INTRODUCTION TO MEDICINAL CHEMISTRY

Introduction to Medicinal Chemistry

How Drugs Act and Why

Alex Gringauz

WILEY-VCH

New York • Chichester • Weinheim • Brisbane • Singapore • Toronto

Dr. Alex Gringauz
Arnold and Marie Schwartz College of Pharmacy and Health Sciences
Long Island University
75 Dekalb Avenue at University Plaza
Brooklyn, NY 11201

This book is printed on acid-free paper. ♾

Library of Congress Cataloging-in-Publication Data

Gringauz, Alex, 1934-
Introduction to medicinal chemistry : how drugs act and why/by Alex Gringauz.
p. cm.
Includes bibliographical references and index.
ISBN 0-471-18545-0 (alk. paper)
1. Pharmaceutical chemistry. I. Title.
[DNLM: 1. Chemistry, Pharmaceutical. 2. Pharmacology. QV 744 G8671 1996]
RS403.G76 1996
615'.7—dc20
DNLM/DLC
for Library of Congress 95-49331
CIP

Printed in the United States of America

ISBN 0-471-18545-0 Wiley-VCH, Inc.

10 9 8 7 6 5 4 3 2

Introduction to Medicinal Chemistry

Preface

This book is intended to be useful, indeed necessary, to students pursuing a career in the health sciences that require a knowledge and understanding of drugs. This includes their rational therapeutic utilization, their shortcomings and hazards, their mechanisms of action, their stabilities in the bottle as well as the in the body, and some grasp of the thinking that goes into drug design and development. The author unabashedly confesses to a highly chemical bias in this presentation, since all aspects of drug comprehension ultimately must be founded on chemistry.

It is the pharmacy student, as the future practitioner of the rapidly changing profession of pharmacy, who will find this book invaluable. It is the pharmacist who is consistently, if not constantly, involved with drugs in all aspects. His or her interest necessarily is not that of the curious bystander. An extensive knowledge of drugs is not only required for professional competency, it is also legally mandated. This requires a background in organic chemistry, biochemistry, and some basic physiology and pharmacology. Since these, and introductory biology courses are somewhat compartmentalized in most undergraduate programs, this book should be viewed as a bridge to the extensive pharmacology and clinical training of the modern pharmacy curriculum.

It is anticipated that this publication will also be used at the early graduate training level, e.g. an M.S. en route to the Ph.D. degree in various pharmaceutical sciences such as medicinal chemistry, pharmacology, and pharmaceutics. The curious bystander who was mentioned previously should not be overlooked. Here one might include the chemist and biologist working in other fields whose interest might be piqued as to what drug chemistry is all about.

This book is not intended for the medicinal chemistry practitioner, one who is practicing its art and science. It also does not purport to make a medicinal chemist out of its reader, although it may be hoped that some will be "turned on" to such a pursuit. Rather, its intent is to explain drugs to the prepared reader as a comprehensive package by combining the necessary biological/physiological concepts with their chemistry so that a more total picture can be seen. After all, drugs must be viewed as complex chemicals used to affect chemical processes in an extremely complex biochemical system: the human mammal. Therefore, any attempt at a complete comprehension of drugs while ignoring their chemistry is an obviously futile endeavor.

Alex Gringauz
Brooklyn, New York

Acknowledgements

No serious effort in life is totally accomplished by oneself. This book is no exception. My wife, Donna, was exceedingly helpful with much of the grunt work, which included adept word processing and very frustrating indexing. The aid was usually cheerfully, and occasionally grudgingly, given. My sons harbored serious doubts regarding the ultimate completion of this effort.

I am also grateful to colleagues who graciously agreed to evaluate portions of the manuscript. Their comments, especially those that were critical, were particularly helpful. I therefore wish to thank Dr. Victoria Roche (Creighton University), Dr. Jack DeRuiter (Auburn University), and Dr. Frank Fillipeli (Drake University). My thanks also to Dr. Ed Immergut for his help and faith in me.

My utmost gratitude, however, must be extended to Steven So, my former student, now colleague and, most of all, friend, without whose creative wizardry at the computer none of the exquisite graphics would have come into existence. I also wish to thank Steve's wife, Mei, for her angelic tolerance of the disruptions this book must have created in her life.

Contents

CHAPTER

1

Basic Considerations of Drug Activity

1.1. Introduction

Voltaire (1694–1778) stated, "Therapeutics is the pouring of a drug of which one knows nothing into a patient of whom one knows less." The medical and pharmaceutical sciences have been working diligently to ameliorate both aspects of the problem. The progress made, especially in the period following World War II, has been impressive, if not astounding. However, there are many important riddles still to be solved and much to be learned.

One of the areas of study has concerned itself with the determination of the factors that affect a drug's activity and the reasons for the effects observed. A relationship between physicochemical properties of a chemical compound and its biological activity has been assumed and sought for more than a century. Our definition of what constitutes physical and chemical properties, however, has been constantly expanding as a result of new ideas, discoveries, and instrumentation. Modern instrumentation in particular has helped to change our outlook on drugs.

1.2. Factors Affecting Bioactivity

The biochemical systems encountered by a drug molecule are extremely complex. Therefore, it should not be surprising that the factors affecting the drug's interactions and contributing to its final effect are also manyfold. The factors may be divided into three categories:

1. Physicochemical properties such as solubility, partition coefficients, and ionization.
2. Chemical structure parameters such as resonance, inductive effect, oxidation potentials, types of bonding, and isosterism.
3. Spatial considerations such as molecular dimensions, interatomic distances, and stereochemistry.

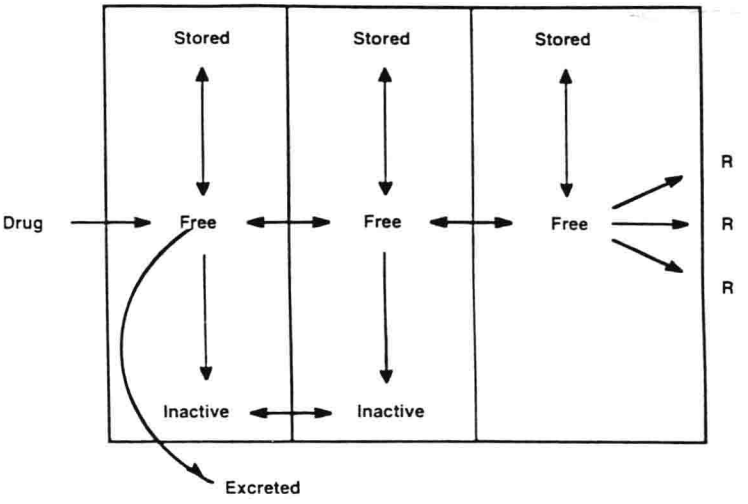


Figure 1-1. The fate of a drug. R is a receptor.

1.2.1. Physicochemical Properties

The physicochemical properties considered in this discussion are important because they all relate to the transport of the drug molecule to its site of action, more than likely a receptor with which the drug will interact in a given tissue or in an invading microorganism. Figure 1-1 represents a simplified distribution chart of a bioactive substance in the body.

A drug given orally or parenterally must traverse several semipermeable membranes before reaching its destination. The efficiency of the passage depends on the solubility characteristics of the drug, that is, its behavior in aqueous solution and toward lipids. Also, note that in each compartment the molecule is subject to various factors tending to decrease the concentration of the active form. Thus the drug may be constantly excreted either directly or following biochemical inactivation. In addition, if the drug is bound in a stored but inactive form, such as to plasma proteins, there tends to be a decrease in its effectiveness. Since it is only the unbound free drug that produces the desired pharmacologic actions, it may be possible to compensate for this phenomenon by increasing the dose.

We are concerned with solubility in polar solvents such as water and in nonpolar solvents such as lipids. More specifically we are interested in a drug's *partition coefficient*, which is the relative solubility between these two phases. Such a coefficient is determined by dissolving the substance in an aqueous solution and equilibrating it by agitation with an organic solvent.[1] The ratio of the concentration of the drug in the two phases is the partition coefficient. Any ratio greater than 0.01 indicates appreciable lipid solubility.

Since most drugs are not structurally similar to normal cellular components, they are not likely to be transported across the membranes by "active transport" mechanisms. Rather, their rate of passage through the lipoprotein membranes is mainly a passive process determined by their degree of lipid solubility, or partition coefficient.

---

[1] Chloroform, olive oil, or 1-octanol to simulate the lipid phase of a biological system.

Solubility is important to bioactivity. Many groups of drugs, especially those with closely related structures, exhibit a direct relationship to solubility (i.e., increased lipid solubility exhibits higher bioactivity). This correlation is true in general anesthetics, local anesthetics, certain antibacterial agents, antiviral agents, and others. Of course, solubility factors are closely related to drug absorption. The degree of absorption is one important determinant of the intensity of the drug's action.

In addition to lipid solubility, another physicochemical property of molecules, which affects solubility directly, is the degree of the drug's electrolytic nature. All chemical compounds can be classified by their electrical conductivity behavior in aqueous solution. When dissolved, inorganic salts will completely dissociate into ions (charged particles). Positively charged ions, which are electron deficient with respect to the neutral atom, are called *cations*, whereas negatively charged ions (carrying excess electrons) are called *anions*. Thus sodium chloride will dissociate, or ionize, yielding sodium ions and chloride ions.

$$NaCl \rightarrow Na^+ + Cl^- \tag{1.1}$$

Substances that ionize completely in solution are considered to be *strong electrolytes*. Compounds that are completely undissociated, but that are still very water soluble, are termed *nonelectrolytes*. They do not ordinarily increase the electrical conductivity of the solution. Examples of nonelectrolytes are such polar organic compounds as sugars, low-molecular-weight alcohols, and urea. A majority of drugs are in a third category, *weak* electrolytes. These substances are only partially ionized in solution. They exist as a mixture of ionized and un-ionized molecular forms. The un-ionized molecular species is the more lipid-soluble form. The ionized portion of such a drug molecule usually has a much lower, often negligible, lipid solubility. Therefore, its passage through membranes frequently approaches insignificant levels. This fact has direct bearing on a drug's capacity for absorption, and therefore activity.

When a drug is a weak acid or a weak base, we find that its lipid solubility is greatly affected by the pH of its environment and by its degree of dissociation, expressed as pKa. The fraction of the total drug concentration that is in the molecular and ionic forms is indicated by the dissociation constant *Ka*. Equations 1.2 and 1.3 illustrate the interaction of weak acids and weak bases with water, which results in dissociation. *A* and *B* represent acids and bases, respectively.

$$HA + H_2O \rightleftharpoons H_3O^+ + A^- \tag{1.2}$$

$$BH^+ + H_2O \rightleftharpoons H_3O^+ + B \tag{1.3}$$

Note that the initial reaction for both substances is shown as a protolytic reaction (protonation) between an acid species and water. The water is present in such large excess that the proton transfer has only a negligible effect on its total concentration. Thus water can be eliminated from the equation without significant error. Our simplified equation for a weak acid now becomes

$$HA \rightleftharpoons H^+ + A^- \tag{1.4}$$

Applying the law of mass action we obtain the general relationship:

$$Ka = \frac{[H^+][A^-]}{[HA]} \tag{1.5}$$

The equation can be rearranged into the more useful Henderson–Hasselbach equation:

$$\text{pKa} = \text{pH} + \log \frac{C_u}{C_i} \tag{1.6}$$

where C_u and C_i represent the concentrations of un-ionized and ionized forms of the drug, respectively. The corresponding relationships for weak bases are:

$$B + H^+ \rightleftharpoons BH^+ \tag{1.7}$$

$$\text{Ka} = \frac{[H^+][B]}{[BH^+]} \tag{1.8}$$

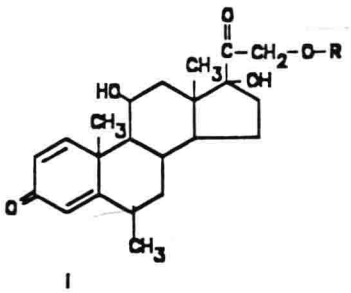
$$\text{pKa} = \text{pH} + \log \frac{C_i}{C_u} \tag{1.9}$$

Weak acids have a higher pKa than stronger ones. Thus, an acid with a pKa of 5 is 100 times weaker than an acid whose pKa is 3; conversely weaker bases have lower pKa values.

It is not surprising that the bioactivity of many weak acids and bases is directly related to their degree of ionization, which in turn is greatly affected by the pH of the medium in which the drug finds itself.

Since many of the drugs we encounter are weak acids or bases, an understanding of their solubility characteristics is important. Because the ionic form is the more water-soluble chemical species and the pH of the solvent environment determines the degree of ionization achieved, it becomes possible, for example, to formulate liquid pharmaceutical products such as injectables, syrups, and elixirs of drugs that would ordinarily be poorly soluble.

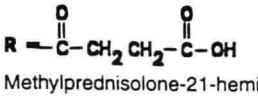
Low-molecular-weight carboxylic acids such as acetic acid and propionic are totally water soluble. However, as they go beyond a five-carbon content their solubility decreases rapidly. An interesting example of how advantage can be taken of these factors to form a water-soluble parenteral dosage form of a drug that is highly insoluble is the steroid methylprednisolone (structure I).



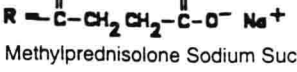
I

R = H

Methylprednisolone



Methylprednisolone-21-hemisuccinate



Methylprednisolone Sodium Succinate

Reacting the drug with succinic anhydride results in the hemisuccinate derivative, obviously now a large 25-carbon carboxylic acid. Its solubility is less than 1 mg/ml. However, by the simple expedient of neutralizing the acidic function and forming the ionic sodium salt the solubility is increased to over 200 mg/ml. This is more than adequate to formulate injectable products of considerable concentrations.

Let us apply these concepts and attempt to make some predictions. The very useful, widely used drug aspirin is a weak acid with a pKa of 3.5. It is usually taken orally. The pH of gastric juice in the stomach is about 1; in the small intestine it is about 6. From which area would the majority of this drug be absorbed into the bloodstream? By applying Equation 1.6 we find that the drug is almost completely un-ionized in the gastric juice.

Since we have already seen that the molecular form of a drug is the lipid-soluble species, we would expect it to be readily absorbed in the stomach, which has lipoprotein membranes in its lining. This is actually the case for many weakly acidic drugs. The converse argument, of course, would apply to weakly basic drugs. We would expect their absorption from the stomach to be poor.

Consider the three barbituric acid derivatives thiopental, secobarbital, and barbital with respective pKa of 7.6, 7.9, and 7.8. These drugs are very weak acids. On the basis of their ionization constants we would expect very little difference in their absorption rates from the stomach, yet the drugs are absorbed at very different rates. The reason becomes apparent when the partition coefficients between chloroform and water are considered. Thiopental's value is over 100, whereas the values of secobarbital and barbital are 23 and 0.7, respectively. Now which would one predict to be the least rapidly absorbed and which the most? By considering only one physicochemical parameter and excluding others, erroneous conclusions can result. Figure 1-2 illustrates a hypothetical relationship of biological activity as a function of pH only.

Studies on the distribution of drugs between the intestine and plasma, between kidney tubules and urine, and between plasma and other body compartments suggests that the important general conclusion that only *lipid-soluble, undissociated forms of a drug passes through membranes* readily. Ionized species usually cannot pass unless a mediated transport system is present for a specific compound (or a close congener) in a given membrane, which is a rare occurrence.

The previous discussion may be an oversimplification since there are some anomalies that are more difficult to explain. For example, almost two thirds of a dose of salicylic acid (pKa 3) is absorbed from the rat stomach in 1 hour at pH 1, as might be expected. However, if the pH is raised to 8, at which point the acid is completely ionized, over one-tenth of the dose is still absorbed. Another possibility that should be kept in mind is that the un-ionized form of some weak electrolyte drugs may have intrinsically poor lipid solubility because of

Basic Consideration of Drug Activity

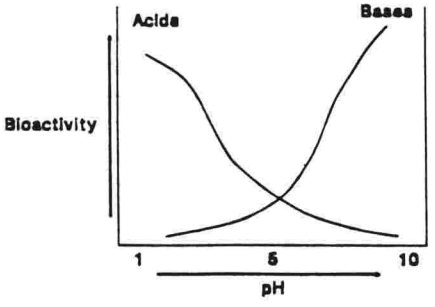


Figure 1-2. Bioactivity as a function of pH.

a high proportion of polar functional groups. The opposite situation, where the ionized form may still have appreciable lipid solubility, where the drug has few polar groups but a relatively large hydrocarbon skeleton, is a possibility. Methyl prednisolone sodium succinate would be an example.

Although lipid solubility at physiological pH enhances a drug's penetrability of a membrane, too much may not necessarily result in increased activity. Many antibacterial sulfonamides exhibit their peak effectiveness at pH values at which they are only approximately half-ionized. These sulfonamides have pKa values in the 6–8 range. The apparent reason is that even though the molecular form can readily penetrate the bacterial membrane, only the anionic form is bacteriostatic once inside. Thus approximately 50% ionization appears to be optimal. Nevertheless, several highly active sulfonamides exist with a pKa considerably outside of this optimal range. Other factors are also presumably involved.

In summary, if bioactivity is caused by ionic forms of drugs, activity will increase as the degree of ionization increases. On the other hand, if undissociated molecules are the active species, then increased ionization will necessarily reduce this activity.

1.2.2. Chemical Structural Aspects

One of the long-term objectives of medicinal chemistry is the establishment of relationships of a drug's structural features to its pharmacological properties [i.e., structure–activity relationships (SARs)]. Although qualitative linkages, often on an intuitive basis, have sometimes been assigned, a quantitative foundation is the goal. Attempts to express pharmacological activity by mathematical means are being made, with some success. Both classical qualitative concepts and the newer more numerical ideas must be taken into consideration to understand drug activities better and, equally important, more rationally to design and then develop new, more effective, and safer drugs. Both aspects will be briefly described here. Some concepts will be developed in somewhat greater detail in subsequent chapters.

1.2.2.1. Resonance and Inductive Effects

Resonance is a concept stating that if we can represent a molecule by two or more structures that differ only in their electron, but not atomic, arrangement then neither (or any) of the representations is satisfactory since the molecule is a *hybrid* of these possible structures. Each structure as depicted contributes to the "real" structure. One advantage of this idea is that it forces us to think of a drug molecule from additional mental angles rather than just those normally printed on a page. Electron density and electron distribution patterns help explain a drug's reactivity.

Unlike the theoretical resonance concept, *inductive effects* are measurable electrostatic phenomena. Inductive effects are caused by actual electron shifts, or displacements, along bonds. These shifts result from attractions exerted by certain groups because of their electronegativity. Thus groups or atoms that attract electrons more strongly than hydrogen have a *negative inductive effect* and tend to displace electron density toward themselves. The halogens are prime examples. Groups with *positive inductive* effect tend to push electrons into the rest of the molecule. These are usually alkyl groups such as methyl and isopropyl. The electronic consequences are a strong influence on physicochemical properties such as acidity. Table 1-1 illustrates this effect. Using formic acid as the prototype, we