2-1}$$

This relationship is illustrated in Figure 2-7.

Metabolism can be saturated because the liver does not have infinite metabolic capacity. A common equation used for this saturation processes is:

$$\text{Response} = \frac{C}{C_{50} + C} \qquad \text{Equation 2-2}$$

"Response" in **Equation 2-2** varies from 0 to 1, depending on the value of C. In this context, Response is the