INTRODUCTION TO GENERAL PHARMACOLOGY

Second Edition

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A solid text...

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APPLETON-CENTURY-CROFTS
New York

79 80 81 82 83 / 10 9 8 7 6 5 4 3 2 1

Prentice-Hall International, Inc., London
Prentice-Hall of Australia, Pty. Ltd., Sydney
Prentice-Hall of India Private Limited, New Delhi
Prentice-Hall of Japan, Inc., Tokyo
Prentice-Hall of Southeast Asia (Pte.) Ltd., Singapore
Whitehall Books Ltd., Wellington, New Zealand

Library of Congress Cataloging in Publication Data
Csáky, T Z
Introduction to general pharmacology.

Bibliography: p.
Includes index.
1. Pharmacology. I. Title.
[DNLM: 1. Pharmacology. QV4.3 C958i]
RM300.C75 1978 615'.1 78-12464
ISBN 0-8385-4331-6

Design: Ronald F. Shey

PRINTED IN THE UNITED STATES OF AMERICA

Preface

Pharmacology is rapidly developing. New, effective but also potentially toxic remedies are continually produced; at the same time steady progress is being made toward a better understanding of the mode of action of drugs and toxic agents. The general principles presented in the first edition of this book are essentially still valid but, in view of the new developments, need to be supplemented and occasionally reinterpreted. Although the book has been substantially revised, its objective remains the same: to serve as an introduction to the general problems of pharmacology and toxicology in concise yet simple language without unnecessary sophisticated discourses and complex mathematical treatment.

I should like to express my gratitude to numerous friends and colleagues for their constructive and helpful criticism of the first edition which aided me in making the improvements in the present one. I should like to express my deep gratitude to my wife who found time midst her own busy professional life to help me and give me support. Mrs. Virginia Crutcher, with her excellent professional skill, helped in preparing the manuscript. Last but not least I should like to acknowledge the continued encouragement I have received from my many students who found the book useful in their studies and cared to tell me about it. This book is written primarily for students with various backgrounds and professional goals; therefore it gives me deep satisfaction if I can help them in any way.

Preface
to the First Edition

Drugs are a necessity in modern man's life as are food, clothing, and shelter. In our civilized society many professions and skills are involved in the process of production, distribution, and application of drugs. A drug usually originates from the laboratory of the chemist who designs and synthesizes the new compound, which is then tested for effectiveness and toxicity by the pharmacologist, toxicologist, and clinical pharmacologist, then distributed by the pharmacist and administered to humans, livestock, or pets by members of the various healing professions. In this cooperative effort the role of the pharmacologist is to examine the intricate interaction between the drug molecule and the living organism. Whereas those in the other sectors of this spectrum of professions need not become fully acquainted with the work of the pharmacologist, it is desirable that all should have some idea of the fundamental principles involved in the action of drugs. The fundamentals of drug action are studied by the branch of pharmacology called *general pharmacology*.

The purpose of this book is to serve as an introduction into the problems of general pharmacology. It cannot and does not attempt to give full explanation of all the phenomena; it only introduces the problems and describes some of the efforts of the human intellect toward solving them. This book is written for readers of diverse backgrounds, therefore the presentation of the material is kept simple and general, without going into superfluous details. Sophisticated explanations as well as complicated mathematical treatments are kept to a minimum. The actual therapeutic application of drugs is not systematically discussed in this volume; for those who wish to have a notion of the remedial use of the agents mentioned in the text, a brief description is given in the glossary.

This book is based on lecture notes prepared for medical, dental, and graduate students at The University of Kentucky. Many have helped in various stages of the preparation of this volume. I should like to express my appreciation to my colleagues in the Department of Phar-

macology who have shared with me the responsibility of teaching the course in General Pharmacology and offered constructive criticism, and to the students who raised many questions and were instrumental in clarifying in many ways my own thinking and expressions. I should like to record my debt in particular to Doctors V. Dischka, W. Waddell, H. Gordon, J. Engelberg, P. Sears, and J. Ambrus and Mr. R. Benjamin for their critical reading of various parts of the manuscript. Thanks are due to Professor P. Koe-Krompecher for contributing the art work in Figure 10. Miss L. Denman, Mrs. V. Crutcher, and Mrs. M. Imredy rendered invaluable technical help in preparing the text for publication. The dedication of this volume to my wife is only a modest expression of my gratitude for the continuous help which she has rendered in every phase of the work.

Contents

CHAPTER 1

Introduction

Pharmacology (Greek: *pharmakon* = drug; *logia* = study) is the study of drugs. A drug is a substance which changes the chemical environment and through this change elicits a reaction in the living tissue. Consequently the concept "drug" includes all biologically active substances, i.e., those produced within the body, called autacoids (Greek: *autos* = self, *akos* = remedy, drug) and those foreign to the body, called xenobiotics (Greek: *xenos* = strange, foreign).

Since drugs are mainly used to treat the sick, pharmacology is a part of the broad science of medicine (this term includes all the healing arts and sciences: human, oral, and veterinarian medicine).

Disciplines involving drugs fall in two main categories: 1.) *pharmacy*, which is engaged in identification (pharmacognosy), synthesis (pharmaceutical chemistry), manufacturing, packaging, marketing, and selling drugs; and 2.) *pharmacology*, which is interested in the mode of action of drugs (pharmacodynamics), of poisonous materials (toxicodynamics, toxicology), and in the use of drugs in therapy (pharmacotherapeutics). A special area of pharmacology is *clinical pharmacology*, which deals with the special problems of drug actions and drug application to man.

Pharmacodynamics is the study of the mechanisms of the action of drugs and of the various factors which influence this action. These problems can be considered generally, regardless of the individual drug (general pharmacodynamics), or in connection with individual drugs or drugs of similar actions (special pharmacodynamics).

Toxicology is the study of the recognition, mechanism, prevention, and treatment of harmful interactions between chemicals and the living tissue. Ever-expanding industrialization, the increasing volume of petroleum products burned in combustion-type motors in vehicular traffic, and the extensive use of chemicals for pest and weed control in food production all create serious chemical pollution of the environment. As a consequence of this toxicologic crisis, environmental toxicology in particular is developing into a formidable science of its own. Nonetheless the basic problems of toxicology are identical with those of pharmacology, namely,

the effect of changes in the chemical environment on the living tissue; therefore pharmacology and toxicology will always be closely related disciplines.

The notes in the subsequent pages were written as an introduction to general pharmacodynamics. The subject can be studied on various levels of integration:

1. All the various complex reactions continually occurring in an organism (the integration of which is called "life") ultimately are interactions between a number of molecules of varying complexity. Since drugs themselves are well-defined molecules, it is reasonable to assume that they also interact with the molecules of the body. This interaction then results in a change of the molecules of the body (pharmacologic effect) and not infrequently in the alteration of the drug (drug metabolism). *Molecular pharmacology* is the study of the action of drugs on the molecular level. The next five chapters deal with the problems of molecular pharmacology.

2. Drug effects can be examined on a higher level of integration. The unit of living substance, the cell, is the composite of a large number of molecules and exhibits the basic functions of life: respiration, assimilation, and reproduction. Drugs change the chemical environment and, by modifying molecular structure, have an influence on the function of the cell. *Cellular pharmacology* is the study of drug action on this level. Some of the most versatile substructures of the cells are the lipoprotein membranes. While Chapter 7 deals with the pharmacodynamics of these structures, a note of caution is sounded in Chapter 8 that not all drug actions are directed to the cell: the extracellular elements may also be the targets.

3. In the practical pharmacotherapeutic application of drugs one deals with patients who are neither molecules nor (as a rule) single cells. If pharmacodynamics is studied in a highly integrated organism, new problems emerge, such as the body distribution of the drug which determines its concentration at the site of action (Chap. 9). Another problem is the multiplicity and complexity of drug action when given alone or in combination with another drug (Chaps. 10, 11). In Chapters 12 and 13 individual variations, including genetic control, in response to drugs is discussed, and in Chapter 14 the organ- and species-selective actions of drugs are described. Chapter 15 concludes *integral pharmacology* with a discussion of some quantitative aspects.

This monograph does not attempt to cover the entire field of general pharmacology or even to give a comprehensive summary of all the problems. Its purpose is to *introduce* the subject, to point out the problems, and to call attention to the fact that a knowledge of the fundamental aspects of pharmacodynamics can be not only a rewarding exercise of

the intellect but also of practical value in attempting to practice the art of medicine on a scientific basis.

For those who desire more extensive information and more sophisticated discussions, a suggested reading list is given at the end of each chapter. Again, these lists are not comprehensive but are sufficient and broad enough to make those who read them well informed on the subject. Preference is given to comprehensive and review articles rather than to detailed individual papers because minutiae are not essential to general understanding. Those who plan to enter research will come around later to studying the description of detailed experimental work.

Some references are so broad that they relate to the subject of several chapters. Instead of listing them repeatedly at the end of each chapter, I have grouped them below. Also, a list of the major pharmacologic reference books and a list of the current (i.e., published within the last five years) pharmacology textbooks in English are provided. Finally those periodicals and periodically published monographs will be recorded, which feature review articles related to pharmacology.

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PART I

MOLECULAR PHARMACOLOGY

CHAPTER 2

Chemical Bonds and Water

On the molecular level the action of drugs undoubtedly involves a reaction between the drug molecule and the molecules of the living organism. For such a reaction to occur, the drug molecule has to combine temporarily with the molecules of the tissues, i.e., it has to hold on by certain forces restricting its random movement. This chapter considers those forces, or chemical bonds, which can be involved in holding two atoms or molecules together.

All living tissues contain water, which is not only a solvent but an integral part of the living machinery. Water is also involved in the bonding between the molecules of the body and of the drug. Consequently some of the biologically important properties of water, particularly with reference to their significance in chemical bonding, will be discussed briefly.

BONDING

It is useful to remember, from elementary chemistry, that an atom consists of a positively charged nucleus surrounded by negatively charged electrons. The simplest atom, hydrogen, contains the simplest nucleus, consisting of a positively charged proton surrounded by one electron containing the same, but negative, charge. The nucleus of the oxygen atom is composed of eight positively charged protons and eight neutrons, the latter having no charge; the surrounding eight negatively charged electrons are necessary to neutralize the quantitative charge of the protons. Atoms with higher atomic weights are composed of heavier nuclei containing more protons and neutrons and also more electrons.

Electrically balanced atoms are neutral. If one or more electrons are removed from a neutral atom, the resulting particle has a positive charge. Conversely, adding more electrons to the atom results in a negatively charged particle. Charged particles are called ions. The simplest positive ion is the hydrogen ion, which is essentially a proton.

Atoms, atomic groups, or molecules are held together by various forces called chemical bonds. The strength of a given bond is usually measured by the energy (in kilocalories per mole) needed to break it. With the exception of covalent bonding (50 to 150 kcal/mole), all attractions in biologic systems are relatively weak (1 to 5 kcal/mole) so that they can be readily formed and broken at the temperature of living tissue.

The following are the commonest chemical bonds:

1. A **covalent bond** occurs when two atoms are held together tightly by sharing a pair of electrons. This very strong chemical bond is responsible for the chemical stability of most nonionic substances. The very high binding energy renders the bond practically irreversibly bound at ordinary temperatures unless a catalytic agent is used. In living organisms, enzymes can provide the catalysis.

2. An **ionic bond** is formed by the electrostatic attraction between oppositely charged particles. The strength of this bond depends on the distance between the two ions and decreases with the square of the distance.

3. A **hydrogen bond** is formed when the hydrogen atom, with only one stable electron orbital, can form only one covalent bond. However, the hydrogen nucleus, a bare proton, because of its strong electropositive nature, can form a bridge between two electronegative groups. This attraction is called the hydrogen bond. It is essentially ionic and is much weaker than a true covalent bond. It can be formed only by hydrogen which can bind only with two strongly electronegative atoms, e.g., fluorine (F), oxygen (O), or nitrogen (N):

F–H····O
N–H····N
N–H····O
O–H····O

(The solid lines represent covalent bonds, the dots represent hydrogen bonds.)

Water, by its chemical nature, is a compound that can readily form hydrogen bonds (both through its H and O). Such bonds are responsible for many of the physical, chemical, and biologic peculiarities of water (see "Structure of Water").

4. A **hydrophobic bond** is the attraction between two apolar groups in aqueous environment. These bonds are of great pharmacologic importance. Because water is essential for their formation, they will be discussed in this chapter in connection with the structure and behavior of water.

5. **The van der Waals-London forces** are very short-range attractive forces between any two neutral atoms or atomic groupings. They become weaker in proportion to the seventh power of the distance between the atoms. Singularly, they represent relatively weak bonds (0.5 to 1.0 kcal/mole), but in the case of close fit their number can become sizable and cause the groups to cling together.

STRUCTURE OF WATER

In the water molecule, one oxygen atom is bound covalently with two hydrogen atoms. Water also can be regarded as a negatively charged oxygen ion with two positively charged hydrogen ions attached to it.[1] The atoms in the water are not arranged in a straight line or in 90° as is usually the case for this type of molecule, but the H–O–H molecule forms an angle of 104.5°, and the charges are separated within the water molecule, causing the center of the positive charge to be one side of the center of the negative charge. Thus the water molecule is a typical strong dipole (Fig. 1). Several important properties follow from this dipolar structure:

1. Water reacts with ions to form hydrates. Negative ions attract the positive end of the surrounding water molecules, positive ions the negative ends. Because of its dipolar (or simply "polar") nature, water is an excellent solvent for ionic materials.

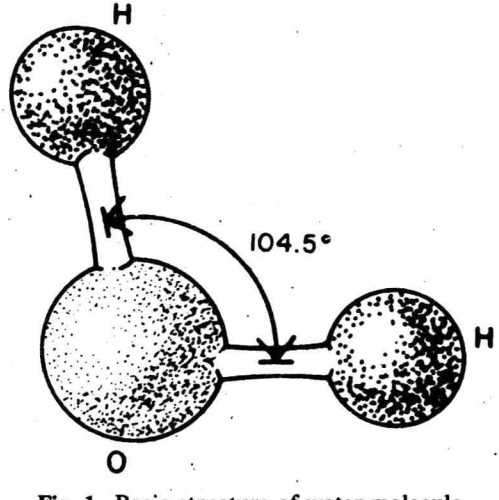

Fig. 1. Basic structure of water molecule.

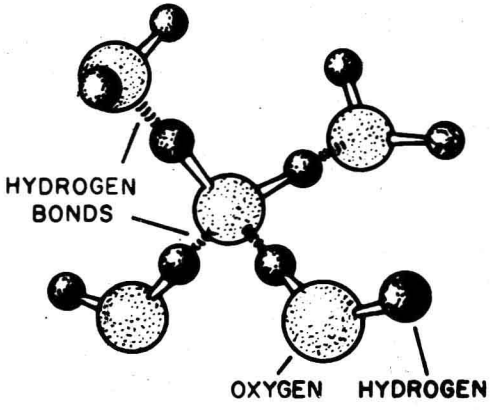

Fig. 2. Building block of structured water.

2. The strongly electronegative oxygen pole of water exerts a weak attraction for the strongly electropositive hydrogen of another water molecule; thus hydrogen can form an electrostatic bridge (hydrogen bond) between two molecules of water. In fact each water molecule is capable of forming four hydrogen bonds. Such five-member units in which four water molecules are arranged in tetrahedral fashion around a center molecule, bound together by hydrogen bonds, form the basic building blocks of structured water, such as ice (Fig. 2). In the structure of ice, each molecule is surrounded by only four immediate neighbors; it is a loose structure; hence it has a low density. When ice melts, part of the structure collapses, but even the liquid water is partially structured: "quasi ice." This is the reason for its high boiling point (the nearest chemical relative of water, hydrogen sulfide, H_2S, boils at $-60°$ C, 160 degrees lower than water).

Hydrogen bonding within water does not represent a rigid structure: the bonds are continually broken and reformed (the average lifetime of a given hydrogen bond is about 10^{-11} second). Hydrogen bonds can also form between water and other polar molecules with appropriate atomic groupings. This is why water is an excellent solvent not only for ions but also for substances with groups which can readily form hydrogen bonds, e.g., —OH, —NH. These groups are called hydrophilic (Greek *hydor* = water, *philos* = loving, fond of) as contrasted with those that cannot form hydrogen bonds, e.g., $—CH_3$, which are called hydrophobic (Greek *phobos* = to shy away).

In living tissue a large part of the water is bound to various hydrophylic groups. Those with charges, including most proteins and some other macromolecules, bind the first layer of water firmly and subsequent