Medical pharmacology

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fourth edition

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Introduction

Chemical agents provide not only the structural basis and energy supply of living organisms but also the regulation of their functional activities. The interactions between potent chemicals and living systems contribute to the understanding of life processes and in addition provide effective methods for the treatment, prevention, and diagnosis of many diseases. Chemical compounds used for these purposes are *drugs*, and their actions on living systems are referred to as *drug effects*.

Pharmacology deals with the properties and effects of drugs or, in a more general sense, with the interactions of chemical compounds and living systems. It is a discipline of biology and is closely related to other disciplines, particularly to physiology and biochemistry.

Despite the considerable overlap among the various disciplines of biology, the rational treatment of the vast body of knowledge concerning drugs and drug effects is the primary domain of pharmacology.

Although the specific aim of pharmacology is to define the biologic activity of chemical compounds, it also contributes greatly to knowledge of living systems. This contribution to the understanding of life processes is valuable to biologic sciences in general and to medicine in particular.

SUBDIVISIONS OF PHARMACOLOGY AND RELATED DISCIPLINES

There are several fields of study which may be considered subdivisions of pharmacology or disciplines related to it.

Pharmacodynamics is the study of drug effects and the handling of drugs by the body. This aspect of pharmacology is perhaps the nearest to a basic science of medicine.

Emphasis on mode of action of chemical compounds distinguishes pharmacology from some of the other basic sciences of medicine. As used in medicine, the term *pharmacology* is essentially synonymous with *pharmacodynamics.*

Chemotherapy is looked upon by many persons as a subdivision of pharmacology. As defined by Paul Ehrlich, the term means the use of drugs to destroy invading organisms without injury to the host.

Pharmacognosy, sometimes referred to as *materia medica,* deals with the properties and identification of crude drugs. This branch of pharmacology was important to physicians when they had to dispense and even prepare their medicaments. With the development of pure drugs prepared by large manufacturing houses, pharmacognosy disappeared from the medical curriculum.

Pharmacy is concerned with the preparation and dispensing of drugs. Today the physician seldom has the need to prepare or dispense his own drugs.

Therapeutics is the art of treatment of disease. *Pharmacotherapeutics* is the application of drugs in the treatment of disease.

Toxicology is the science of poisons and poisonings. Although toxicology is a special aspect of pharmacology, a separate discipline developed for various reasons. The specialized techniques of the toxicologist are of great importance in forensic medicine and in public health, particularly as related to industrial medicine.

HISTORICAL DEVELOPMENT OF PHARMACOLOGY

Although no detailed discussion will be attempted, it should be pointed out that the history of pharmacology can be divided into two periods. The early period goes back to antiquity and is characterized by empirical observations in the use of crude drugs. It is interesting that even primitive people could discover relationships between drugs and disease. The use of drugs has been so prevalent throughout history that Sir William Osler stated (1894) with some justification that "man has an inborn craving for medicine."

In contrast to this ancient period, modern pharmacology is based on experimental investigations of the site and mode of action of drugs. Studies of this type were first carried out in the eighteenth century and were expanded considerably during the nineteenth century. The name of Oswald Schmiedeberg (1838-1921) is commonly associated with the development of modern pharmacology. The field was greatly stimulated by the rise of synthetic organic chemistry which provided new tools and new therapeutic agents. More recently pharmacology has benefited from the impressive growth of other basic sciences and in turn has contributed to their growth.

PLACE OF PHARMACOLOGY IN MEDICINE

There are several reasons for considering pharmacology one of the increasingly important basic sciences of medicine. Some of these are obvious; others are not yet generally recognized.

Large numbers of drugs are used in the practice of medicine. They cannot be applied intelligently or even safely without some understanding of their mode of action, side effects, toxicity, and metabolism. As powerful new drugs are introduced, the necessity of adequate pharmacologic knowledge on the part of the physician becomes increasingly mandatory. Unfortunately, drugs are often prescribed without this prerequisite, partly as a result of the rapid expansion of the field.

Pharmacology is taught in medical schools for other reasons. As a basic science it contributes important concepts to the understanding of various functions in health and disease. In research, drugs are used increasingly as chemical tools for elucidating basic mechanisms. Also, drugs are being utilized more frequently for diagnostic purposes.

Pharmacology is also important in medicine because of the commercial influences which are exerted upon the physician in his selection of drugs. A good understanding of the principles of pharmacology should provide the physician with a critical attitude and the ability to evaluate rationally the claims made for various new drug preparations.

Finally, it is increasingly recognized that many functions of the body are controlled by endogenously produced chemical compounds. In addition to the hormonal agents synthesized by endocrine glands, other endogenous compounds exert regulatory effects on body functions. There is now little doubt that acetylcholine and norepinephrine represent such autoregulator drugs. There are probably many others. It is quite likely that such potent agents as histamine, 5-hydroxytryptamine, heparin, and kinins may act as endogenous regulators of various functions.

Many pharmacologic agents mimic or oppose the actions of these "local hormones" or else affect their binding or metabolism. The recognition that many body functions are normally regulated by drug action has interesting implications. When viewed in this light, pharmacology is not simply the experimental basis of drug therapy but is a basic science of medicine whose tools are highly active chemical compounds by which physiologic and biochemical processes can be influenced.

CLINICAL PHARMACOLOGY

Although pharmacology is concerned with drug effects in all species of animals, there is increasing interest in medicine in clinical pharmacology, which concerns itself with pharmacologic effects in man.

There are many reasons for this increasing interest. Results of pharmacologic studies on animals sometimes cannot be applied to human beings because of

species variations in the response to the drug or in its metabolism. Clinical pharmacology also provides scientific methods for the determination of usefulness, potency, and toxicity of new drugs in man himself. This is of great practical importance these days when the efficacy and safety of drugs are being reassessed.

Although based on controlled experiments and statistical evaluations rather than on clinical impressions, clinical pharmacology has certain limitations imposed by difficulties inherent in experimentation in human beings. It is reasonable, therefore, to expect that new drug developments and the elucidation of basic mechanisms will continue to originate from animal experiments rather than from clinical pharmacology.

Pharmacologic knowledge essential for good medical practice includes not only the findings of clinical pharmacology but also those principles and concepts generally derived from animal experiments which are necessary for thorough understanding of drug effects. Without these principles and concepts rational therapeutics is impossible.

Section I

General aspects of pharmacology

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Basic mechanisms of drug action

Most drugs differ from inert chemicals or foods by their *potency, selectivity,* and *structural specificity.* Digitoxin, reserpine, atropine, LSD, and penicillin are a few examples of potent, selective, and structurally specific compounds. A few milligrams of these drugs can alter normal or pathologic physiology or, as in the case of penicillin, can rid the body of invading microorganisms.

Intuitively, *potency* suggests an interaction with a biologic control system; *selectivity* points to a favored *localization* or *affinity* for some site of action. Finally, *structural specificity* brings to mind an interaction of the drug with some cellular constituent that is *complementary* to it in three-dimensional space.

Much of experimental pharmacology suggests that these suppositions are correct. While seemingly academic, an understanding of current views on the basic mechanisms of drug action should promote a way of thinking about drugs that should favor their correct use in therapeutics.

Sites of drug action on biologic systems

The specificity of most drug actions suggests a bond formation, generally reversible, between the drug and some cellular constituent. This cellular constituent is generally referred to as the *receptor.* Paul Ehrlich visualized receptors as parts of macromolecules with which drugs combine (for details of Ehrlich's views see the monograph by Albert[11]).

Drug-receptor interactions may initiate responses by altering the permeability of membranes, by interfering with carrier mechanisms, by modifying templates, or by acting on enzymes.

It has been customary to attribute the great potency of most drugs to an action on *enzymes.* A traditional view of biochemists is that any substance which in minute amounts exerts a great effect on living systems is either an enzyme or part of an enzyme. Because of this belief, potent drugs are often assumed to act primarily on enzymes.

Drug effects are often attributed to a primary interaction with enzymes on the basis of insufficient evidence. Inhibition of an enzyme by a drug in the test tube can be misleading. Its effect in the body may depend upon an entirely different action. Nevertheless, there are a few examples in which drug effects undoubtedly are a result of enzymatic action. The anticholinesterases such as physostigmine or the organophosphorus compounds, the carbonic anhydrase inhibitors such as acetazolamide (Diamox), and the monoamine oxidase inhibitors such as iproniazid exert many pharmacologic effects as a consequence of enzyme inhibition. Also, disulfiram (Antabuse) causes severe effects in a person who drinks alcohol because it blocks the enzyme that catalyzes the oxidation of acetaldehyde, a toxic product of alcohol degradation. The antimetabolites, of great interest in chemotherapy of infections and cancer, compete with normal metabolites for an enzyme.

Even when drugs act on enzymes and modify metabolic rates, their potency is derived from acting at a rate-limiting step in a chain of biochemical reactions (Krebs, 1957). The rate-limiting step does not have to be an enzymatic reaction. It could be the selective permeability of a membrane or a carrier mechanism. Insulin controls the hexokinase reaction, presumably by regulating the entry of sugar into the cell (p. 494).

When the primary action of a drug is on an enzyme, the receptor is the enzyme itself. In most cases, however, drug effects cannot be explained by a primary interaction with an enzyme. In other words, enzymes may be receptors, but receptors are not always enzymes.

Quantitative aspects of drug potency and efficacy

A drug is said to be potent when it has great biologic activity per unit weight. When the dose of a drug is plotted on a logarithmic scale against a measured effect, a sigmoid curve is obtained, usually referred to as a log *dose-response* curve. Any point on such a curve could indicate the potency of a drug, but most often, for comparative purposes, the dose which gives 50% of the total or maximal effect is selected. This dose is the ED_{50} or effective $dose_{50}$. In Fig. 2-1, drugs A and B produced parallel dose-response curves. The ED_{50} of drug B may be ten times greater than that of drug A. As a consequence, it may be said that drug A is ten times as potent as drug B. *It is essential to realize that potencies are compared on the basis of doses which produce the*

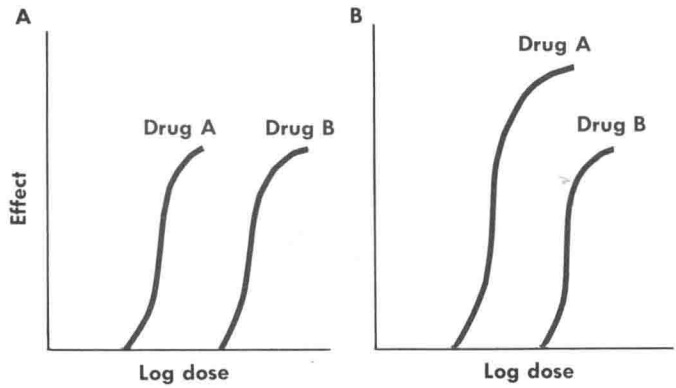

Fig. 2-1. Log dose-response curves, illustrating the difference between potency and efficacy. **A,** Drug A is much more potent than drug B, but both have the same maximal effect. **B,** Drug A is not only more potent but has a greater efficacy. It produces a higher peak effect than drug B.

same effect and not by comparing the magnitudes of effects elicited by the same dose.

A clinically important example of a potency relationship very similar to that given in Fig. 2-1, *A*, is given by the diuretic drugs chlorothiazide and hydrochlorothiazide. One hundred milligrams of hydrochlorothiazide given orally to a patient in twenty-four hours promotes a significant increase in the urinary output of sodium chloride. It takes about 1 Gm. of chlorothiazide to achieve the same effect. As a consequence, one may say that hydrochlorothiazide is ten times as potent as chlorothiazide.

Fig. 2-1, *B*, illustrates another property of a drug which should not be confused with potency. Drug A is not only ten times as potent as drug B but it also has a higher maximum or "ceiling" of activity. The maximum effect is commonly referred to as efficacy or power and is illustrated by the following example.

Chlorothiazide as well as hydrochlorothiazide has a definite "ceiling" of activity. Two grams of chlorothiazide will exert its maximal effect on salt excretion and further increases in dosage will not result in a greater effect. Furosemide, however, is not only more potent than chlorothiazide but also has a higher ceiling. It can cause the excretion of a larger percentage of the total amount of sodium chloride filtered by the glomeruli. Consequently, furosemide is not only more *potent* than chlorothiazide but it also has greater *efficacy* or power.

Potency and efficacy are often confused in medical terminology. Potency alone is an overrated advantage in therapeutics. If drug A is ten times as potent as drug B but has no other virtues, this means only that the patient will have to swallow smaller tablets. Pharmaceutical companies often emphasize that

a drug is more potent than some other drug. This in itself has very little importance to the physician. On the other hand, if the drug has a greater efficacy, it may accomplish things that are unattainable with a less efficacious compound.

Selectivity

It is a truism in pharmacology that there is no drug with a single action. Nevertheless, it is quite remarkable how selective many of our drugs are. In fact, one of the aims of pharmacology is to provide highly selective therapeutic agents. What is the basis of the selective action of drugs?

When a drug has a much greater effect on some structures than others, one obvious explanation might be that it tends to concentrate in such structures. This simple explanation holds true in only a few cases. For example, the mercurial diuretics tend to concentrate in the renal tubules and exert a diuretic activity at relatively low doses. In the majority of cases, however, selectivity cannot be shown to depend on a special localization of the drug. The affinity for a site of action may be similar to the affinity of dyes for certain materials and not others,[11] the selective permeability of some membranes (this would lead to changes in concentration at subcellular sites), or the existence of specific combining sites in or on the susceptible cells—the *receptors*.

A good example of selectivity due to specific receptors is the effect of acetylcholine on the motor end plate. The direct application of the drug to the end plate results in the production of an action potential. The end plate is so susceptible to the drug that 10^{-15} moles or less will produce a response. At the same time, acetylcholine has no effect when applied to the muscle at a distance from the end plate.[4] It is reasonable to postulate that the end plate must have some combining sites for acetylcholine which the rest of the muscle does not have. This postulate is greatly reinforced by the fact that these sites (receptors) can be blocked by specific antagonists, such as *d*-tubocurarine, which compete with acetylcholine for the receptor site.

Structural specificity

The action of most drugs is greatly influenced by slight structural modifications. Furthermore, alterations of structure cannot only cause a change in potency but also the formation of compounds that *inhibit* the action of the parent drug. The dependence of drug action on a three-dimensional structure is well illustrated by the greatly differing potencies of stereoisomers. *d*-Amphetamine (Dexedrine) has a greater stimulant effect than *l*-amphetamine (or racemic *l*-amphetamine sulfate, Benzedrine). Structural specificity provides evidence that drugs interact with a configurational site or *receptor*, analogous to the active site of an enzyme.

There is reason to believe, however, that not all drugs act on specific receptors. Some drugs probably distribute themselves in an important phase in or on the surface of the cell and interfere with some function or metabolic

process. This nonspecific drug effect differs in many respects from the previously discussed drug actions. The biologic activity of anesthetics, hypnotics, volatile insecticides, and some other drugs depends not on drug-receptor interactions but on the *relative saturation* at some cellular phase (Ferguson's principle).[3] Whenever compounds which are chemically widely different and whose "thermodynamic activity" is similar give the same effect, the drugs may be assumed to have a nonspecific or physical type of activity or toxicity. Thermodynamic activity is approximately equal to S_t/S_o, where S_t is the concentration necessary to give a biologic effect and S_0 is the solubility of the drug.

In simple terms, if two drugs produce the same effect when their solutions are half-saturated or one-tenth saturated, they are not likely to act on specific receptors. It is more probable that by reaching a certain level of saturation at some cellular site (the so-called biophase) they hinder some metabolic function.[3]

Drug-receptor interactions as the molecular basis of specific drug action

As early as 1878 the inhibitory effects of atropine on the actions of pilocarpine were interpreted by Langley[5] as a competition for some "receptive substance." The concept of receptors as a cellular combining site for drugs was effectively used by Ehrlich (see Mautner[16] for details). Mathematical formulations of drug-receptor interactions were postulated by many workers, but especially by Clark,[1] Ariëns,[12] Schild,[9] Stephenson,[10] and Paton.[7]

It has been suggested by Clark[1] that drug-receptor interactions were analogous to adsorption and that drug effect was proportional to drug-receptor combinations. In an extension of this concept and by analogy with enzyme-substrate interactions, it was postulated by Ariëns[12] that

$$[A] + [R] \underset{k_2}{\overset{k_1}{\rightleftarrows}} AR \xrightarrow{k_3} \text{Response} + [A] + [R]$$

where [A] = agonist, a drug with stimulant properties; [R] = concentration of free receptors; and [AR] = concentration of drug-receptor complex.

As in the formulation by Michaelis and Menten,[6] where the velocity of an enzyme reaction is proportional to the concentration of enzyme-substrate complex, drug effect is proportional to drug-receptor concentration or [AR].

The varying potencies of members of a homologous series were explained by varying *affinities* of the drugs for the receptor, affinity being the reciprocal of the dissociation constant ($1/K_A$) of the drug-receptor combination.

Further work has shown, however, that when the potencies of members of a homologous series are compared, not only is the log dose-response curve in the case of the weaker members shifted to the right but the maximum also becomes lower. Because of this finding, it seemed reasonable to postulate that the response was not only dependent on the concentration of drug-receptor complex but also on what is termed intrinsic activity[12] or efficacy.[10] Numerically,