江苏省药理学全英语教学精品课程教材

Pharmacology

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主编 封 云 刘晗青
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前　言

药理学是一门为疾病的预防治疗和药物的合理应用提供基础知识理论的学科，既是临床医学专业的基础课程和药学专业的专业课程，也是基础医学、临床医学和药学的桥梁学科。

随着我国医学教学改革的推进，以及医学留学生教育的拓展，国内双语教学和全英语教学亟需适用的全英文药理学教材。现有的原版国外教材价格昂贵，而且从结构到内容均不完全适用于我们的药理学教学。2006 版的全国统编全英语药理学教材已经使用十年，不能反映药理学近期发展。因此，编写一本合适的教材迫在眉睫。

本书的主要特色如下：

1. 注重教学内容国际化，教材编写参照国际通用教材。
2. 尊重国内教师授课习惯，教材内容安排顺序符合国内教学习惯。
3. 添加课程内容的结构导图，以帮助使用者归纳总结梳理每章内容。
4. 增加课后复习题和答案，便于使用者深入理解课程内容。
5. 增加学习自查清单，方便使用者自学和复习。
6. 增加病例讨论，帮助使用者进行 PBL，DBL 学习和教学。

在整个编写过程中我们参考了国际经典教材如 Bertram G. Katzung, Susan B. Masters, Anthony J. Trevor 编写的 *Basic & clinical pharmacology*, 12th ed. 以及 Richard A. Harvey, Wolters Kluwer 编写的 *Lippincott's illustrated reviews*: pharmacology, 5th ed. 还有 *Goodman & Gilman's The pharmacological basis of therapeutics*, 12th ed. 等，同时还参考了大量的最新中外文文献。此外，在本教材编写过程中得到了江苏大学、南通大学、徐州医科大学、扬州大学、昆明医科大学、潍坊医学院、滨州医学院等单位药理学系（教研室）各位留学生教学老师的大力支持，以及 MBBS 留学生的帮助，在此一并致以诚挚的谢意。

特别感谢美国约翰霍普金斯大学医学院 Alfredo Quinones Hinojosa 教授及其团队成员的关心帮助。

由于我们的学术水平、编写经验有限，本教材难免存在疏漏和不足之处，恳请读者批评指正。

封云

2016 年 2 月

Preface

This book is designed to help students learn pharmacology well in China. We recommend several strategies to make the learning more effective.

First, each chapter opens with an "Introduction" that organizes the group of drugs visually in diagrammatic form. It's good for students to practice reproducing the main contents from memory.

Second, each of the chapters contains "Multiple-choice questions" which is followed by a set of answers with explanations. After ansuering every question, you can go through all the answers given by this book. When you are thinking these answers, make sure you understand why each choice is either correct or incorrect.

Third, each chapter includes a "Checklist" of focused tasks that you should be able to do when you finished the study of corresponding chapter.

Fourth, most chapters end with "Summary tables" that lists the most important drugs and includes key information concerning their clinical uses, mechanism of action, effects, pharmacokinetics, drug interactions, and toxicities.

We appreciate the invaluable contributions afforded by the editorial team very much.

Yun Feng

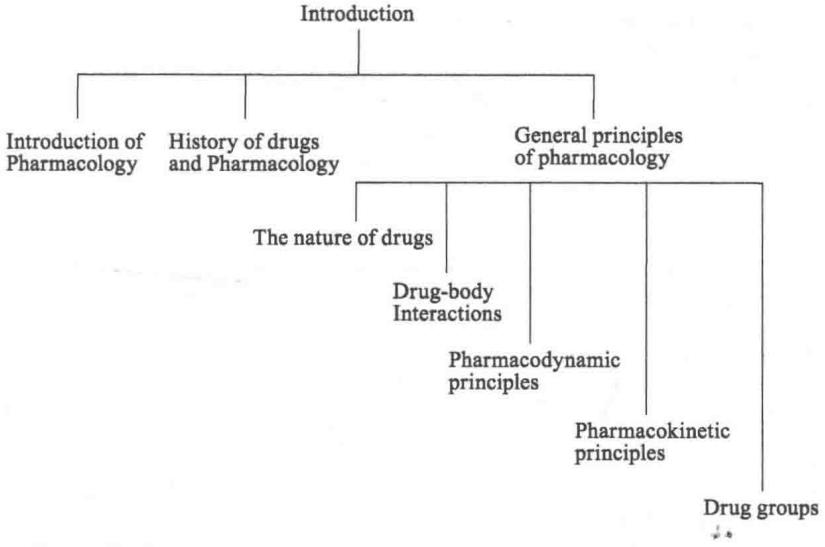
CONTENTS

PART I BASIC PRINCIPLES

CHAPTER 1

Introduction

Pharmacology is the body of knowledge concerned with the action of substances on living systems. Pharmacodynamics denotes the actions of the drug on the body, such as mechanism of action and therapeutic and toxic effects, and plays the major role in deciding whether that group is appropriate therapy for a particular symptom or disease. The actions of the body on the drug are called pharmacokinetic processes which govern the absorption, distribution, and elimination of drugs and are of great practical importance in the choice and administration of a particular drug for a particular patient. This chapter introduces the basic principles of pharmacokinetics and pharmacodynamics that will be applied in subsequent chapters.



I. Introduction of pharmacology

Pharmacology can be defined as the study of substances that interact with living systems through chemical processes, especially by binding to regulatory molecules and activating or inhibiting normal body processes. These substances may be chemicals administered to achieve a beneficial therapeutic effect on some process within the patient or for their toxic effects on regulatory processes in parasites infecting the patient. Medical pharmacology is the

area of pharmacology concerned with the use of substances in the prevention, diagnosis, and treatment of disease, especially in humans. Toxicology is that branch of pharmacology concerned with the undesirable effects of substances on living systems, from individual cells to complex ecosystems.

Ⅱ. The history of drugs and pharmacology

As a science, pharmacology was born in the mid-19th century, one of a host of new biomedical sciences based on principles of experimentation rather than dogma that came into being in that remarkable period. Long before that-indeed from the dawn of civilisation-herbal remedies were widely used, pharmacopoeias were written, and the apothecaries' trade flourished, but nothing resembling scientific principles was applied to therapeutics. Even Robert Boyle, who laid the scientific foundations of chemistry in the middle of the 17th century, was content, when dealing with therapeutics, to recommend concoctions of worms, dung, urine, and the moss from a dead man's skull. In the late 18th and early 19th centuries, Francois Magendie, and later his student Claude Bernard, began to develop the methods of experimental animal physiology and pharmacology. Advances in chemistry and the further development of physiology in the 18th, 19th, and early 20th centuries laid the foundation needed for understanding how drugs work at the organ and tissue levels. Paradoxically, real advances in basic pharmacology during this time were accompanied by an outburst of unscientific promotion by manufacturers and marketers of worthless "patent medicines". Not until the concepts of rational therapeutics, especially that of the controlled clinical trial, were reintroduced into medicine only about 50 years ago, did it become possible to accurately evaluate therapeutic claims?

The extension of scientific principles into everyday therapeutics is still going on, although the medication-consuming public unfortunately is still exposed to vast amounts of inaccurate, incomplete, or unscientific information regarding the pharmacologic effects of chemicals. This has resulted in the faddish use of innumerable expensive, ineffective, and sometimes harmful remedies and the growth of a huge "alternative health care" industry. Conversely, lack of understanding of basic scientific principles in biology and statistics and the absence of critical thinking about public health issues have led to rejection of medical science by a segment of the public and to a common tendency to assume that all adverse drug effects are the result of malpractice.

Two general principles that the student should always remember are, first, that all substances can under certain circumstances be toxic; and second, that all dietary supplements and all therapies promoted as health-enhancing should meet the same standards of efficacy and safety, i. e. , there should be no artificial separation between scientific medicine and "alternative" or "complementary" medicine.

Ⅲ. General principles of pharmacology

A. The nature of drugs

In the most general sense, a drug may be defined as any substance that brings about a change in biologic function through its chemical actions. Drugs in common use include inorganic ions, nonpeptide organicmolecules, small peptides and proteins, nucleic acids, lipids, and carbohydrates. Some are found in plants or animals, but many are partially or completely synthetic. Many biologically important endogenous molecules and exogenous drugs are optically active; that is, they contain one or more asymmetric centers and can exist as enantiomers. The enantiomers of optically active drugs usually differ, sometimes more than 1 000-fold, in their affinity for their biologic receptor sites. Furthermore, such enantiomers may be metabolized at different rates in the body, with important clinical consequences.

1. Size and molecular weight

Drugs vary in size from molecular weight (MW) 7 (lithium) to over MW 50 000 (thrombolytic enzymes, other proteins). Most drugs, however, have molecular weights between 100 and 1 000. Drugs smaller than MW 100 are rarely sufficiently selective in their actions, whereas drugs much larger than MW 1 000 are often poorly absorbed and poorly distributed in the body.

2. Drug-receptor bonds

Drugs bind to receptors with a variety of chemical bonds. These include very strong covalent bonds (which usually result in irreversible action), somewhat weaker electrostatic bonds (e. g. ,n Between a cation and an anion), and much weaker interactions (e. g. , hydrogen, van der Waals, and hydrophobic bonds).

3. Drug shape

The shape of a drug molecule must be such as to permit binding to its receptor site via the bonds just described. Optimally, the drug's shape is complementary to that of the receptor site in the same way that a key is complementary to a lock. Furthermore, the phenomenon of chirality (stereoisomerism) is so common in biology that more than half of all useful drugs are chiral molecules; that is, they exist as enantiomeric pairs. Drugs with two asymmetric centers have four diastereomers, e. g. , ephedrine, a sympathomimetic drug. In most cases, one of these enantiomers is much more potent than its mirror image enantiomer, reflecting a better fit to the receptor molecule.

B. Drug-body interactions

The interactions between a drug and the body are conveniently divided into two classes. The actions of the drug on the body are termed pharmacodynamic processes. These properties determine the group in which the drug is classified and play the major role in deciding whether that group is appropriate therapy for a particular symptom or disease. The actions of the body on the drug are called pharmacokinetic processes. Pharmacokinetic processes govern the absorption, distribution, and elimination of drugs and are of great practical importance in the choice and administration of a particular drug for a particular patient, e. g. , a patient with impaired renal function. The following paragraphs provide a brief introduction to pharmacodynamics and pharmacokinetics.

C. Pharmacodynamic principles

1. Receptors and inert binding sites

Drug actions are mediated through the effects of drug molecules on drug receptors in the body. Most receptors are large regulatory molecules that influence important biochemical processes (e. g. , enzymes involved in glucose metabolism) or physiologic processes (e. g. , neurotransmitter receptors, neurotransmitter reuptake trans-porters, and ion transporters).

Because most drug molecules are much smaller than their receptor molecules (discussed in the text that follows), specific regions of receptor molecules often can be identified that provide the local areas for drug binding. Such areas are termed receptor sites. In addition, drugs bind to other nonregulatory molecules in the body without producing a discernible effect. Such binding sites are termed inert binding sites. In some compartments of the body (e. g. , the plasma), inert binding sites play an important role in buffering the concentration of a drug because bound drug does not contribute directly to the concentration gradient that drives diffusion. Albumin and orosomucoid (α_1-acid glycoprotein) are two important plasma proteins with significant drug-binding capacity.

2. Types of drug-receptor interactions

Agonist drugs bind to and activate the receptor in some fashion, which directly or indirectly brings about the effect. Some receptors incorporate effector machinery in the same molecule, so that drug binding brings about the effect directly, e. g. , opening of an ion channel or activation of enzyme activity. Other receptors are linked through one or more intervening coupling molecules to a separate effector molecule. Pharmacologic antagonist drugs, by binding to a receptor, prevent binding by other molecules. For example, acetylcholine receptor blockers such as atropine are antagonists because they prevent access of acetylcholine and similar agonist drugs to the acetylcholine receptor and they stabilize the receptor in its inactive state. These agents reduce the effects of acetylcholine and similar molecules in the body.

3. Agonists that inhibit their binding molecules and partial agonists

Some drugs mimic agonist drugs by inhibiting the molecules responsible for terminating the action of an endogenous agonist. For example, acetylcholinesterase inhibitors, by slowing the destruction of endogenous acetylcholine, cause cholinomimetic effects that closely resemble the actions of cholinoceptor agonist molecules even though cholinesterase inhibitors do not bind or only incidentally bind to cholinoceptors. Other drugs bind to receptors and activate them but do not evoke as great a response as so-called full agonists. Thus, pindolol, a adrenoceptor "partial agonist" may act as either an agonist (if no full agonist is present) or as an antagonist (if a full agonist such as epinephrine is present).

4. Duration of drug action

Termination of drug action at the receptor level results from one of several processes. In some cases, the effect lasts only as long as the drug occupies the receptor, so that dissociation of drug from the receptor automatically terminates the effect. In many cases, however, the action may persist after the drug has dissociated, because, for example, some coupling molecule is still present in activated form. In the case of drugs that bind covalently to the receptor site, the effect may persist until the drug-receptor complex is destroyed and new receptors or enzymes are synthesized, as described previously for aspirin. Finally, many receptor-effector systems incorporate desensitization mechanisms for preventing excessive activation when agonist molecules continue to be present for long periods.

D. Pharmacokinetic principles

In practical therapeutics, a drug should be able to reach its intended site of action after administration by some convenient route. In some cases, a chemical that is readily absorbed and distributed is administered and then converted to the active drug by biologic processes inside the body. Such a chemical is called a prodrug.

In only a few situations is it possible to directly apply a drug to its target tissue, e. g. , by topical application of an anti-inflammatory agent to inflamed skin or mucous membrane. Most often, a drug is administered into one body compartment, e. g. , the gut, and must move to its site of action in another compartment, e. g. , the brain. This requires that the drug be absorbed into the blood from its site of administration and distributed to its site of action, permeating through the various barriers that separate these compartments. For a drug given orally to produce an effect in the central nervous system, these barriers include the tissues that make up the wall of the intestine, the walls of the capillaries that perfuse the gut, and the "blood-brain barrier", the walls of the capillaries that per-

fuse the brain. Finally, after bringing about its effect, a drug should be eliminated at a reasonable rate by metabolic inactivation, by excretion from the body, or by a combination of these processes.

1. Permeation

Permeation is the movement of drug molecules into and within the biologic environment. It involves several processes, the most important of which are discussed next.

1) Aqueous diffusion—Aqueous diffusion occurs within the larger aqueous compartments of the body (interstitial space, cytosol, etc) and across epithelial membrane tight junctions and the endothelial lining of blood vessels through aqueous pores that in some tissues permit the passage of molecules as large as MW 20 000 – 30 000. _ *

Aqueous diffusion of drug molecules is usually driven by the concentration gradient of the permeating drug, a downhill movement described by Fick's law (see below). Drug molecules that are bound to large plasma proteins (e. g. , albumin) do not permeate most vascular aqueous pores. If the drug is charged, its flux is also influenced by electrical fields (e. g. , the membrane potential and in parts of the nephron the transtubular potential).

2) Lipid diffusion—Lipid diffusion is the most important limiting factor for drug permeation because of the large number of lipid barriers that separate the compartments of the body. Because these lipid barriers separate aqueous compartments, the lipid:aqueous partition coefficient of a drug determines how readily the molecule moves between aqueous and lipid media. In the case of weak acids and weak bases (which gain or lose electrical charge-bearing protons, depending on the pH), the ability to move from aqueous to lipid or vice versa varies with the pH of the medium, because charged molecules attract water molecules. The ratio of lipid-soluble form to water-soluble form for a weak acid or weak base is expressed by the Henderson-Hasselbalch equation (see below).

3) Special carriers—Special carrier molecules exist for certain substances that are important for cell function and too large or too insoluble in lipid to diffuse passively through membranes, e. g. , peptides, amino acids, glucose. These carriers bring about movement by active transport or facilitated diffusion and, unlike passive diffusion, are saturable and inhibitable. Because many drugs are or resemble such naturally occurring peptides, amino acids, or sugars, they can use these carriers to cross membranes.

Many cells also contain less selective membrane carriers that are specialized for expelling foreign molecules. One large family of such transporters bind adenosine triphosphate (ATP) and is called the ABC (ATP-binding cassette) family. This family includes the P-glycoprotein or multidrug-resistance type 1 (MDR1) transporter found in the brain, testes, and other tissues, and in some drug-resistant neoplastic cells. Similar transport molecules from the ABC family, the multidrug resistance-associated protein (MRP1 through MRP5) transporters, play important roles in excretion of some drugs or their metabolites into urine and bile and in resistance of some tumors to chemotherapeutic drugs. Several other transporter families have been identified that do not bind ATP but use ion gradients for transport energy. Some of these are particularly important in the uptake of neurotransmitters across nerve ending membranes.

4) Endocytosis and exocytosis—A few substances are so large or impermeant that they can enter cells only by endocytosis, the process by which the substance is engulfed by the cell membrane and carried into the cell by pinching off of the newly formed vesicle inside the membrane. The substance can then be released inside the cytosol by breakdown of the vesicle membrane. This process is responsible for the transport of vitamin B_{12}, complexed with a binding protein (intrinsic factor) across the wall of the gut into the blood. Similarly, iron is transported into hemoglobin-synthesizing red blood cell precursors in association with the protein transferrin. Specific receptors for the transport proteins must be present for this process to work.

The reverse process (exocytosis) is responsible for the secretion of many substances from cells. For example, many neurotransmitter substances are stored in membrane-bound vesicles in nerve endings to protect them from metabolic destruction in the cytoplasm. Appropriate activation of the nerve ending causes fusion of the storage vesicle with the cell membrane and expulsion of its contents into the extracellular space.

2. Fick's law of diffusion

Fick's law predicts the rate of movement of molecules across a barrier. The concentration gradient (C_1—C_2) and permeability coefficient for the drug and the area and thickness of the barrier membrane are used to compute the rate as follows:

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

Thus, drug absorption is faster from organs with large surface areas, such as the small intestine, than from organs with smaller absorbing areas (the stomach). Furthermore, drug absorption is faster from organs with thin membrane barriers (e. g. , the lung) than from those with thick barriers (e. g. , the skin).

3. Water and lipid solubility of drugs

Ionization of weak acids and bases—The electrostatic charge of an ionized molecule attracts water dipoles and results in a polar, relatively water-soluble and lipid-insoluble complex. Because lipid diffusion depends on relatively high lipid solubility, ionization of drugs may markedly reduce their ability to permeate membranes.

Weak bases are ionized-and therefore more polar and more water-soluble-when they are protonated. Weak acids are not ionized-and so are less water-soluble-when they are protonated. The following equations summarize these points:

Protonated weakbase (charged, more water-soluble) = unprotonated weakbase (uncharged, more lipid-soluble) + proton

Protonated weak acid (uncharged, more lipid-soluble) = unprotonated weak acid (charge, more water-soluble) + proton

"Protonated" means associated with a proton(a hydrogen ion); this form of the equation applies to both acids and bases.

Solubility-The aqueous solubility of a drug is ofien a function of the electrostatic charge (degree of ionization, polarity) of the molecule, because water molecules behave as dipoles and are attracted to charged drug molecules, forming an aqueous shell around them. Conversely, the lipid solubility of a molecule is inversely proportional to its charge.

Many drugs are weak bases or weak acids. For such molecules, the pH of the medium determines the fraction of moleculescharged (ionized) versus uncharged (nonionized). If the pKa of ie drug and the pH of the medium are known, the fraction of molecules in the onized state can be predicted by means of the Henderson-Hasselbalch equation:

$$\log\left(\frac{\text{Protonated form}}{\text{Unprotonated form}}\right) = \text{pKa} - \text{pH}$$

This equation applies to both acidic and basic drugs. Inspection confirms that the lower the pH relative to the pKa, the greater will be the fraction of drug in the protonated form. Because the uncharged form is the more lipid-soluble, more of a weak acid will be in the lipid-soluble form at acid pH, whereas more of a basic drug will be in the lipid-soluble form at alkaline pH.

Application of this principle is made in the manipulation of drug excretion by the kidney. Almost all drugs are filtered at the glomerulus. If a drug is in a lipid-soluble form during its passage down the renal tubule, a significant fraction will be reabsorbed by simple passive diffusion. If the goal is to accelerate excretion of the drug (e. g., in a case of drug overdose), it is important to prevent its reabsorption from the tubule. This can often be accomplished by adjusting urine pH to make certain that most of the drug is in the ionized state, as shown in Figure 1-1. As a result of this partitioning effect, the drug will be "trapped" in the urine. Thus, weak acids are usually excreted faster in alkaline urine; weak bases are usually excreted faster in acidic urine. Other body fluids in which pH differences from blood pH may cause trapping or reabsorption are the contents of the stomach and small intestine; breast milk; aqueous humor; and vaginal and prostatic secretions

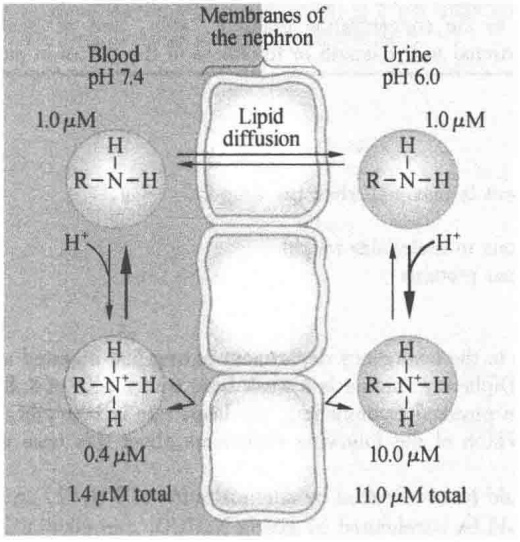


Figure 1-1 Trapping of a weak base (pyrimethamine) in the urine when the urine is more acidic than the blood. In the hypothetical case illustrated, the diffusible uncharged form of the drug has equilibrated across the membrane, but the total concentration (charged plus uncharged) in the urine is almost eight times higher than in the blood.

E. Drug groups

To learn each pertinent fact about each of the many hundreds of drugs mentioned in this book would be an impractical goal and, fortunately, is unnecessary. Almost all of the several thousand drugs currently available can be arranged in about 70 groups. Many of the drugs within each group are very similar in pharmacodynamic actions and often in their pharmacokinetic properties as well. For most groups, one or more prototype drugs can be identified

that typify the most important characteristics of the group. This permits classification of other important drugs in the group as variants of the prototype, so that only the prototype must be learned in detail and, for the remaining drugs, only the differences from the prototype.

CHECKLIST

When you complete this chapter, you should be able to:

◇Define and describe the terms receptor and receptor site.

◇Predict the relative ease of permeation of a weak acid or base from an knowledge of its pKa, the pH of the medium, and the Henderson-Hasselbalch equation.

Chapter 1 Summary Table

Major concept	Description
Pharmacology	The study of substances that interact with living systems through biochemical processes
Pharmacodynamics	The actions of a drug on a living organism, including mechanisms of action and receptor interaction
Pharmacokinetics	The actions of the living organism on the drug, including absorption, distribution, and elimination
Nature of drugs	Drugs are chemicals that modify body functions. They may be ions, carbohydrates, lipids, or proteins. They vary in size from lithium (MW 7) to proteins (MW≥50 000)
Drug permeation	Most drugs are administered at a site distant from their target tissue. To reach the target, they must permeate through both lipid and aqueous pathways. Movement of drugs occurs by means of aqueous diffusion, lipid diffusion, transport by special carriers, or by exocytosis and endocytosis
Rate of diffusion	Aqueous diffusion and lipid diffusion are predicted by Fick's law and are directly proportional to the concentration gradient, area, and permeability coefficient and inversely proportional to the length or thickness of the diffusion path

QUESTIONS

1. Bioavailability of an agent is maximal when the drug is( ).

(A) Highly lipid soluble

(B) Larger than 100 Daltons in molecular weight

(C) Highly bound to plasma proteins

(D) Highly ionized

(E) Lowly lipid soluble

2. A 3-year-old is brought to the emergency department having just ingested a large overdose of diphenhydramine, an antihistaminic drug. Diphenhydramine is a weak base with a pKa of 8.8. It is capable of entering most tissues, including the brain. On physical examination, the heart rate is 100/min, blood pressure 90/50 mm Hg, and respiratory rate 20/min. Which of the following statements about this case of diphenhydramine overdose is most correct? ( )

(A) Urinary excretion would be accelerated by administration of NH_4Cl, an acidifying agent

(B) Urinary excretion would be accelerated by giving $NaHCO_3$, an alkalinizing agent

(C) More of the drug would be ionized at blood pH than at stomach pH

(D) Absorption of the drug would be faster from the stomach than from the small intestine

(E) Hemodialysis is the only effective therapy

3. Botulinum toxin is a large protein molecule. Its action on cholinergic transmission depends on an intracellular action within nerve endings. Which one of the following processes is best suited for permeation of very large protein molecules into cells? ( )

(A) Aqueous diffusion

(B) Aqueous hydrolysis

(C) Endocytosis

(D) Lipid diffusion

(E) Special carrier transport