BETA-ADRENOCEPTOR BLOCKING AGENTS

THE PHARMACOLOGICAL BASIS OF CLINICAL USE

Edited by

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and

Ralph P. Forsyth

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PREFACE

This book is a collection of the text of the invited lectures and research reports delivered at a two-day international symposium on "BETA-ADRENOCEPTOR BLOCKING AGENTS" held under the joint auspices of the Capita Selecta Committee of the Faculty of Medicine, Erasmus University, Rotterdam and the Clinical Pharmacology and Biopharmacy Section of the Dutch Society for Physiology and Pharmacology on October 17-18, 1975 at Rotterdam. This symposium was primarily intended for providing an over-all view of the subject. For this purpose a number of specialists were invited to deliver lectures on different aspects of beta-adrenoceptor blocking agents. Furthermore, a panel discussion on the relative importance of different pharmacological properties of these drugs in connection with their therapeutic uses is included. In order to expedite the publication of this book we decided to reproduce the typed manuscripts directly rather than have them type-set. This decision has resulted in some lack of uniform appearance of the different chapters, but we hope that the currency of the material will compensate for any sacrifice of esthetics.

We would like to thank Professor Bart Leijnse, the Vice Chancellor of Erasmus University, Rotterdam, Dr. Jasper Scholte, the Chairman of the Capita Selecta Committee and Dr. Wybren de Jong from the Dutch Physiology and Pharmacology Society for their interest and support in the organization of the symposium. Financial support for the symposium was provided by Sandoz B.V., the Netherlands, and we are particularly grateful to two of their representatives Messrs. Piet Baan and Ed Krops for their help at various stages. The secretarial work was ably done by Mrs. Magda Busscher-Lauw who typed many of the manuscripts.

P.R.S.
R.P.F.

February 1976

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PHARMACOLOGY

BETA-ADRENOCEPTOR BLOCKING AGENTS, P.R. Saxena and R.P. Forsyth eds.

RECEPTORS AND RECEPTOR MECHANISMS

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The receptor concept, indispensable in efforts to interpret the action mechanisms of bioactive agents on a molecular level, is developed step by step. Principles such as affinity, intrinsic activity, full agonists, partial agonists and competitive antagonists are elucidated on basis of a simple kinetic model for drug action and experimental data.

Attention is paid to the amplifier system linking the receptor molecules with the effector system. In relation therewith the concept of spare receptors and the inherent consequences of irreversible receptor blockade are discussed.
An analysis of structure-activity relationship leads to the concept of accessory receptor sites: binding sites adjacent to the receptor sites for the agonistic agents and of special importance for the binding of competitive blocking agents, particularly for the selectivity in action of the blockers.

On a physiological basis - namely the existence of receptor sites for the adrenergic transmitter, norepinephrine, at the sympathetic nerve endings and the existence of receptor sites for the adrenergic hormone, epinephrine - a classification of adrenergic and adrenergic blocking agents is outlined. This classification is substantiated by an analysis of the relationship between structure and activity for adrenergic and adrenergic blocking agents. This results in a concept of β_T and α_T (transmitter) adrenergic receptors and β_H and α_H (hormonal) adrenergic receptors. The distinction between β_T- and β_H-receptors parallels to a certain degree the empirical distinction between β_1- and β_2-receptors, also known as the receptors for "cardioselective" agents and those for "bronchoselective" agents or "metabolically active" agents.

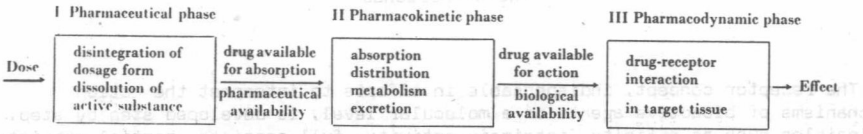
Since in various tissues both adrenergic transmitter receptors and hormonal receptors are found, selectivity is relative and determined by the proportion of β_T- and β_H-receptors, which varies from tissue to tissue.
An experimental approach to a further substantiation of the differentiation between adrenergic transmitter and adrenergic hormonal receptors is outlined.

Finally reference is given to various efforts for receptor isolation and identification.

An understanding of drug action requires a molecular approach, since an active agent can only induce a pharmacodynamic effect in a biological object as the resultant of an interaction between its molecules and certain molecules in the biological object. The chemical properties of a drug, therefore, are determinant for its action and activity. Thus a relationship between chemical structure and action must exist (2,7).

The sequence of processes at the basis of drug action can be divided into three main phases: the pharmaceutical phase comprising the release processes of the active drug from the dosage form, and thus determining the concentration available for absorption (the pharmaceutical availability); the pharmacokinetic phase comprising the processes that play a part in the absorption, distribution, metabolic conversion and excretion of the drug, and thus determining the

concentration of the active agent at the site of action in the target tissue (the biological availability); the pharmacodynamic phase comprising the molecular interaction between the active agent and its sites of action, which initiates the biological effect (scheme I) [9,10,15].



scheme I

RECEPTORS

Although the molecular sites of action form an indispensable concept in the understanding of drug action, their molecular characteristics such as chemical properties, location and number are unknown. To indicate them they are termed receptors. The use of this term emphasizes our lack of concrete knowledge about them.

Sometimes the receptors, or better receptor sites, are the active sites on enzymes, like for the MAO-inhibitors and acetylcholinesterase-inhibitors. In other cases, too, the receptor sites appear to be closely involved in enzyme action, possibly by an allosteric change in the enzyme. Receptor sites probably also can be located on functional macromolecules or macromolecular complexes, such as particular lipoproteins, determinant for the properties of, for instance, membranes. The various types of binding sites for bioactive agents that are not directly involved in the induction of the effect, such as those on plasma albumin, are indicated as silent receptors or sites of loss. They are important in pharmacokinetics. The same holds true for the active sites on enzymes involved in the biochemical conversion of the drug.

The drug-receptor interaction is much more dynamic than the classical lock-and-key model suggests. It is actually an interaction by intermolecular forces, mutually molding drug and receptor. Therewith conformational changes in the receptor molecule are induced that trigger the sequence of biochemical and biophysical events leading to the effect. Although dynamic, the receptors can yet be regarded as preformed structural entities since, for instance, the activities of optical isomers often largely differ. The structural requirements for action are not always very specific. For the various gaseous anesthetics, for instance, a certain lipophilicity seems to be the only requirement. Their anesthetic action is mainly based on a change in the cell membrane properties due to diffuse

accumulation in the lipid fraction of the membrane. For plasma extenders and osmotic diuretics the term receptor is hardly applicable anymore since they mainly act by binding of water (7). The receptors for a drug do not necessarily have to be located in the organ in which its response is observed. Strychnine causes convulsions in striated muscle that are induced on receptors in the central nervous system.

Analogously to the differentiation between the active site on an enzyme and the enzyme, the molecule as a whole, it makes sense to distinguish between the receptor site and the receptor molecule - the receptor - bearing the receptor site. Enzymes can be isolated, but not the active sites; similarly receptor molecules (or molecular complexes) may be isolated but not the receptor sites. Since structure-action relationship is based on the interaction between the drug molecule and the receptor site it may give information on the properties of this site but not on the receptor molecule as a whole.

Isolated enzymes as a rule retain their properties: they still can convert substrates and can be inhibited by inhibitors. In the case of receptors, however, the active agent induces conformational changes in the receptor molecule that are propagated to adjacent molecules and finally lead to the effect. This implies a tight interrelation of receptor molecules and their surrounding. Isolation of the receptor molecule from its surrounding may well disturb its specific conformation. The receptors are denaturated, then, to a certain degree. Due to the dissociation of receptor and effector system, via the isolated receptors, no biological effect is obtained anymore. The consequence is that for detection of the receptors in the procedure of receptor isolation, one has to use particular techniques such as: affinity labeling with compounds that are selectively and irreversibly bound to the receptor molecules and, thus, can serve as radioactive labels; selective binding studies, based on the stereospecificity of the receptor sites with regard to the binding of optical isomers; or, affinity chromatography where drug molecules are fixated on a macromolecular stationary phase with, as a goal, selective adsorption of the receptor molecules. Finally, incorporation of the isolated receptors into, e.g., the original or artificial membranes, to regenerate the functional characteristics of the receptor molecules can be considered.

AMPLIFIER SYSTEMS

Bioactive agents may be extremely potent. This implies that apparently only a few molecules of the active agent have to interact with their receptors to induce a massive response in which tremendous numbers of molecules are involved. This requires amplifier mechanisms. The simplest unit for assembling strong amplifier systems is the activation of an enzyme molecule by a drug molecule. The activated enzyme molecule then can convert hundreds of substrate molecules to product molecules. Such an amplifier unit can be coupled to a second one if the product molecules in their turn can activate a second type of enzyme molecules. A

sequence of such enzyme activation steps results in a tremendous amplification. Such an amplifier system is involved, for instance, in the action of various hormones and drugs that act by the activation of adenyl cyclase. This enzyme converts ATP to cyclic AMP, which in its turn is an enzyme activator, etc. (Fig.1) (7 ,22). The bioactive agents may act as direct or indirect allosteric activators or inhibitors (modulators) of the enzyme. The receptor sites may be located on the enzyme molecule itself, for instance on a soluble enzyme. For membrane-bound enzymes the receptor sites for enzyme modulation may be located on macromolecules functionally tied up to the enzyme.

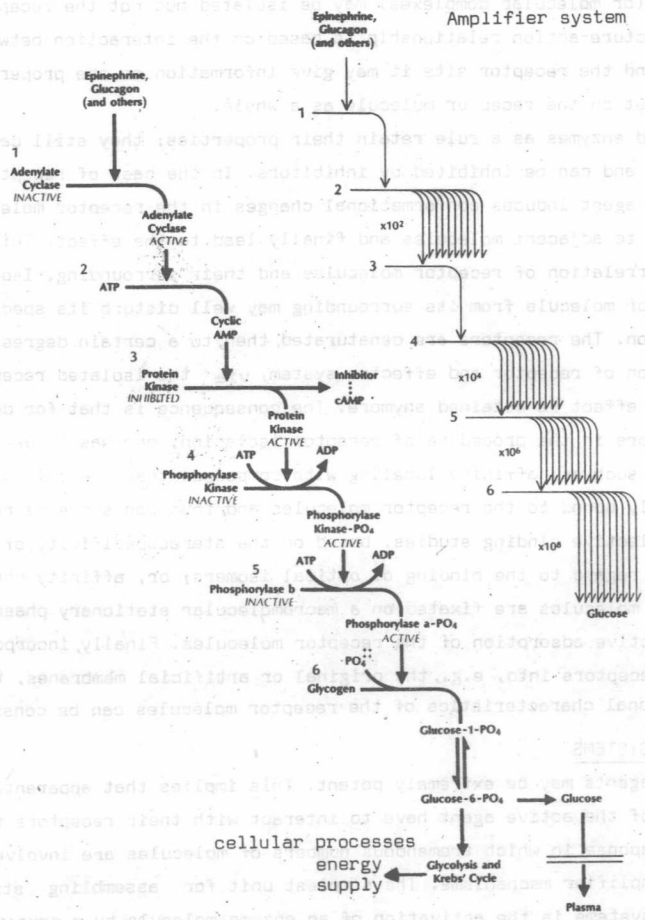
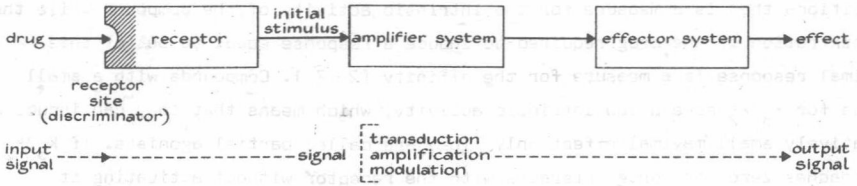


fig. 1 Schematic representation of the amplifier system involved in the action of various agents acting by activation of adenylate cyclase (After Goldberg 22).

Bioactive agents may also act as a cofactor. Examples are the vitamins and vitamin analogues that serve as cofactors for apoenzymes. The binding of steroid hormones such as estrogens to the hormonal receptor protein in the cytoplasma which then is transported into the nucleus where it finally appears to act as a derepressor (39), can be regarded as a combination of a cofactor, the steroid, with an "apoderepressor" under formation of the active derepressor. The mRNA induced by the activated derepressor, and the protein (possibly enzyme) synthesis induced by the mRNA constitute amplifier units. The interaction of drug molecules with their receptor sites in a membrane may imply conformational changes in the receptor molecules, e.g. membrane proteins or protein complexes functionally involved in membrane permeability. This can result in a change of the size of and/or the charge on the wall of the pores (2). One drug molecule can be sufficient then to change the properties of a pore. The consequential change in the flux through the pore of ions, such as K^+, Ca^{++}, and Na^+ that can act as modulators of enzyme action (selective ion-dependent enzymes), constitutes an amplifier system.

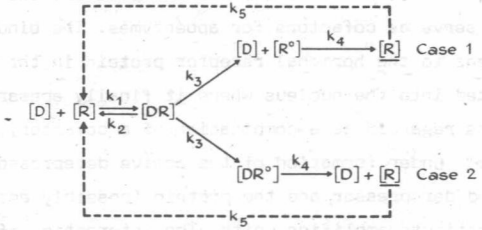
The model for drug action (the pharmacodynamic phase) outlined here may well reflect the main mechanism of drug action. Schematically drug action can be represented then by: the input signal (drug concentration) a specific receptor site (the discriminator), and the receptor molecule, activation of which implies generation of a stimulus that transduced via an amplifier system reaches the effector system that generates the effect measured, the output signal (scheme II).



Scheme II

AFFINITY AND INSTRINSIC ACTIVITY

Drug action is based on the formation of a drug-receptor complex, a process that is governed by the mass-action law. The receptor activation is based on particular conformational changes induced by the drug molecule in the receptor molecule or on a functioning of the drug molecule as a cofactor in the activated receptor molecule. The main variants of the receptor occupation - activation concept are represented in scheme III (9). The stimulus induced by the receptor activation is defined to be proportional to the fraction of the total number of receptors in the activated state, i.e. to DR^* or R^*. In scheme III case 2



Occupation-activation models for drug action
D = drug; R = receptor; R° = activated receptor

Scheme III

represents the situation that the receptor activation requires the presence of the drug molecule on the active site. The drug then acts as a "cofactor"; the receptor activation is based on a co-operative action of drug and receptor. Case 1 represents the receptor activation based on a hit-and-run process; it is closely related to the "rate model" described in the literature (2 ,23,32). In the induction of a stimulus two parameters are important: the affinity of the drug molecules to the receptors dominated by k_1/k_2, and the capacity of the drug molecule to activate the receptor, the intrinsic activity, dominated by k_3/k_2.

In the simplest case, the response will be proportional to the stimulus, that, as already mentioned, is proportional to the fraction of receptors in the activated state. The maximal response obtained with a compound in equilibrium conditions then is a measure for the intrinsic activity of the compound while the concentration of the drug required to induce a response equal to 50% of this maximal response is a measure for the affinity (2 ,7). Compounds with a small value for k_3/k_2 have a low intrinsic activity, which means that they can induce a relatively small maximal effect only. They are called partial agonists. If k_3/k_2 approaches zero, the drug interacts with the receptor without activating it, having an affinity to the receptors but lacking an intrinsic activity on the receptors. The drug then acts as a competitive antagonist of compounds for which k_3/k_2 is larger.

If the rate constant for the regeneration of the receptor in its sensitive state, k_5, is small, a fade phenomenon will occur. This means that initially when the drug is added and all receptors are in the sensitive state (R), a peak response is obtained which levels off then to a lower equilibrium response because part of the receptors are in a non-sensitive state (R) then. If k_5 is very small, the initial response will level off to zero and for a certain period the system will not respond to the drug at all. This phenomenon is known as tachyphylaxis (2 ,7 ,23). One should be aware of the fact that tachyphylaxis may also result