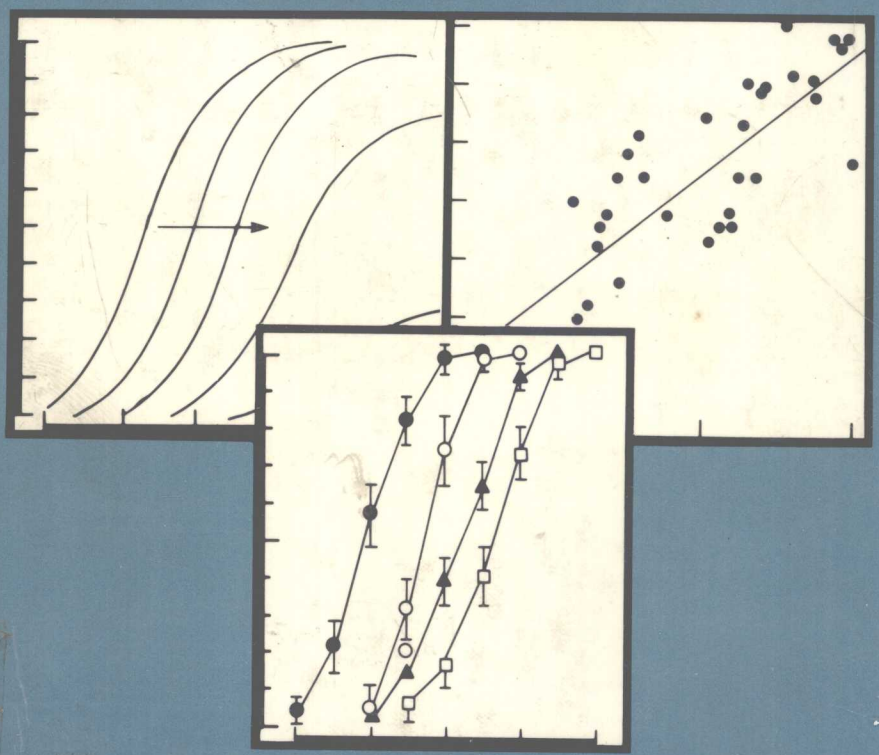
# Pharmacologic Analysis of Drug-Receptor Interaction

Terrence P. Kenakin



Raven Press

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# Preface

The receptor can be considered a crossroads where a vast array of hormones, autacoids, neurotransmitters, drugs, and other foreign substances meet the cell and transmit their messages to another vast array of stimulus-response mechanisms. In this sense, the study of drug-receptor interactions touches all aspects of pharmacology, and a great many aspects of biochemistry and physiology. Thus, by necessity, the discipline of drug-receptor kinetics enters the lives of scientists concerned with a variety of biological mechanisms, forcing them to go into the realm of kinetic processes in diffusion-restricted systems observed in an indirect manner.

This volume considers the pharmacologic analysis of the interactions of drugs and drug receptors as a problem of classification, the ultimate aim of which is to define the properties of drugs on biological systems. In the process, this same exercise is capable of classifying physiological processes as well. Unlike many treatises on drug-receptor pharmacology, little emphasis is placed on the structure of the receptor, the definition of its nature being subordinate to its function as a looking glass into the properties of drugs and physiological mechanisms.

For the pharmacologist, the techniques for study of drug-receptor interaction are major tools in the quest for new drugs of therapeutic benefit. Definition of the properties of drugs is an essential part of this process, and from this standpoint, every newly discovered selective drug *begins* the pharmacologist's primary task of classification. Thus, the discovery of the drug becomes both the endpoint (delivery of a therapeutic entity for the benefit of humans) and the starting point (defining what makes it a benefit to humans) for pharmacologic research. It will be axiomatic that this latter process is essential to the former.

TERRENCE P. KENAKIN

# Acknowledgments

It would have been impossible for me to write this book without a great deal of help from many people. I learned autonomic-receptor pharmacology from a most patient teacher, David Cook. My years with Sir James Black exposed me to lateral thinking and a totally unique view of pharmacologic analysis; some of these approaches I have tried to present in this book. No better touchstone could be found for my musings than my friend and colleague Jeff Leighton. Without the meticulous experimental acumen of Deborah Beek, few data would have been available to both fuel and temper the fires of speculation.

I wish also to thank Don Namm and Burroughs Wellcome Company for support during this project, and Pedro Cuatrecasas for showing faith in me. The talented efforts of Linda deLeon, Marci Raneri, Beverly Nobles, Michael Smith, Susan Sadler, Barbara Shaw, Patty Iannone, and Elizabeth Majors made possible the figures in this volume. As for the words, only the tenacious and highly skilled efforts of Tonya Beasley turned the scribble into legibility. The multitudinous little things that go into such a project would have remained undone without the careful efforts of Margaret McIntyre.

I wish also to thank my mother and father for unfailing support, Walter for inspiration through conversation, Nade for food for thought, and my wife and children for boundless understanding while I wrote this book.

# Contents

# 1

# Drug-Receptor Theory

*That combining group of the protoplasmic molecule to which the introduced group is anchored will hereafter be termed receptor.*

—PAUL EHRLICH, 1909

## DEFINITION OF THE "KEY"

When a medicinal chemist synthesizes a compound that does something extraordinary to a physiological system, this compound enters an elite class of chemicals and becomes classified as a drug. Let us suppose that this drug has one and only one property in its interactions with all physiological systems and thus possesses the property of specificity. Under these circumstances it can be used to perturb a variety of physiological and biological systems, and by observing the way these systems accommodate the perturbations, we can gain physiological knowledge. In short, the drug becomes a "key." It will be one premise of this book that the obvious value of such keys can lead to tacit assumptions of specificity and that the challenge of these assumptions is a critical function of pharmacologists.

Experience demonstrates that drugs more often are selective rather than specific, in that a specific activity is incontrovertibly linked to a concentration range (therapeutic window). Therefore, a drug is useful therapeutically if the dosage is kept within the range in which only the desired property is expressed. If this range is exceeded, other properties of the drug may complicate the therapy; as stated by Walter Straub (1874–1944), "there is only a quantitative difference between a drug and a poison." A drug discovered to possess one property, when subjected to scrutiny, often is found to have another. For instance, cocaine is known mainly as a central-nervous-system stimulant and local anesthetic, but it also is a potent inhibitor of the uptake of catecholamines by nerves. Hydrocortisone is a well-known antiinflammatory drug, but it also blocks the ability of muscle to take up and degrade catecholamines. *It is the major thesis of this book that pharmacologists should be concerned primarily with the discovery of and quantification of the properties of drugs, not the physiological systems with which they interact*—in essence, the definition of the key. This is not a new idea. It was proposed over a century ago by the German pharmacologist Rudolf Buchheim (1820–1879) in his statement that "we pharmacologists must acquire a knowledge of the tools which we use" (3).

Not only pharmacologists should be concerned with the classification of drugs, but also every biological scientist who uses drugs to delineate physiological mechanisms.

There are at least three reasons that pharmacology should be concerned with the definition of the key. First, if specificity is erroneously assumed for a given drug, then all subsequent classifications utilizing this drug are in danger of being irrelevant. Considering the numbers of drugs, receptors, tissues, and species, this could lead to an enormous amount of contradictory data. For example, suppose a new drug is classified as being a stimulant of a particular cellular mechanism on the basis of limited data and then is shown to produce a stimulant response in an organ previously thought, on the basis of other data, not to possess that particular mechanism. An interesting dilemma presents itself: Does one reclassify the drug or reclassify the organ? If an error is made at this point, a second dissimilaritude occurs, because all subsequent classifications using either the misclassified drug or organ will be incorrect as well.

The third reason for questioning specificity is the possible therapeutic benefit of the process. Let us assume that a drug has been discovered that produces a specific action *in vivo* and that current classifications of the known receptors cannot explain the specificity attained. One point of view assumes that the drug is a key that has unlocked another secret of physiology; it has led to the discovery of a new receptor. Considering the limited numbers of hormones, autacoids, and neurotransmitters that cells have to deal with, a parsimonious view of membrane receptors would discourage such speculation unless it is inescapable. In the process of defining possible receptor heterogeneity, exploration of other possible properties of the drug that could be responsible for the selectivity would be warranted. Thus, an alternative point of view would seek to explain the selective effect of the drug in terms of a more commonly encountered phenomenon, namely, multiple drug properties. In this setting, the selectivity would result from the drug acting on two or more biological mechanisms that interact in the host (whether this be cell, tissue, or whole body) in a complex manner. The definition of such selectivity theoretically could suggest new and better ways to attain selectivity, because delineation of the various processes would suggest to the synthetic organic chemist new structures for future molecular design. If a drug is selective because it interacts with a newly discovered cellular process, the chemist has a limited data base on which to design analogues of the drug, namely, those structures synthesized en route to the drug. If, on the other hand, the selectivity of the drug is found to result from interaction of the drug with two already known cellular processes, then all other chemical structures known to interact with these cellular processes become relevant to the drug design process.

## DRUG NOMENCLATURE

The label attached to a drug often determines how it is used, and some guidelines to drug nomenclature should be noted before discussion of the properties of drugs.

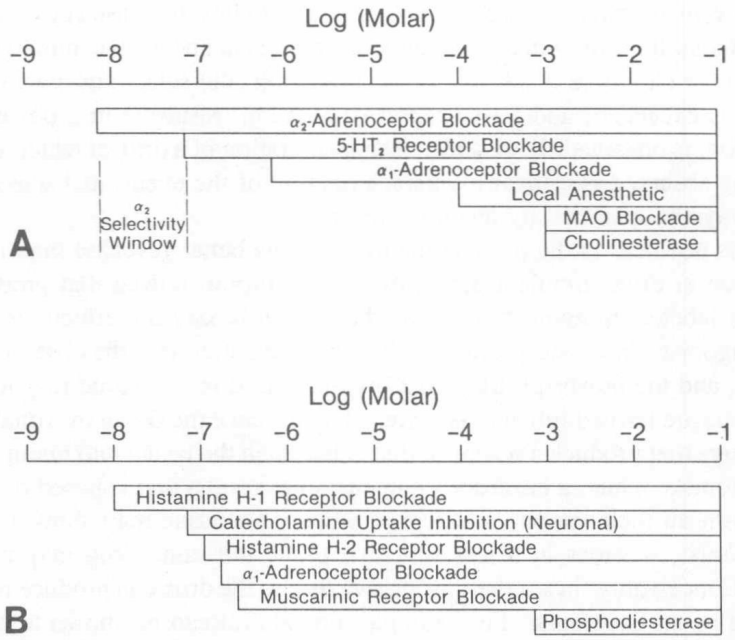



**FIG. 1.1** The necessity for a procrustean approach to specificity. **A:** Yohimbine concentration ranges (on a logarithmic molar scale) necessary for activity for a series of autonomic receptors and functions. **B:** Similar data for amitriptyline.

Some ambiguities involved in the utilization of drugs as tools arise from their sometimes protean nature, a property that often can be controlled by limiting the concentration, because it becomes evident when selectivity windows are exceeded. In general, a drug is known for and used for its most prominent property, though it may have other properties. This necessitates a procrustean approach to the attainment of pharmacologic specificity. Like the giant Procrustes in Greek mythology, who made his hapless victims lie upon a bed and either stretched or truncated them until they fit the bed,[1] pharmacologists often find themselves truncating the concentration ranges of their drugs in order to achieve some measure of specificity. For example, yohimbine can be thought of as a competitive antagonist of $\alpha_2$-adrenoceptors, $\alpha_1$-adrenoceptors, serotonin receptors, and acetylcholinesterase, as well as a local anesthetic (Fig. 1.1A). An even more extreme case of multiple personality is exhibited by amitriptyline, which boasts no fewer than six prominent properties (Fig. 1.1B). However, by using yohimbine within a concentration range of 6 to 60 nM and amitriptyline between 8 and 60 nM, selective $\alpha_2$-adrenoceptor blockade and histamine H-1 receptor blockade, respectively, can be achieved. Thus, a window of selectivity is obtained by judicious restriction of concentration. An example of how the nature of a drug can change when these windows are exceeded

[1]Good for Procrustes, until Theseus did the same to him.

is provided by clonidine, which at concentrations below 30 nM selectively depresses electrically stimulated twitch contraction of the rat anococcygeus muscle (Fig. 1.2). When 30 nM clonidine is added to the organ bath, the selectivity window for this property is exceeded, and postsynaptic stimulation, resulting in a powerful tissue contraction, is observed. In general, the concentration of a drug at which a particular activity is observed is critical to characterization of the event, and selective labels must always be qualified by quantitative limits.

Perhaps nowhere is the protean nature of drugs better revealed than in the variations seen in drug stimulant activities. By definition, a drug that produces stimulation is labeled an agonist, whereas that which blocks the effects of an agonist is an antagonist. The tissue producing the response determines the observed maximal response, and the powerful drugs that produce the same maximal responses in any given tissue are termed full agonists; i.e., they produce the tissue maximal response. Those drugs that produce a response that is less than the tissue maximum are termed partial agonists. Thus, a hazardous nomenclature results that is based on biological tissues with all their variances. Clearly, a sensitive tissue may show a drug to be a full agonist, whereas in a less sensitive tissue the same drug may be a partial agonist. Conceivably, in a rather insensitive tissue, the drug can produce no response at all and be an antagonist. For example, prenalterol can be shown to be nearly a full agonist in thyroxine-treated guinea pig right atria, a weak partial agonist in cat papillary muscle, and a pure competitive antagonist in canine coronary artery (Fig. 1.3). Tissues are amplifiers of the effects of drugs and can vary dramatically in their threshold and maximal limits of amplification. To discuss this point further requires definition of the two fundamental properties of drugs: affinity and intrinsic efficacy. The affinity of a drug is the tenacity with which it binds to its biological receptor on the cell membrane. Clark (4), in his classic treatment of drug-receptor theory, discussed affinity as the ability of drugs to be "fixed" to cells. In statistical terms, the affinity is the probability of a drug molecule binding to a free drug

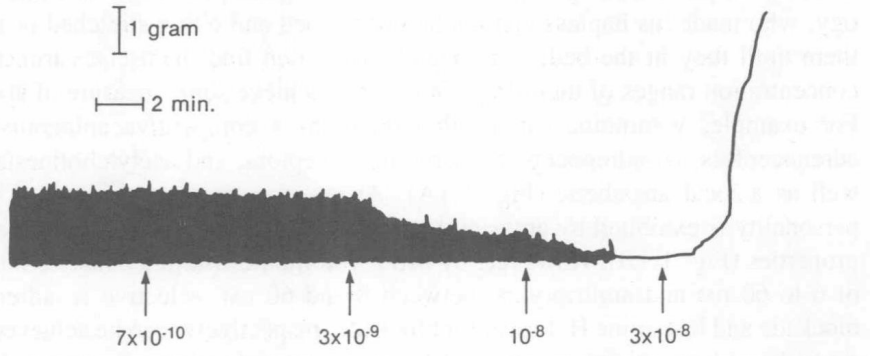



**FIG. 1.2** Effects of clonidine on electrically stimulated isometric twitch in rat anococcygeus muscle. Concentrations between 0.7 nM and 10 nM depress twitch by $\alpha_2$-adrenoceptor-mediated inhibition of neurotransmission. At a concentration of 30 nM, clonidine produces a sustained contraction by $\alpha_1$-adrenoceptor activation. (From ref. 14.)

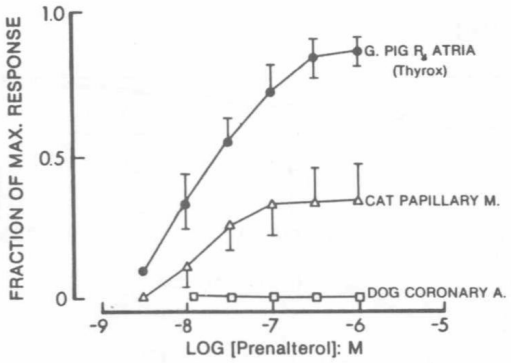



**FIG. 1.3** Concentration-response curves in isolated tissues for prenalterol. Ordinate: Responses as fractions of maximal responses to the full agonist isoproterenol. Abscissa: Logarithms of molar concentrations of prenalterol. Responses of right atria from thyroxine-pretreated guinea pigs [(●) $N = 4$], cat left atria ($N = 6$), and canine coronary [(●) $N = 4$]. Bars represent SEM. (Adapted from refs. 12 and 13.)

receptor at any given instant. The intrinsic efficacy of a drug is that inherent property that imparts the biological signal to the drug receptor (and thus to the cell) to result in a biological response. Intrinsic efficacy is a property of the drug, not the tissue, and is a very important parameter in the classification of drugs and drug receptors (*vide infra*). Thus, the affinity gets the drug to the receptor, and the intrinsic efficacy determines what it does when it gets there. The pharmacologist observes what the tissue does with the signal; it can greatly amplify it to yield a response, or it may deem the signal too weak to bother about and not give a response.

The production of a biological response by a drug can be thought of as the addition of a weight to one side of a lever balance. The weight is the intrinsic efficacy of the drug, an inviolate property. As the weight is added to the lever, the opposite end is displaced in proportion to the weight (Fig. 1.4). Where, along the lever, we view this process determines what displacement we observe. If we equate the magnitude of displacement with maximal response, the different vantage points along the lever represent different tissues. Thus, referring to Fig. 1.4, tissue I would demonstrate very little response for the drug, tissue II would show the drug to be a partial agonist, and tissue III a full agonist. Considering the multitude of tissues and variations in intrinsic efficacies of drugs, it can be seen that the designations full agonist, partial agonist, and antagonist may sometimes be ambiguous. In practice, most drugs have intrinsic efficacies that either greatly exceed tissue limits (thus uniformly are full agonists) or are well below tissue thresholds (antagonists). Therefore, ambiguities arise only with drugs of intermediate intrinsic efficacies (partial agonists).

In summary, it would seem to be prudent to interpret drug labels in terms of the nature of the drug activity and extent of selectivity (or claimed specificity) with some latitude, keeping in mind the dependence of these factors on the nature of the test system and the concentration of the drug.

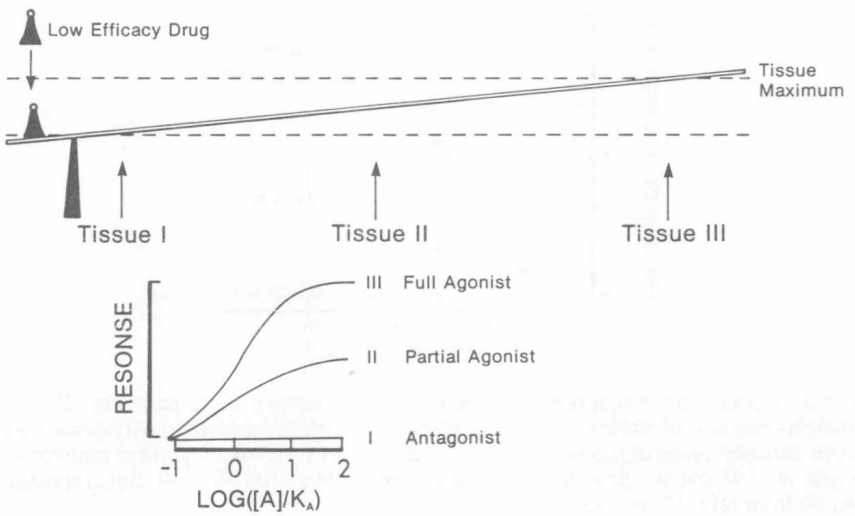



**FIG. 1.4** An operational view of intrinsic efficacy. **Top:** The drug is considered a mass with a given weight corresponding to its intrinsic efficacy. The tissue response is considered to be displacement of the lever as a result of placement of the weight to the left of the fulcrum. The downward displacement can be thought of as the stimulus, with the upward displacement the amplified maximal response. Where, along the lever, this process is viewed determines the amplification factor; these vantage points correspond to different tissues. **Bottom:** The predicted dose-response curves to the drug in tissues I, II, and III, these corresponding to the labeled vantage points.

## DRUG RECEPTORS

The definition of a drug as any chemical that perturbs a biological system suggests a broad category of substances. Thus, drugs can produce effects by virtue of their acidic or basic properties (antacids, protamine), surfactant properties (amphotericin), ability to denature proteins (astringents), osmotic properties (laxatives, diuretics), and physicochemical interactions with membrane lipids (general and local anesthetics). However, a vast array of hormones, autacoids, toxins, neurotransmitters, and drugs can transfer information to cells by interaction with specific membrane proteins given the general name receptors. The concept of specific sites residing on cell membranes with cognitive and transitive properties for drugs emerged at the turn of the century as a result of studies by Ehrlich (1854–1915), through his experiments with tissue stains, snake venoms, and bacterial toxins, and Langley (1852–1926), who studied the effects of pilocarpine and atropine on salivary secretion.

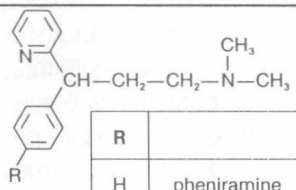
There are certain extraordinary properties of drug actions that invite, if not compel, the postulate of a specific receptor on a cell membrane capable of binding drugs and serving also as a transducer for biological stimuli. First, many drug responses are obtained at very low concentrations. Calculations from studies of atropine binding to guinea pig ileum suggest that only 0.02% of the cell surface is

composed of specific receptors for acetylcholine. Thus, if a muscle cell were compared to a sphere the size of the earth, an area the size of Iceland would contain the complete acetylcholine-receptor population. Clark (1885–1941) calculated that the area on a frog heart cell covered by a concentration of acetylcholine sufficient to reduce heart rate by 50% would be 0.001%, or an area the size of the Caribbean island of Jamaica if the heart cell were the size of the heart. Such extraordinary potencies suggest specific receptors linked to amplification processes. Second, responses to drugs can be very selectively blocked by other drugs of specific chemical structures. For example, the antihistaminic drug mepyramine blocks isolated tissue responses to histamine at concentrations of 0.4 nM, whereas concentrations 30,000 times higher (12 μM) are required to block the effects of acetylcholine. Third, the selectivities of drugs as stimulants and antagonists are extremely dependent on chemical structures, and very small changes in the structures of drugs can lead to profound changes in pharmacological activities. Thus, extension of the methylene side chain of alkyltrimethylammonium salts by one methylene bridge (*n*-propyl to *n*-butyl) changes the potency for stimulation of guinea pig ileum by a factor of 145 (Fig. 1.5A). Addition of a single chlorine atom to pheniramine produces a tenfold

**A**

| | | Relative Potency |
|---|---|---|
| n-propyl TMA | $CH_3-CH_2-CH_2-N^{\oplus}(CH_3)_3$ | 1 |
| n-butyl TMA | $CH_3-CH_2-CH_2-CH_2-N^{\oplus}(CH_3)_3$ | 145 |

**B**



| R | | $pA_2$ | Relative Potency |
|---|---|---|---|
| H | pheniramine | 7.82 | 1 |
| Cl | chlorpheniramine | 8.82 | 10 |

**FIG. 1.5** Dependence of drug potency on chemical structure. **A:** Addition of one methylene bridge to *n*-propyltrimethylammonium (to form *n*-butyltrimethylammonium) increases the potency by a factor of 145. Shown are the concentrations producing 50% maximal response in guinea pig ileum. (Data from Stephenson, ref. 21.) **B:** Addition of a single chlorine atom on the para-ring position of pheniramine increases antihistaminic potency by a factor of 10. Shown are the $pA_2$ values minus logarithms of the molar concentrations of antagonist producing a twofold shift to the right in a concentration-response curve to histamine in guinea pig ileum. (Data from ref. 17.)

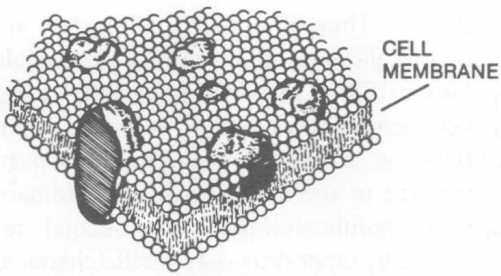



**FIG. 1.6** The fluid-mosaic model of a cell membrane (cross-sectional and schematic three-dimensional view). Solid bodies represent globular integral proteins (i.e., receptors). (From ref. 20.)

enhancement of potency for antihistaminic activity (Fig. 1.5B). The dependence of activity on structure impressed Clark, who wrote that "the most interesting feature of drug action is the extraordinary specificity of action of drugs and the manner in which slight changes in chemical constitution alter their action." These data, and much recent biochemical data, have led to important operational concepts concerning the receptor, a protein usually embedded in the plasma membrane that serves to recognize drugs and transmit their information to the cell. This protein may be continuous with the extracellular and intracellular spaces (as postulated for membrane ion channels) or may be a plasma membrane protein, with only one surface exposed to the extracellular space, floating in the lipidous membrane to collide with transducer proteins to form an active ternary complex (Fig. 1.6). There is a substantial branch of pharmacology dedicated to studying the structures and functions of these most important proteins with techniques employing affinity labels, biochemical binding, and reconstitution biochemistry. These studies undoubtedly will furnish valuable data for an understanding of pharmacologic effects and further design of drugs. This monograph will consider drug receptors strictly operationally. In this sense, receptors will be considered somewhat like "black boxes," yielding quantal (but uniform) units of stimuli to biological apparatus in response to drugs that can be quantified. However, it will be seen from subsequent discussion that complete ignorance of the nature of these black boxes is obstructive to the classification of drugs, and consideration of drug binding sites and transducer function, which necessitates discussion of the nature of receptors, sometimes is required.

Considering drug receptors as operational black boxes raises a fundamental question for pharmacologic analysis of drugs as it can be applied to the design of human therapeutic agents, namely, Are the black boxes studied by experimental pharmacologists the same black boxes that clinicians deal with in the treatment of disease? In this regard, pharmacologists have been fortunate in the apparent uniformity of receptors in animals and humans. While it is true that protein configurations often differ between other species and humans, as, for example, the subtle differences in amino acid sequences in atrial natriuretic factor between rats and humans (Fig. 1.7), these differences appear to be of minor consequence to the pharmacologic response. The correspondence between some drug receptors in a wide variety of animals and humans, as measured by interactions with selective drugs, can be documented (Table 1.1). In fact, this correspondence forms the basis of experimental pharmacology as it is applied to the drug discovery process.

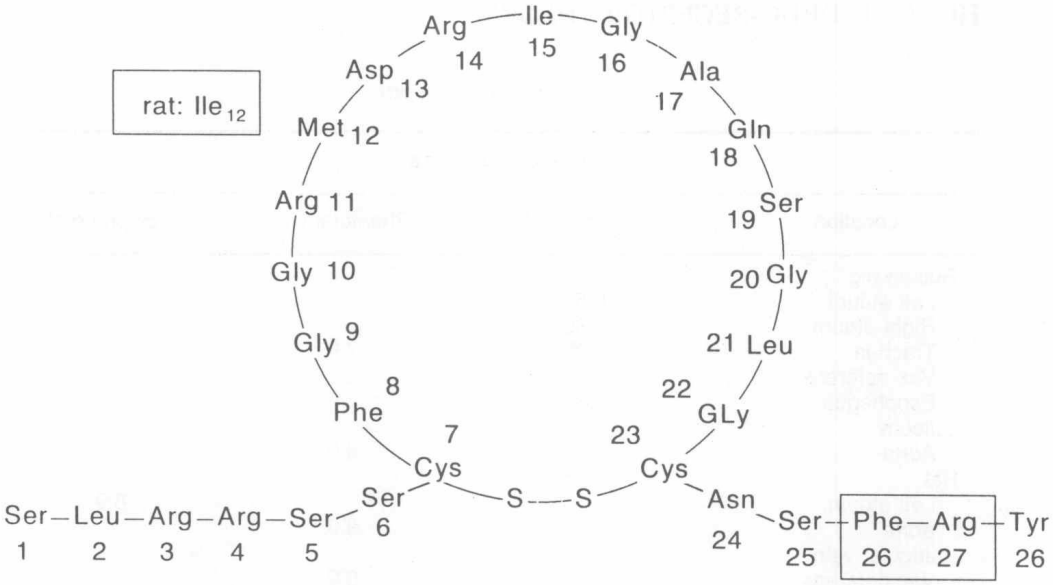



**FIG. 1.7** Amino acid sequence for $\alpha$ human atrial natriuretic factor (ANF). Substitution of Ile-12 constitutes the difference between human ANF and rat ANF. (From Palluk et al., ref. 18.)

TABLE 1.1. *Equilibrium dissociation constants for drug-receptor complexes in animals and humans* in vitro

| β-Blockers[a] | | | | |
|---|---|---|---|---|
| | Atria | | Bronchi | |
| Drug | Guinea pig | Human | Guinea pig | Human |
| Propranolol | 8.5 | 8.36 | 8.25 | 8.56 |
| Pindolol | 8.67 | 8.8 | 8.83 | 8.64 |
| RO 3-4787 | 8.39 | 8.3 | 7.95 | 8.36 |
| Practolol | 6.5 | 6.44 | 4.87 | 4.65 |
| Atenolol | 7.21 | 6.95 | 5.57 | 5.33 |
| Acebutolol | 6.54 | 6.76 | 5.13 | 5.06 |
| Metoprolol | 7.43 | 7.44 | 6.06 | 6.35 |
| H87/07 | 6.66 | 6.45 | 4.98 | 5.01 |
| Tolamolol | 8.37 | 7.91 | 7.16 | 7.02 |

| β- and α-Blockers | | | |
|---|---|---|---|
| Location | Propranolol | Phentolamine | Bupranolol |
| Human | | | |
| Left atrium | 8.36[b] | | |
| Bronchus | 8.4 | | |
| Papillary muscle | | | 8.96 |
| Metacarpal artery | | 7.8 | |

(*Continued*)

TABLE 1.1. *(continued)*

| | β- and α-Blockers | | |
|---|---|---|---|
| Location | Propranolol | Phentolamine | Bupranolol |
| Guinea pig | | | |
| Left atrium | 8.5 | | |
| Right atrium | 8.35 | | |
| Trachea | 8.25 | 7.9 | |
| Vas deferens | 8.9 | | |
| Esophagus | 8.3 | | |
| Ileum | 8.7 | | |
| Aorta | | 8.0 | |
| Rat | | | |
| Left atrium | | | 8.9 |
| Aorta | | 8.0 | |
| Jugular vein | 8.7 | | |
| Vas deferens | | 8.2 | |
| Uterus | 8.5 | | |
| Cat | | | |
| Papillary muscle | 8.7 | | 9.0 |
| Right atrium | 8.5 | | |
| Aorta | | 8.0 | |
| Nictitating muscle | | 7.5 | |
| Uterus | 8.8 | | |
| Ventricle | | | 9.1 |
| Rabbit | | | |
| Aorta | 8.9 | 8.0 | |
| Stomach | | 8.0 | |
| Left atrium | 8.4 | | |
| Duodenum | | 8.1 | |
| Ileum | 8.7 | | |
| Mouse | | | |
| Uterus | 8.4 | | |
| Vas deferens | | 8.3 | |
| Spleen | | 8.2 | |
| Pig | | | |
| Coronary artery | 8.4 | | |
| Cow | | | |
| Trachea | 8.2 | | |

[a] From Harms (10).
[b] Data as $-\log K_{\text{equilibrium}}$.

Clearly, a dogmatic belief in the homogeneity of the receptors used to classify drugs can be obstructive to the classification process. However, the fact that new receptor subtypes are discovered only after the discovery of new selective drugs raises the specter of circular reasoning; this will be dealt with more fully in Chapter 11. The general approach to be taken here is that before a new receptor can be

convincingly defined, evidence must be presented to *disprove* the null hypothesis that the receptor in question is a sample of a homogeneous population.

Hopefully, it will be apparent that the strictly operational view of receptors used in drug-receptor theory is satisfactory for the pharmacologic purpose of quantifying the elemental properties of drugs, namely, the ability to bind to cells and initiate or block a response. The simple kinetic models that describe these processes on a molecular level provide the basis for what is generally referred to as drug-receptor theory.

## ON MATHEMATICAL MODELING

The basis for quantification of drug actions is the verisimilitude of experimental results to mathematical models of drug actions. This monograph will present these mathematical models, oftentimes with derivations, leaving the reader the choice whether or not to work through the equations. Such models are valuable in that they define the assumptions and the limitations of the tools for classification of drugs (see Chapter 11). More than that, good mathematical models are predictive in that they can be used to design experiments, the results of which can disprove the model and/or tell us a great deal about how drugs work and how to make them work more effectively. In a sense, an understanding of the basic equations used to construct a model can be likened to assembling a race car, and the use and extension of the equations describing the model likened to putting the car on the track to see what it can do. In general, a model is only as good as its limitations, and by finding these and modifying the model to accommodate them, we can improve the models. The existing models have furnished valuable relationships to measure and quantify the affinity and relative efficacy of drugs. In the sense that these tools can be used with no theoretical background and can still yield valuable data for drug classification, mathematics is not a prerequisite for receptor pharmacology.

## DRUG-RECEPTOR THEORIES

Numerous mathematical, thermodynamic, and biochemical models have been put forth to describe the interactions of drugs with drug receptors. The preeminent theory from the point of view of attempting to describe drug-receptor interaction has been *occupation theory,* in which a response is thought to emanate from a receptor only when it is occupied by an appropriate drug molecule. This model was the first proposed, and its historical development traces the essential elements of drug-receptor interactions. Another model, termed *rate theory,* equates drug-receptor activation with the kinetic rate of offset of drugs and describes activation in terms of kinetics rather than binding. A model termed the *inactivation model* mathematically bridges these two approaches and warrants discussion. Although protein allosterism, that property that views proteins as malleable structures with a spectrum of conformations, as opposed to rigid matrices, is not precluded with the foregoing