REVIEW ARTICLE

J. Sci. Soc. Thailand, 3 (1977), 61-72

RECEPTOR THEORY OF DRUG ACTION

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(Received 31 May 1977)

Introduction

How do drugs, which are small molecules, produce dramatic effects (altered biological functions) that may either be curative or toxic? This is not a single question; there are questions like: what drug? which effect? which curative and which toxic effects? The last two questions clearly involve events that form an orderly sequence leading from one to the other; the various connecting links are extra questions that must also be answered. It is natural to tackle the question from both ends; the starting end is what the molecule of drug does in tissue; the other end can be arbitrarily set at any biological function.

General Properties of Drug Action

Drugs act on biological systems to produce some effects. The two fundamental questions are: how do they act, and how are the effects produced? Production of effect is largely a physiological problem. It is a very heterogeneous parameter: it can be membrane permeability, electrical properties, mechanical properties, or behavior of the animal—in fact, the entire range of biological parameters from molecular to social and ecologic; the only necessary requirement is that they must be observable. An undeniable fact is that our observing power is limited by equipment and knowledge; we cannot conclude that there is no effect beyond what we know we can observe. An important consequence is that an effect brought up for consideration usually carries a number of preceding and following events that can be arranged into a sequence of effects. Often, physiological considerations alone create several preceding sequences of effects converging on the one in focus as well as several diverging ones to follow.

The two fundamental questions thus can often be answered partially: the physiological events leading to the effect in focus is part of the mechanism of drug

action. It is well known that various drugs do not act in the same manner; even drugs that produce the same effect often act very differently. An important corollary is that there are many different mechanisms by which drugs act and we cannot classify them by their effects. Moreover, every drug produces several separate effects simultaneously, sometimes even in the same cell; some even produce the same effect by several different actions on the same cell. As a rule rather than an exception, the effect produced by a single drug is the combination of each of these actions. The mode of combination is often complex with different weighting factors for each action. In general, drug concentration and time of exposure are important determinants of the weighting factors. Knowing all the actions is problematic enough; learning specifically how they should be combined is even more formidable.

Drug action is a function of concentration, time of exposure, and the organism; in experimental observation, the real function is also open to bias and artifacts inherent in the methods. Furthermore, each variable is also dependent on the other two. Definite functional relationship of any of these parameters has not been obtained for practically all drugs. In spite of this, it is possible to understand these factors qualitatively.

All organisms, including the unicellular ones, have both capability to respond to drugs as well as to "act" on drug. Their biochemical machineries can alter the chemical nature of drug molecule in a time-dependent process which results in decrease in concentration of the original drug and build-up of metabolites. Some of the metabolites may be active—they are different drugs by definition. Higher animals have organs like liver, kidney, lung and the cardiovascular system that participate in maintaining a constant composition of its internal fluid environment. Their functions are coordinated by the central nervous system which controls them through hormones and neurotransmitters; these can be taken as the body's own drugs. The organism thus determines not only what type of response but also may show indirect responses by its own physiological adjustments as well as producing other drug molecules by secreting endogenous active substances and synthesizing others from the drug given to it.

Intensity of a drug-effect usually increases with concentration; but concentration also determines what other effects will appear. Each single effect may be related to concentration linearly, hyperbolically, or in any other ways; some even show biphasic and multiphasic relationships. These relationships often vary with time of exposure. This variation does not have to be due to changes in concentration of drug and metabolites alone since other intrinsic properties of drug action may also be responsible. Only the concentration of drug near its site of action is relevant; this is usually unknown. It is easy to know the concentration of drug in the solution that the tissue or cell are immersed in, but the drug has to pass through barriers and distribute across these barriers according to various physico-chemical rules before it reaches the site of action deep in the tissue. In most situations, the drug concentration near the site of action cannot be the same as the fluid outside; the exact value is impossible to ascertain and we can only assume that a steady-state

or equilibrium can be attained and under that condition, that the two concentrations are proportional. Effect thus varies also with time of exposure before steady-state is established.

The Receptor Concept

Since drug action invariably involves the physiological mechanisms, these events leading to the effect in focus is naturally part of the mechanism of drug action. The sequence of events between administration of drug to the first observable physiologic effect is the real unknown in studies of drug mechanism.

It has always been a simple matter for scientists to conceive that the first event might be binding of drug to some molecule in the organism. Paul Ehrlich[1] expressed the feeling in 1906, that this is a self-evident conclusion which may be part of man's inborn inheritance. He cited a medieval physician who speculated that drugs may have spicules to anchor to various tissues. Postulating the obvious can be significant only when it can be proven or lead to advances. The receptor concept has, in fact, led to highly significant progress in many fields of researches. Proof of its existence is quite strong in some specific cases, but there are still several important issues that must be resolved. I shall discuss only some of the problems using the adrenergic drugs as an example. This is the area where great progresses have been achieved with the guidance of the receptor theory; in return, the results obtained provide a basis for testing and improving the theory and its application in other drugs.

Ehrlich is widely credited to be the originator of the receptor concept. He presented evidences that certain dyes stained specifically the nerve cells. This was combined with his observations in antimicrobial drugs and immunological studies into a set of principles and logical approaches to deduce the existence and properties of receptor and how to utilize them in both scientific investigations and clinical applications. Although this is the result of his interests in pharmacology, his contributions in applying the theory are in the areas of immunology and chemotherapy of infectious diseases. Today, interaction between antibiotics and microbes has been understood down to details at the molecular level. It is heuristic that such interactions has rarely been thought of as drug-receptor interaction.

The receptor concept became important in pharmacology following the works of J.N. Langley and A.J. Clark; but progresses are the results of ingenious works by many other pharmacologists. Some of the most important contributors did not even believe in the usefulness of the concept. An exchange of opinions between Sir Henry Dale and H.R. Ing during a meeting of the Faraday Society in 1943 illustrates several important points.[2]

Sir Henry Dale: "It is a mere statement of fact to say that the action of adrenaline picks out certain effector cells and leaves others unaffected; it is a simple deduction that the affected cells have a special affinity of some kind for adrenaline; but I doubt whether the attribution to such cells of 'adrenaline-receptor' does much more than restate this deduction in another form".

Dr. Ing: "Sir Henry Dale criticized the receptor theory on the ground that it added nothing to our knowledge, but was only an alternative way of describing the well-established pharmacological facts. The theory is not meant to be other than an alternative method of describing the known facts, which, however, is thought to have the additional advantages of suggesting new approaches to the problems and of providing a much-needed intellectual link between the diverse concepts of chemical structure and pharmacological action."

It is obvious that both men agreed that certain properties of drug action indicate naturally the existence of some factors responsible for selective interaction between drug and cells; this realization by no means explains how selective interaction is achieved. There were alternative explanations in the forties but little supportive evidence for the existence of receptor. It was necessary then to avoid the circular reasonings such as: because we postulated that drug A acts on receptor in a tissue, therefore, other tissues that respond to A also contain receptor for A and a tissue that respond to A as well as other drugs possesses receptors for each of them. We now have good evidence that receptors truly exist; but we also know more alternative possibilities and see more widespread use of circular logics. Fortunately, we have also achieved the advantages that Dr. Ing had hoped for. The two most important and productive developments in receptor research are quantitative analysis of drug-receptor interaction and isolation of receptors. The ground-works for the latter are provided by the former.

Quantitative Relationship between Drug Concentration and Effect

Drug effect possesses a number of intriguing characteristics. Although some (like anesthetics, antibiotics) act at mM concentration, the majority produce dramatic effects at μM levels or below. The latter (unlike the former group) also show high degrees of selectivity (with respect to number of tissue that can respond) and specificity (with respect to chemical constitution of active and antagonistic compounds). These properties lead naturally to postulation of receptor. But the explanations of how drug and receptor interact and how such interaction produces the effect do not come naturally. These are two separate questions. There has been no direct answer for any of them from experimental results, but there are several theories derived from experimental testing of models. The most important one was developed from attempts to explain the shape of the concentration-effect curve.

These curves are often hyperbolic. The minimal effective concentration is usually several hundred fold smaller than the one producing maximal effect. It becomes more convenient to plot log concentration versus effect; the curves become sigmoidal in shape.

Basic Definition and Assumptions

1. The receptor is defined as a molecular species in the tissue that interacts with drug molecules in a stoichiometric way. The receptor may be a macromole-

cule with multiple sites. The simplest definition is therefore that each site is the receptor which interacts with only one drug molecule.

2. The interaction is assumed to be direct binding. This is obviously only the simplest possibility.

3. Law of mass action is followed. All the pre-requisites and properties of this type of interaction are thus assumed. For examples every drug and receptor molecules are identical among themselves, each drug-receptor complex has no influence on formation or dissociation of the other, and binding is reversible with no chemical alteration of both drug and receptor.

These allowed derivation of equations relating drug-receptor complex to drug concentration. The first equation was published by A.V. Hill for nicotine and curare in 1910[3]; they were formally similar to the Michaelis-Menten equation developed several years later.

There are still the problems of relating drug receptor interaction with effect. There is no model system for this purpose; arbitrary postulation is the only means. In 1937, A.J. Clark reviewed many existing data and concluded that concentration-effect curves fit the simple Langmuir equation[4]. Such equation was developed earlier to describe physical adsorption of gas to polished metal surface; it is formally similar to the simplest equation derived from law of mass-action for drug-receptor interaction. Intensity of effect was thus assumed to be directly proportional to concentration of drug-receptor complex.

Major Principles and Concepts

In principle then, the existence of receptor is postulated, its properties are defined *a priori*, its mode of interaction with drug molecules assumed; these allowed derivation of equations to describe the interaction. The same process is applied again to derive a functional relationship between drug-receptor interaction and the observable effect. The validity of the theoretical equations is then tested by fitting with concentration-effect data obtained experimentally.

The model explained in the preceeding section is now known as the occupancy theory. Its general form is[5]:

$$E_A/E_M = f(S_A/S_M) = \alpha f(RA/R_t) = \alpha f(A/A + K_A) \quad (1)$$

The effect E produced by concentration A of a drug is expressed at the fraction of the maximal effect that the biological system can produce (E_M) under the best hypothetical circumstances. This is assumed to be a function of a hypothetical stimulus S which is, in turn a function of fraction of receptor occupied (RA/R_t). By law of mass action, the equilibrium is reached when this is equal to $A/A + K_A$. The proportionality constant α is introduced to allow for the fact that some drug cannot produce as high a maximal effect as others.

The concepts derived from this theory are that drugs must have affinity (reciprocal of K_A) for the receptor; active drugs (called agonists) must also be able to activate the receptor; this is measured by the intrinsic activity (α) (numerically 0

to 1). A competitive antagonist has affinity but no intrinsic activity; those with intermediate intrinsic activity have both agonist and antagonistic activities.

To account for the fact that some effects of drug fade or disappear spontaneously during exposure, Paton proposed a rate theory in which association of drug with receptor constitutes activation; the complex is inactive. Another more recent modification was prompted by reports of cooperative behavior in some drug effects. It is an extension of the allosteric model of enzyme: receptors are assumed to exist in an active and an inactive states in equilibrium; they group together such that every individual receptor in a group is forced to assume the same state. These and other modifications all result in predictions which are either formally similar or show small quantitative differences that cannot be detected experimentally. Their main supportive evidences can often be explained by modifications of the occupancy theory[6].

It is obvious that all these theories derive their strength from fitting theoretical equations with experimental data. It should also be obvious that fitting with Langmuir equation cannot be taken as proof that drug-receptor interaction is the same as adsorption of gases on polished metal surface. There have been cases where experimental data do not fit the equations. On the other hand, fitting results with competitive antagonists invariably yielded supportive evidence even though behavior of agonists may not. Analysis of competitive antagonism thus becomes the most important part of receptor research.

Quantitative Evaluation of Competitive Antagonism

The formal similarity between agonistic action of drug and Michaelis-Menten kinetics of enzyme also extend to actions of antagonists. However, relatively tangible basis can be derived only for competitive inhibition. In the presence of a concentration B of antagonist, the effect produced by concentration A of agonist will become less. To produce the same intensity of effect as before, it is necessary to increase agonist concentration to xA (x is called the dose-ratio which is the ratio of the higher over the lower concentrations). The fraction of occupied receptor is given by:

$$RA/R_t = xA/xA + (B/K_B + 1)K_A \qquad (2)$$

Gaddum made an ingenious assumption that the fraction of occupied receptor should be the same when the agonist produces the same magnitude of effect in the presence and absence of a competitive antagonist. This allowed setting

$$A/A + K_A = xA/xA + (B/K_B + 1)K_A. \qquad (3)$$

which reduces to $x = 1 + B/K_B$ or $x - 1 = B/K_B$. This approach nullifies the uncertainty in the functional relationship between receptor occupation and agonistic action. Furthermore, the final equation is independent of the agonist. Thus, as long as the antagonist follows the law of mass action in a bimolecular, pseudo first-order reaction the equations will be valid.

The two final equations thus provide a basis for testing competitive inhibition as well as determination of dissociation constant of the antagonists. In a plot of

log concentration versus effect, log x is the difference between the logarithmic values of the two concentrations that give the same effect or the distance by which the curve is shifted by the addition of antagonist. This distance will be the same at any magnitude of effect; a parallel shift along the abscissa thus occurs; the distance is predicted by the equations.

In practice, the form of equation most extensively studied was due to Schild[7]:

$$\log (x - 1) = \log B - \log K_B \quad (4)$$

$$= - \log A_x - \log K_B \text{ if } pA_x = - \log B. \quad (5)$$

pA_x is thus the negative log concentration of antagonist which makes it necessary to increase agonist concentration by x-times in order to produce the same effect; pA_2 ($= - \log K_B$) is log affinity of antagonist; and $pA_2 - pA_{10} = 0.95$. Applications of pA_x versus log $(x - 1)$ plot has been surveyed by Ourai Chungcharoen and Schild[8]. All agonists that yield the same pA_2 values for a single competitive antagonist should act on the same receptor. A pair of agonist and antagonist should yield the same pA_2 values in several tissues that contain the same receptor. Parallel shift of concentration-effect curve has the same meaning as fixed y-intercept but different x-intercept in a double-reciprocal plot. pA_x plot is to determine further the relation between shift in x-intercept and blocker concentration.

pA_x analyses performed in various laboratories employing widely different preparations and techniques yielded remarkably constant values for cholinergic, adrenergic and histaminergic drugs. There are very few instances where deviation from unit slope was obtained. These results endowed the occupancy theory and the simple Langmuir relationship with unequalled strength even though deviations from predictions in agonist effect curve are numerous. Such deviations are therefore thought to be due to wrong assumptions in relationship between receptor activation and effect production rather than in the nature of interaction at the receptor.

Application of Receptor Theory

It is apparent from the above discussions that investigation of receptor has a theoretical basis that contains many rather arbitrary, simplified postulates and numerous assumptions selected with a major objective of simplifying further analysis. Furthermore, each assumption usually carries a number of prerequisites, and it is difficult to remain alert of their importance in further analysis and application. It is like navigating through unknown waters following a course chosen by visual inspection of safety and convenience. The tools are agonists and antagonists and the approach is analysis of dose-effect relationships.

In actual practice involving specific drugs, we wonder constantly whether we are dealing with the receptor. There are many examples of close chemical analogues acting on different receptors, antagonists blocking production of effect rather than the receptor, and agonists which act indirectly by releasing endogenous substances. The necessity of choosing an effect as near to the receptor as possible in the sequence of activation and effect production is widely appreciated but rarely practised. This is often impossible, usually difficult, and of doubtful benefit. The practice of ignoring

detailed physiological knowledge of a part of drug action in order to treat them as hypothetical stimulus is widespread. The important prequisites are often assumed: for example, several agonists may be said to act on the same receptor simply because they produce the same effect or because of their chemical similarity by subjective impression; a blocker effective against one agonist is often treated as being competitive without sufficient testing and usually presumed to be effective against other agonist in the same series. The meaning of receptor becomes different from that defined in the more rigorous theoretical analysis. The term "operational receptor" has been proposed as a substitute and isolation of receptor seems to be the ultimate way to a clear understanding of receptor.

The operational receptor[9] comprises the molecule that binds drug together with an undetermined sequence of steps following such binding. With few exceptions, this is the more faithful definition for studies of receptors reported in the literature. Despite the shortcomings and valid criticisms, this type of study has been the source of many advantages derived from the receptor cencept. It also provides criteria of drugs for use as tools and approaches for identifying isolated receptors. Isolation of a receptor involves a protracted difficulty in providing proofs that the drug-binding molecules can actually produce a physiological effect. Similarity in specificity of agonists and antagonists for the operational receptor in previous studies is invariably cited as evidence to authenticate the isolated receptor.

Classification of Adrenergic Receptors

Development in this area parallels the development in receptor theory. Application of the receptor concept has resulted in synthesis of drugs with predicted actions that become important in clinical practice and receptor researches. A summary is given here to illustrate some important points explained above.

Epinephrine and norepinephrine are the two adrenergic agonists present in all mammals. They both produce effects reminescent of stimulation of the sympathetic nervous system. These include increased rate and force of contraction in the heart, contraction of smooth muscle in arteries resulting in elevation of blood pressure, relaxation of smooth muscle in intestine and airways in the lung and increased glucose and fatty acid in blood.

It was known around the beginning of the century that the two agonists have some different actions especially in the presence of certain naturally occurring alkaloids. These alkaloids seemed to block some but not all of the effects. In its presence, an effect of one agonist simply disappeared; that of the other agonist not only disappeared, but became opposite. The agonist thus seemed to produce a mixture of two effects; one was blocked by available antagonists the other was not. Later, Ahlquist[10] showed that some agonists are more potent in producing some effects than in some others. This could be shown by measuring the relative potencies of several agonists. The effects produced by the adrenergic agonists could be divided into two types each showing characteristic relative potencies. He assumed that they are mediated by different receptors and called them alpha and beta. Only alpha-blockers were available at that time; the beta-blocker predicted by the classification was first discovered more than ten years afterward.

Theoretical basis of classifying receptors by relative potencies of agonists

Since ability to produce an effect is related to affinity toward receptor and also to intrinsic activity, potency of a drug depends on both factors. If we have several agonists with the same affinity their potencies will depend on their intrinsic activities. Similarly, potencies of agonists with the same intrinsic activity will depend on their varying affinities. Affinity depends on factors in both receptor and ligands; it is therefore a characteristic property of the ligand-receptor interaction. Affinity of competitive antagonists can be measured by the pA_x method; but affinity of agonists can be determined with difficulty and in only a few instances. Thus, although both are theoretically usable, agonist affinity is not practically so. But if several agonists are employed, their relative affinities (and therefore their relative potencies) can also characterize a receptor. This is the basis of Ahlquist's method of classification. Agonists with the same affinity but varying intrinsic activity is less desirable because this parameter is not as well defined as affinity. It has been assumed to be a property of agonists alone. This is clearly unnecessary because agonists, receptor, and coupling mechanisms may be the determinants separately or simultaneously. In any case, the assumption and the uncertainty militate against its use to characterize a receptor.

Shortcomings in Practice

Thus there are only two methods for pharmacological characterization of receptor: by competitive antagonist and relative potencies of several agonists. The use of blockers is more practical and rigorous even though it is still possible to cast some uncertainties by taking alternative models of receptor. For example, receptor can be defined such that a blocker binds with sites different from an agonist but with other properties that classical picture of competitive inhibition can still be obtained. pA_2 measurement becomes useless in testing similarity of agonist binding sites in different tissue. This is only an uncertainty inherent in the receptor theory rather than any real threat or misuse of the method. The more serious and widespread malpractice is to employ it without ascertaining the prerequisites and use of circular logic in interpretation of results. The ability of a single concentration of blocker to block the effect due to a single concentration of agonist often leads to erroneous conclusions; in some cases, it was even known that a concentration-effect curve cannot be obtained.

Validity of relative potency measurement depends on excluding all factors that can alter concentration of agonist near the receptor[11]. There are two well-known ones: uptake of agonist into nerve and other cells near the site where receptors are located and destruction of agonist by enzymes near the receptor. The quantitative significance of these are not known; they can be prevented by adding drugs; but these drugs have other actions that may interfere with agonists.

One prerequisite for using relative potencies in characterizing receptor is that all agonists employed act on the same receptor. The best way to assure this is to measure pA_2 of a competitive antagonist using each of the agonists; the same value should be obtained in each case. If this is performed, every agonist employed are

blocked competitively by the antagonist. The receptor is characterized almost entirely by the blocker; the set of relative potencies of agonists is not an essential characteristic. In the literature, however, such test is rarely performed. Since the prerequisite is not met, blocker and relative potency characteristics are complementary properties required to characterize the receptor.

The adrenoceptors are now distinguished into the alpha type which is characterized by a potency order in which norepinephrine > epinephrine > phenylephrine > isoproterenol and is blocked by phentolamine; the beta type shows isoproterenol > norepinephrine ≫ epinephrine > phenylephrine and is blocked by propranolol. There are other agonists and antagonists that one can use; those mentioned are readily available and most frequently employed. We showed recently that phenylephrine is not blocked competitively by propranolol in isolated rat heart. Its use in characterizing receptor is thus questionable. Other uncertainties stem from our recent findings of interaction between cholinoceptor and adrenoceptor agonists.

Interaction between Different Receptors

Heart and smooth muscle cells and the nerve cells can respond to many different agonists. Their responses to each type of agonists may be the same, but they are blocked by different antagonists. For example, heart rate may increase in response to histamine, angiotensin, glucagon and epinephrine; but propranolol blocks only the effect of epinephrine; other agonists remain active in the presence of propranolol. Each agonist is said to bind with its own specific receptor; the same cell thus possesses several different receptors. Although they obviously must converge on some common physiological pathway, there has been no reason to think that they can interact with each other. But this is actually formidably complex and we do not know how to look for evidence of their interaction. Based on the occupancy theory, it has been assumed that interaction can occur at the stimulus and effect level. For example, if two agonists each activates simultaneously its own receptor to produce opposite changes of the same physiological parameter, the combined effect can be the results of interaction of either the stimuli or effects they produce. The former is called functional and the latter physiological interactions. Obviously, these are not clearly defined; there is no biological basis for the interactions and there is no experimental method to detect them. An *a priori* postulation of algebraic summation of stimulus or effect have been made to allow prediction of behaviors of concentration-effect curves[12]. Very limited cases which fit the model have been reported; but this cannot be taken as proof or employed to detect these type of interaction. Interaction between different receptors thus remains an essentially untouched area both theoretically and experimentally.

Interaction between Cholinoceptor and Adrenoceptor

Physiologists interested in autonomic regulation of heart rate have reported since 1935 that influence of vagus nerve can dominate influence of sympathetic nerve[13]. Stimulation of vagus nerve releases acetylcholine which activate cholinoceptor on pacemaker cells to reduce heart rate; sympathetic nerve releases norepinephrine

which act on adrenoceptor to increase heart rate. But when both nerves are stimulated at the same time, the effect is decrease in heart rate like stimulating the vagus nerve alone. Similar results was obtained in experiments using exogenous acetylcholine and norepinephrine. This indicates that the interaction is at the level of pacemaker cell rather than the nerves. But the possibility of interaction between the two receptors has not been thought of even though pharmacologists had observed the phenomenon incidentally[14].

We showed that the phenomenon is a new type of drug antagonism[15]; it has several unique properties that have never been observed in any other type of antagonism[16]. For example: the most potent agonist (isoproterenol) is blocked most markedly; the least potent agonist, (phenylephrine) is not blocked; blockade is associated with increases in slope and amplitude (the maximal effect) of concentration-effect curve. All cholinoceptor agonists have the same inhibitory effect on the adrenoceptor agonists. But, as mentioned, the adrenoceptor agonists do not behave in the same way.

The slowing of heart rate due to the cholinoceptor agonists is blocked by atropine; this is thought to be a character of one type of cholinoceptor, the muscarinic receptor. The other two cholinoceptors are blocked by d-tubocurarine, but can be blocked differently by decamethonium and hexamethonium; they are both called nicotinic receptor. Both cardiac slowing and adrenergic blockade produced by the cholinoceptor agonist are blocked by atropine. But many nicotinic blockers can reverse the adrenergic blockade without affecting the cardiac slowing action[17,18]. A complex situation thus exists such that activation of muscarinic receptor is necessary to produce adrenergic blockade, but this particular action is blocked by nicotinic blockers. It may be conceived that cardiac slowing (result of activating muscarinic receptor) somehow leads to adrenergic blockade. This is not the case because lowering of temperature, quinidine and adenosine which decrease heart rate by various mechanisms do not produce the adrenergic blockade[19]. Furthermore, elevation of pH abolishes the ability of a cholinoceptor agonist to slow down heart beat, but adrenergic blockade persists[20]. We visualize that activation of muscarinic cholinoceptor causes the appearence of a new nicotinic cholinoceptor. Activation of the new receptor by the same muscarinic agonist then produces adrenoceptor blockade.

During full blown blockade by cholinoceptor agonist, the relative potencies of the adrenoceptor agonists are converted from the beta type to the alpha[17], but propranolol remains an effective antagonist. This is the first incidence in which blocker and relative potency lead to different conclusions about nature of receptor. Measurement of pA_2 of propranolol in the presence of cholinoceptor agonist indicates that there is no alteration in the case of norepinephrine and epinephrine, but the pA_x line is altered markedly when isoproterenol is employed[18]. We must therefore, conclude that only the receptor for isoproterenol is altered by activity of cholinoceptor. This forces us to conclude further that the adrenoceptor mediating the effects of each adrenoceptor agonist is a heterogeneous population.

Concluding Remarks

Receptor is a common word, but its common meaning has no place in science. Its use in theory of drug action may give the feeling that we know what we are dealing with; some researchers may be quick to see an analogy with other more familiar systems like enzyme and hemoglobin. But the use of the term testifies our ignorance and speciousness of the analogies. Simplification is characteristic of the theoretical bases of drug-receptor interaction; oversimplification is the constant flash-back during assimilation of experimental supports. It seems paradoxical that such a theory has proven to be important in unifying scientific principles giving rise to new concepts and experiments, and leads to discoveries of new and new uses of drugs; even more fascinating is that it constantly contributes to its own improvement and seems to have generated the conclusive proofs of its existence. There is no paradox, however, because investigators have been utilizing the model properly with full realization of its shortcomings.

References

1. Shuster, L. (1962) *Reading in pharmacology*, p. 231, Little, Brown, Boston.
2. Ing, H.R. (1943) *Trans. Faraday Soc.* **39,** 320-380.
3. Hill, A.V. (1910) *J. Physiol. (Lond.)* **39,** 361-373.
4. Clark, A.J. (1937) *Heffters Handbuch der experimentellen Pharmakologie,* vol. **4,** *General Pharmacology,* Springer-Verlag, Berlin.
5. Furchgott, R.F. (1964) *Ann. Rev. Phamacol.* **4,** 21-50.
6. Rang, H.P. (1975) *Quart. Rev. Biophys.* **7,** 283-399.
7. Schild, H.O. (1947) *Brit. J. Pharmacol.* **2,** 189-206.
8. Arunlakshana, O., and Schild, H.O. (1959) *Brit. J. Pharmacol.* **14,** 48-58.
9. Moran, N.C. (1967) *Ann. N.Y. Acad. Sci.* **139,** 545-548.
10. Ahlquist, R.P. (1948) *Am. J. Physiol.* **153,** 586-599.
11. Furchgott, R.F. (1967) *Ann. N.Y. Acad. Sci.* **139,** 553-570.
12. Van den Brink, F.G. (1973) *Eur. J. Pharmacol.* **22,** 270-278.
13. Samaan, A. (1935) *J. Physiol. (Lond.)* **83,** 332-340.
14. Koppanyi, T. and MacFarlane, M.D. (1967) *Ann. N.Y. Acad. Sci.* **144,** 543-557.
15. Sadavongvivad, C. and Satayavivad, J. (1974) *Brit. J. Pharmacol.* **52,** 93-96.
16. Sadavongvivad, C., Sanvarinda, P. and Satayavivad, J. (1974) *Brit. J. Pharmacol.* **52,** 97-100.
17. Sanvarinda, P. (1975) *Survey of pharmacologic factors that reverse isoproterenol-inhibition produced by pilocarpine.* Ph. D. thesis, Mahidol University.
18. Prachayasittikul, V. (1975) *Reevaluation of the bases for classifying adrenergic receptor using adrenoccptor agonists.* M.S. thesis, Mahidol University.
19. Sadavongvivad, C., Satayavivad, J., Prachayasittikul, V. and Mo-Suwun, L. (1977) *Gen. Pharmacol.* (in press).
20. Ratanapongse, K. (1977) *Roles of calcium and acidity on interactions between cholinoceptor and adrenoceptor agonists in isolated rat atrium.* M.S. thesis, Mahidol University.