WILSON AND GISVOLD'S

Textbook of Organic Medicinal and Pharmaceutical Chemistry

Ninth Edition

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CHAPTER 2

Physicochemical Properties in Relation to Biologic Action

John H. Block

INTRODUCTION

Modern drug design, as compared with, *Let's make a change on an existing compound or synthesize a new structure and see what happens*, is a fairly recent discipline still in its infancy. It is based on modern chemical techniques utilizing recent knowledge of disease mechanisms and receptor properties. A good understanding of how the drug is transported into the body, distributed throughout the body compartments, metabolically altered by the liver and other organs, and excreted from the patient is required, along with the structural characteristics of the receptor. Acid–base chemistry is utilized to aid in formulation and biodistribution. Those structural attributes and substituent patterns responsible for optimum pharmacologic activity can be predicted many times by statistical techniques, such as regression analysis. Conformational analysis permits the medicinal chemist to predict the drug's three-dimensional shape that is *seen* by the receptor. With the isolation and structural determination of specific receptors and the availability of computer software that can estimate the three-dimensional shape of the receptor, it is possible to design molecules that will show an optimum fit to the receptor.

HISTORY

Initially, drugs were extracted from plant sources to obtain agents such as digitalis, quinine, and morphine, medicinal agents that are still in use today. Specific plants are selected by the chemist because the crude preparations were being used for treatment of medical conditions by the local population where the plant grew.

Early drug design started with elucidation of the structure of the natural product, followed by selective changes in the molecule. The latter was done for many reasons, including the reduction of an undesirable pharmacologic response (side effect); obtaining a better pharmacokinetic response; altering the drug's metabolism; securing a more plentiful, less costly supply; and producing a competing product. Let us use the morphine alkaloid as an example. Literally thousands of compounds have been synthesized in an attempt to separate the desired analgesia from the undesirable addiction liability. This tremendous effort in numerous research laboratories, over many years and involving many scientists, had been minimally successful until a better understanding of the opiate receptor developed (see Chap. 9).

In other examples, there has been good success at this empirical approach. Alteration of the cocaine structure has led to the very successful local anesthetics that lack cocaine's undesirable central effects (see Chap. 15). In contrast with this success story, there have been no significant commercial synthetic replacements for digitalis or colchicine.

Synthetic medicinal chemistry as a discipline became more intense in the 1900s, but many of the so-called principal compounds still were based on a natural product, a fortuitous observation, or an unsuspected chemical reaction. The phenothiazines (see Chap. 9) were first synthesized as antihistamines, but a careful pharmacologic evaluation led to their use as major tranquilizing agents that revolutionized the care of the severely mentally ill patient. The benzodiazepines (see Chap. 9) originated from an unexpected ring enlargement and resulted in a very important group of central nervous system relaxants.

Economic factors have stimulated the type of scientific investigations required to carry out focused

new drug development. It has become increasingly costly to develop a new drug that will be approved by the U. S. Food and Drug Administration (FDA). At one time, safety was the main criterion for FDA approval. Today, demonstration of efficacy is an essential requirement, along with safety considerations. This has led to (1) increased basic research on the disease process for which a drug treatment is sought, (2) mathematically modeling the pharmacokinetics of the drug's distribution, (3) elucidation of the biochemistry of the pharmacologic response from the drug, (4) learning the metabolic fate of the drug, (5) defining those specific structural characteristics of the drug responsible for the desired pharmacologic response, and (6), where possible, visualizing the structural characteristics of the receptor. Although the number of new compounds introduced annually has decreased from earlier years, the products now coming into use are showing dramatic effects in the treatment of disease. More importantly, because of the intensive background investigation that has led to the design of today's new agents, a better understanding of the drug's mechanism of action is known. Indeed, this is an exciting time to practice pharmacy.

OVERVIEW

A drug is a chemical molecule. Following introduction into the body, a drug must pass through many barriers, survive alternate sites of attachment and storage, and avoid significant metabolic destruction before it reaches the site of action, usually a receptor on or in a cell (Fig. 2-1). At the receptor, the following equilibrium usually holds.

$$\text{Drug} + \text{Receptor} \rightleftharpoons \text{Drug–Receptor Complex} \downarrow \text{Pharmacologic Response} \quad \text{(Rx. 2-1)}$$

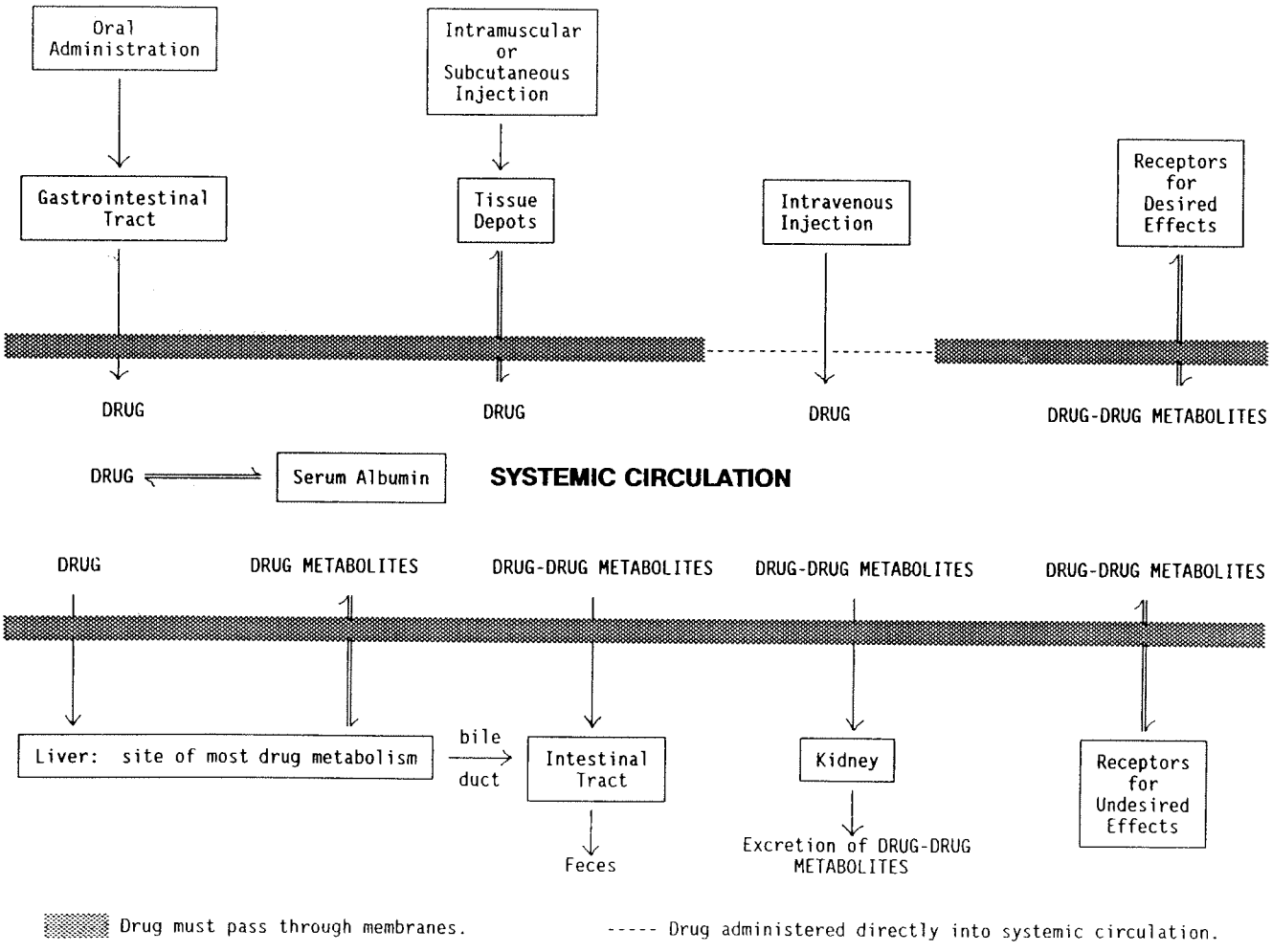


FIG. 2-1. Summary of drug distribution: Solid bars: Drug must pass through membranes. Broken lines: Drug administered directly into systemic circulation.

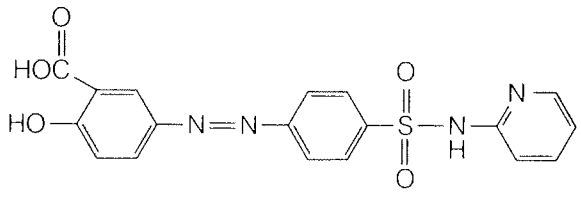
The ideal drug molecule will show favorable-binding characteristics to the receptor, such that the equilibrium lies to the right. At the same time the drug will be expected to dissociate from the receptor and reenter systemic circulation to be excreted. The major exceptions include the alkylating agents used in cancer chemotherapy (see Chap. 8) and a few inhibitors of the enzyme, acetylcholinesterase (see Chap. 12). Both of these subclasses of pharmacologic agents form covalent bonds with the receptor. In these cases the cell must destroy the receptor or, as with the alkylating agents, the cell would be replaced, ideally with a normal cell. In other words, the usual use of drugs in medical treatment call for the drug's effect to last for only a finite period. Then, if it is to be repeated, the drug will be administered again. If the patient does not tolerate the drug well, it is even more important that the agent dissociate from the receptor and be excreted from the body.

DRUG DISTRIBUTION

ORAL ADMINISTRATION

An examination of the *obstacle course* (see Fig. 2-1) faced by the drug will give a better understanding of what is involved in developing a commercially feasible product. Assume that the drug is administered orally. The drug must go into solution for it to pass through the gastrointestinal mucosa. Even drugs administered as true solutions may not remain in solution as they enter the acidic stomach and then pass into the alkaline intestinal tract. (This will be explained further in the discussion on acid–base chemistry.) The ability of the drug to dissolve is governed by several factors, including its chemical structure, variation in particle size and particle surface area, nature of the crystal form, type of coating, and type of tablet matrix. By varying the formulation containing the drug and physical characteristics of the drug, it is possible to have a drug dissolve quickly or slowly, the latter being the situation for many of the sustained-action products. An example is orally administered sodium phenytoin; for which variation of both the crystal form and tablet adjuvants can significantly alter the bioavailability of this drug, which is widely used in the treatment of epilepsy.

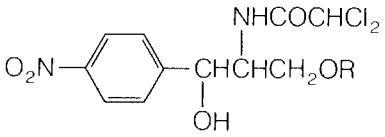
Chemical modification is also used to a limited extent. For example, sulfasalazine, used in the treatment of ulcerative colitis, passes through a substantial portion of the intestinal tract before being metabolized to sulfapyridine and 5-aminosalicylic acid. The latter compound is believed to be the active agent for the treatment of ulcerative colitis.



Sulfasalazine

Any compound passing through the gastrointestinal tract will encounter the many and various digestive enzymes that, in theory, can degrade the drug molecule. In practice, when a new drug entity is under investigation, it will probably be dropped from further consideration if it is found unable to survive in the intestinal tract. An exception would be a drug for which there is no other effective product available, or one that provides a more effective treatment over existing products and can be administered by an alternate route, usually parenteral.

In contrast, these same digestive enzymes can be used to advantage. Chloramphenicol is water-soluble enough that it comes in contact with the taste receptors on the tongue, producing an unpalatable bitterness. To mask this intense bitter taste, the palmitic acid moiety is added as an ester of the chloramphenicol's primary alcohol. This reduces the parent drug's water solubility so much that it can be formulated as a suspension that passes over the bitter taste receptors on the tongue. Once in the intestinal tract, the ester linkage is hydrolyzed by the digestive esterases to the active antibiotic, chloramphenicol, and the very common dietary fatty acid, palmitic acid.



Chloramphenicol: R = H;

Chloramphenicol Palmitate: R =

Sulfasalazine and chloramphenicol palmitate are examples of *prodrugs*. Most prodrugs are compounds that are inactive in their native form, but are easily metabolized to the active agent. Sulfasalazine and chloramphenicol palmitate are examples of prodrugs that are cleaved to smaller compounds, one of which will be the active drug. Others are metabolic precursors to the active form. An example of this type of prodrug is menadione, a simple naphthoquinone, which is converted in the liver to vitamin $K_{2(20)}$.

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