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E. PHARMACOLOGICAL CHARACTERIZATION OF ADRENERGIC RECEPTORS[1]

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We dance round in a ring and suppose
But the Secret sits in the middle and knows.
Robert Frost

The most direct characterization of the adrenergic receptors would be the actual isolation of the receptor system to allow precise analysis of drug-receptor interaction. Since isolation has not been accomplished, indirect methods must be used. Two approaches have yielded most of our present knowledge of the characteristics of adrenergic receptors. One is based upon the structure-activity relationships of agonists, especially with reference to comparisons of orders of potency of sympathomimetic drugs on several physiological systems. The other is based on the specificity of blocking drugs. In the following discussion many important aspects of receptor analysis will not be considered, such as quantitative relationships of agonists and antagonists, concepts of receptor occupancy, and distinctions between affinity and intrinsic activity of agonist and antagonist. Discussions of these concepts can be found in a number of publications (4, 7, 8, 17, 23).

In simplest form, the effect of a drug is expressed as a reaction between agonist and tissue. In most experimental situations, all that is known is the structure of the agonist, its concentration, the type of tissue, and the effect. From this limited base and several assumptions one can construct a conceptual framework to help explain the action of the agonist.

First, it is assumed that there are constituents of cells, *e.g.*, receptors, which react selectively with certain agonists. Secondly, it is assumed that the receptor-agonist interaction represents the first step of a multistep sequential reaction which leads to the response of the cell. Such a sequential reaction can be viewed symbolically as

$$A + R \rightarrow AR \rightarrow a \rightarrow b \rightarrow c \rightarrow n \rightarrow Ef$$

where R is the receptor, AR the complex of agonist and receptor, a, b, c, n, the sequential steps subsequent to the receptor, and Ef the effect.

Since the individual steps in most reactions are unknown, the receptor can be viewed most conviently in an operational sense as the entire sequence from R to n,

$$A + \boxed{R \rightarrow AR \rightarrow a \rightarrow b \rightarrow c \rightarrow n} \rightarrow Ef$$

where all of the intermediate steps are unknown. As knowledge of the individual

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steps is derived, the operationally defined receptor will become more precisely defined, ultimately to equal R, *e.g.*,

$$A + \boxed{R \rightarrow AR \rightarrow a \rightarrow b} \rightarrow c \rightarrow n \rightarrow Ef$$

(some steps known),

$$A + \boxed{R} \rightarrow AR \rightarrow a \rightarrow b \rightarrow c \rightarrow n \rightarrow Ef$$

(all steps known). Although R is the initial step in this scheme, steps antecedent to R involving penetration of drugs to the receptor are important. If they cannot be identified precisely, however, they become part of the operationally defined receptor.

The utility of blocking drugs in the characterization of receptors has been recognized for many years and is generally due to their high specificity. In simplest form antagonism can be looked upon as the prevention of an expected effect in a tissue in response to an agonist in the presence of another chemical compound. However, specificity of antagonism must be demonstrated if further analysis is to be valid. For instance, dichloroisoproterenol (DCI) and pronethalol block the cardioaccelerator action of intrinsic and extrinsic adrenergic stimuli but not that of methyl xanthines. These blocking drugs do not antagonize the cardiodecelerator action of acetylcholine; nor does atropine, which blocks cholinergic stimuli to the heart, antagonize adrenergically-induced cardioacceleration. Similar specificity for DCI and pronethalol can be shown for cardiac contractile force.

In the absence of knowledge of intermediate steps in the reaction sequence the site of action of a blocking drug (B) must be viewed broadly as on the operationally defined receptor, *e.g.*,

$$A + \underbrace{\boxed{R \rightarrow AR \rightarrow a \rightarrow b \rightarrow c \rightarrow n}}_{\text{Site of action B}} \rightarrow Ef$$

Two drugs which appear to be specific blocking drugs may, in fact, act at two different sites in the sequence, *e.g.*,

$$A + \underbrace{\boxed{R}}_{\text{Site of } B_1} \rightarrow AR \rightarrow a \rightarrow b \rightarrow \underbrace{\boxed{c}}_{\text{Site of } B_2} \rightarrow n \rightarrow Ef$$

An interesting example of multiple sites of action of two blocking drugs is found in the antagonism of catecholamine-induced hyperglycemia. Mayer *et al.* (13b) found the hyperglycemia induced by epinephrine (E) in anesthetized dogs to be antagonized by DCI, a *beta* adrenergic blocking drug, and not by phenoxybenzamine, an *alpha* adrenergic blocking drug, a result that suggests that the adrenergic receptor in this reaction is of the *beta* type. Yet, ergotamine,

classed as an *alpha* adrenergic antagonist, also blocked the hyperglycemia. Since both phenoxybenzamine and ergotamine were used in large doses and both reversed the vasopressor effect of E, it was reasonable to assume that *alpha* adrenergic blockade had been obtained in the animals. Obviously, these data do not permit classification of the adrenergic receptor involved in hyperglycemia as either *alpha* or *beta*.

Recent work by Northrop and Parks (18) offers a reasonable explanation for these results. The hyperglycemic effect of E in rats was blocked by both DCI and dihydroergotamine, but the effect of cyclic 3′,5′-AMP was antagonized only by the latter. Assuming that both E and cyclic 3′,5′-AMP induce glycogenolysis through the same pathway but at different steps [E on the adenyl cyclase system (16, 22) and cyclic 3′,5′-AMP on phosphorylase kinase (11)], DCI must block at a step proximal to that of dihydroergotamine that is closer or on the adrenergic "receptor." An alternative explanation for these results is an inhibition of liver uptake of cyclic 3′,5′-AMP by ergotamine simultaneously with an antagonism of the effect of epinephrine on adenylcyclase.

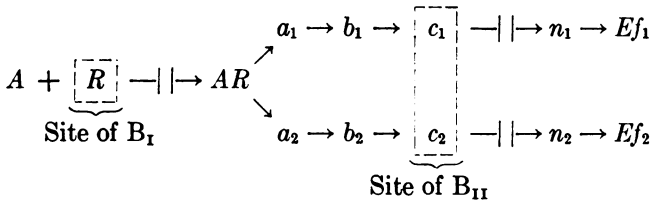
So far, only a single tissue and a single effect have been considered. However, several different effects can be measured in one tissue in response to a sympathomimetic amine. Conceptually, they can be considered to emanate from the activation of a single receptor, through divergent pathways, *e.g.*,

$$A + R \rightarrow AR \begin{cases} \nearrow a_1 \rightarrow b_1 \rightarrow c_1 \rightarrow n_1 \rightarrow Ef_1 \\ \searrow a_2 \rightarrow b_2 \rightarrow c_2 \rightarrow n_2 \rightarrow Ef_2 \end{cases}$$

Several conditions must be met to satisfy the assumption of a single receptor and multiple effects. 1) All agonists of a given chemical series that produce one effect produce all of the effects. Those of the series which do not groduce one effect do not produce the others. For example, whereas most phenylethylamines elicit multiple responses in the heart (increased rate, augmented contractile force, and activation of glycogen phosphorylase) (10, 13) some compounds in this series are nearly devoid of these cardiac actions even though they are sympathomimetic on certain other tissues. Norepinephrine (NE), E, and isoproterenol stimulate the heart, but the vasoconstrictor sympathomimetic drug, methoxamine, has little if any effect on the heart (9, 13). 2) The order of potency of a series of agonists must be the same for all of the effects. For example, the order of potency of the three catecholamines, NE, E, and isoproterenol (I), is the same for their effects on heart rate, heart contractile force, and activation of myocardial phosphorylase (*e.g.*, 13). 3) A blocking drug which antagonizes one effect must antagonize all the effects. For example, DCI (13) and pronethalol (13a) antagonize the effects of catecholamines on cardiac rate and force and on activation of myocardial phosphorylase. Phenoxybenzamine and ergotamine, on the other hand, antagonize the effects neither on rate and force (15) nor on phosphorylase (13).

It is possible, however, that two drugs, such as DCI and pronethalol, which

appear to block at the same site, may in fact, block at two separate sites in the divergent reaction sequences, *e.g.*,



Unless the individual steps in the reaction are known in this hypothetical scheme, differentiation of the two sites is not possible.

Multiple adrenergic receptors in one or several tissues which react to a given class of agonists can be considered as initiating parallel sequential reactions,

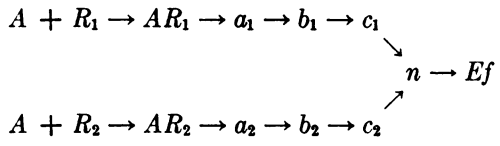
$$A + R_1 \rightarrow AR_1 \rightarrow a_1 \rightarrow b_1 \rightarrow c_1 \rightarrow n_1 \rightarrow Ef_1$$
$$A + R_2 \rightarrow AR_2 \rightarrow a_2 \rightarrow b_2 \rightarrow c_2 \rightarrow n_2 \rightarrow Ef_2$$

If the individual steps are unknown, the receptors can be distinguished by analysis of the orders of potency of agonists and particularly by differential blockade, that is, blockade of one effect by a drug which does not block the other effect. Schematically, this can be depicted as

$$A + B_I + R_1 \dashv\vdash E_1, \qquad A + B_{II} + R_1 \rightarrow Ef_1$$
$$A + B_{II} + R_2 \dashv\vdash E_2, \qquad A + B_I + R_2 \rightarrow Ef_2$$

An example of this is the differentiation of the receptors which subserve adrenergically-mediated vasoconstriction and vasodilatation. The order of potency of the agonists as vasoconstrictors is NE $\geqq$ E $\rangle\rangle\rangle$ I and as vasodilators, I $>$ E $\rangle\rangle\rangle$ NE. Vasoconstriction is antagonized by so-called *alpha* adrenergic blocking drugs, such as phenoxybenzamine, and not by *beta* adrenergic blocking drugs. Vasodilation, on the contrary, is blocked by DCI and related *beta* adrenergic blocking drugs and not by the *alpha* adrenergic blocking drugs. These relationships constitute the justification for the classification of adrenergic vasoconstriction as an *alpha* receptor-mediated function and vasodilatation as a *beta* function.

The possibility of two or more specific adrenergic receptors in a single tissue with sequential reactions converging upon a common effect can be expressed as



An example of this is the inhibition of intestinal motility by sympathomimetic amines. Ahlquist and Levy (3) postulated the existence of both *alpha* and *beta* adrenergic receptors in the small intestine *in situ* in the dog on the basis of the

observation that the inhibitory effect of isoproterenol is blocked by DCI and not by Dibozane, an *alpha* adrenergic antagonist, and that the inhibitory effect of NE is blocked by Dibozane and not by DCI. They also suggested that E activates both receptors in the intestine since only partial antagonism of its intestinal inhibitory action could be achieved with either blocking drug alone, but complete antagonism occurred with a combination of the two blocking agents. Reddy (20) has confirmed this pattern of adrenergic blockade in the isolated small intestine of the rabbit. In addition, he has shown that isolated segments of the pyloric region and the ileocolic region (sphincters) contract in response to NE, E, I and methoxamine and that the same pattern of two receptor types prevails, a DCI-sensitive one and a phentolamine-sensitive one.

One additional scheme to be considered involves two tissues, two effects and two blocking drugs of close chemical relationships. On the basis of orders of potency of agonists the two tissues appear to have the same type of receptor, a conclusion supported by blockade of both effects by one antagonist. However, the second blocking drug blocks only one of the two effects, that is,

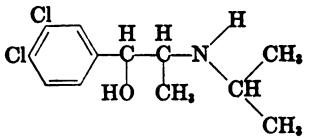
$$A + B_I + R \text{—}|\,|\rightarrow Ef_1\,, \qquad A + B_{II} + R \rightarrow Ef_1$$
$$A + B_I + R \text{—}|\,|\rightarrow Ef_2\,, \qquad A + B_{II} + R \text{—}|\,|\rightarrow Ef_2$$

This scheme can be explained in at least two ways. 1) The receptors are of the same type, but the two reaction sequences differ, B_{II} blocking at a site distal to that of B_I in one of the two sequences, *e.g.*,

$$A + \boxed{R} \text{—}|\,|\rightarrow AR \rightarrow a_1 \rightarrow b_1 \rightarrow c_1 \rightarrow n_1 \rightarrow E_1$$
$$A + \underbrace{\boxed{R}}_{\text{Site of } B_I} \text{—}|\,|\rightarrow AR \rightarrow a_2 \rightarrow b_2 \rightarrow \underbrace{\boxed{c_2}}_{\text{Site of } B_{II}} \text{—}|\,|\rightarrow n_2 \rightarrow E_2$$

2) The receptors are slightly different, both being complementary to the agonist and to B_I, but only one showing complementarity to B_{II}.

An example of this pattern has been discovered recently in our laboratory (24, 25). DCI, as shown previously (14), selectively antagonizes the cardiac stimulant and vasodilator effects of isoproterenol, lending support to the proposal of Ahlquist that the adrenergic receptors of the heart and those which subserve vasodilatation are of the same type. In the course of studying the α-methyl derivatives of some *beta* adrenergic blocking drugs, it was noted that vasodilatation was antagonized but cardiac stimulation was not. A comparison of the effect of DCI and α-methyl DCI,



will illustrate this difference. DCI, given intravenously to anesthetized dogs, selectively blocked both the cardiac stimulant effect of isoproterenol (as compared

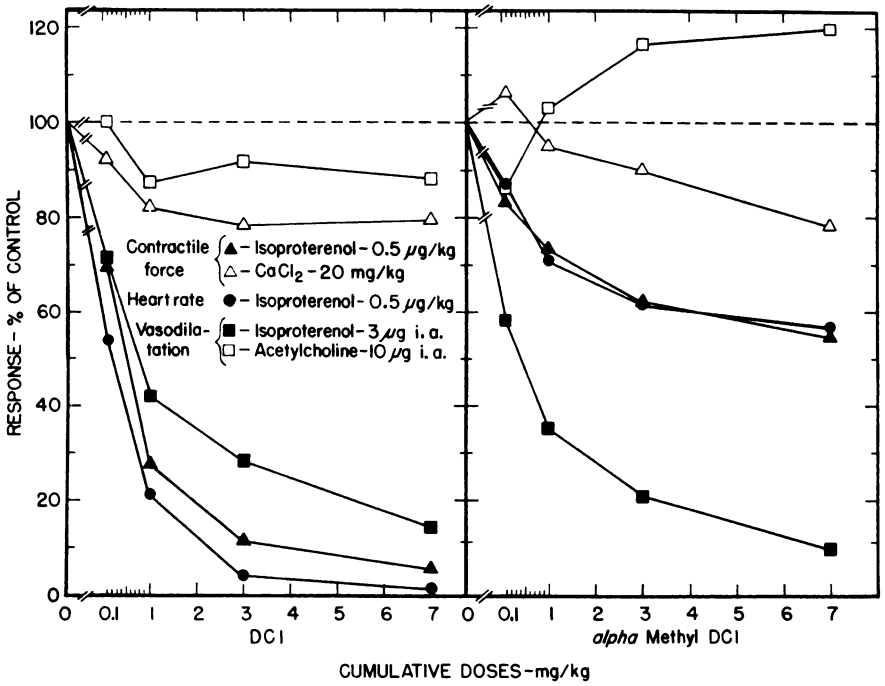


FIG. 1. Comparison of adrenergic blocking effects of DCI and α-methyl DCI in anesthetized dogs. Cardiac contractile force and heart rate responses obtained with i.v. injections of agonists, vasodilator responses with intraarterial injections of agonists in constant flow, autoperfusion of hind limb. All points are mean responses as percent of control responses before administration of blocking drugs. DCI and α-methyl DCI were given in increasing doses, with agonists tested after each dose. Data derived from experiments performed in collaboration with Dr. D. R. VanDeripe.

with that of calcium chloride) and the vasodilator effect of the catecholamine (as compared with acetylcholine). In contrast α-methyl DCI clearly produced a selective antagonism of the vasodilator effect of isoproterenol but not of the positive inotropic effect. Whereas the potency of the two blocking agents in terms of antagonism of isoproterenol-induced vasodilatation was nearly equal (that is it required about 0.4 mg/kg of each to reduce by 50% the vasodilator effect of 3 μg of the amine injected intraarterially. DCI was at least 15 times more potent than α-methyl DCI in blocking the positive inotropic effect of isoproterenol. Figure 1 summarizes some of the data from these experiments. Since none of the steps in these reactions is known, it is not possible to conclude whether the difference in blocking actions is due to slightly different *beta* adrenergic receptors in the heart and blood vessels or whether α-methyl DCI antagonizes the vasodilator response by an action on a step distal to the receptor. Because of the minor difference in the chemical structure of the two compounds it seems more reasonable to assume the former, that is slightly different receptor types.

Two other new compounds have brought further complexities into the classi-

fication of adrenergic receptors. Burns *et al.* (5) and Salvador *et al.* (21) have described the metabolic blocking actions of isopropylmethoxamine (IMA). This compound produces reflex bradycardia, slowly developing hypertension, piloerection, and myocardial depression; it prevents both the elevation of blood sugar, free fatty acids, and lactic acid in response to E in dogs and the reactivation of rabbit liver phosphorylase by E *in vitro*. Although IMA resembles DCI in chemical structure and in its blockade of certain metabolic effects of E, it differs from DCI in several respects. Levy (12) concluded that IMA selectively antagonized only the inhibitory effect of adrenergic agonists in the isolated rat uterus. He found no evidence of specific *beta* adrenergic blockade in dogs in vasodilatation, tachycardia, and intestinal motility. We have noted other differences between DCI and IMA (13a). In anesthetized dogs doses of IMA as large as 30 mg per kg failed to block the cardiac stimulant effect of E, NE, I, and sympathetic nerve stimulation. In fact, the cardiac stimulant effect of I was augmented. The vasodepressor effect of I was converted to a strong vasopressor action by IMA, in contrast to the simple antagonism of the effect by DCI. Of greatest interest was the observation that the activation of myocardial phosphorylase by E in dogs was transiently inhibited by IMA but that by I was not. A summary of some of these experiments is presented in figure 2. As a further complication of the action of IMA is the discovery that it is converted to methoxamine in the body (4a). Since methoxamine produces many of the effects of IMA, it is difficult to distinguish the action of IMA from its metabolite. These findings are of interest in reference to the report by Sutherland at this conference that IMA does not block the E-induced increase in cyclic 3′,5′-AMP, phosphorylase a and contractile force in the perfused rat heart.

A second new compound is the N-tertiary butyl derivative of methoxamine described by Burns and Lemburger (6) as having metabolic blocking actions similar to those of IMA but none of the sympathomimetic actions and no *beta* adrenergic blockade of physiological responses. The butyl derivative is specific for E in that it does not block the metabolic effects of I (4a), a differentiation in terms of specificity for an agonist similar to that of IMA on cardiac phosphorylase.

Although these new methoxamine derivatives present a complex pattern of blockade which does not fit clearly into either the *alpha* or *beta* receptor schemes, they do not offer a readily apparent alternative classification of adrenergic receptors. It is difficult to justify classifying IMA (and the butyl derivative) as a major antagonist for metabolic actions of catecholamines as Nickerson (17) has done for the phosphorylase-activating actions of catecholamines since the blockade appears to be valid for only E and not for I. Before these drugs are classified as other than simply metabolic blocking drugs, careful evaluation is required of their indirect actions and of their effects on intermediate steps in these metabolic reactions.

Ahlquist's original classification of *alpha* and *beta* receptors (1, 2) has been strengthened by events in the past 17 years, especially by the discovery of DCI (19) and subsequent *beta* adrenergic blocking drugs. At present, the broad classification of two main adrenergic receptor types is the simplest and most conven-

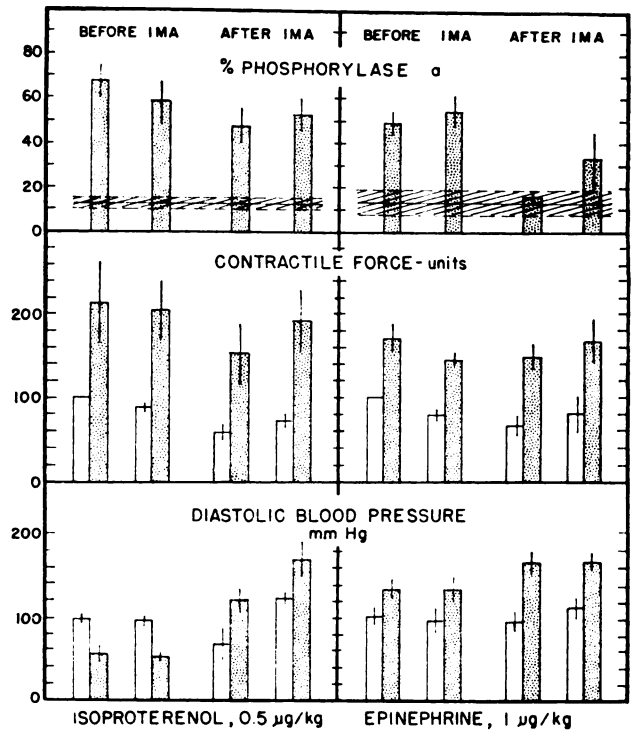


FIG. 2. The influence of isopropylmethoxamine (IMA) on the effects of isoproterenol (I) and epinephrine (E) on myocardial glycogen phosphorylase, cardiac contractile force, and diastolic blood pressure in anesthetized dogs. Two responses to i.v. injections of I and E are depicted before and after administration of IMA (10 mg/kg i.v.). Each bar is the mean result in 4 dogs each for I and E. Lines on bars are S.E. Cross hatched area on phosphorylase graph is mean control phosphorylase $a \pm 2$ S.E. based upon several samples throughout each experiment. IMA had no effect on the enzyme. Open bars in lower graphs depict control values just before injection of I and E. Data derived from experiments performed in collaboration with Dr. S. E. Mayer.

ient. On the basis of analyses of receptor types as described above, most "physiological" effects of sympathomimetic drugs can be placed in one of these two broad categories (except for those drugs whose actions are indirect through the release of endogenous catecholamines). The metabolic actions of sympathomimetic drugs are more difficult to classify on this basis, mainly because of the more diverse types of antagonists and less rigorous analysis in terms of orders of potency of agonists and specificity of blockade. Nonspecific antagonism, that is to say, antagonism at steps distal to the receptor or by indirect actions, must be considered more carefully in the evaluation of blockade of metabolic effects of catecholamines, as has been exemplified by the demonstration of the hyperglycemic blocking action of dihydroergotamine at a step distal to that of DCI.

There is little need now to introduce more Greek letters to label more adrenergic receptors. Furchgott's proposal at the first Catecholamine Symposium to

extend the classification of adrenergic receptors to *gamma* and *delta* (7) types has not been verified experimentally. The classification of adrenergically induced inhibition of rhythmic contraction of smooth muscle as a *delta* receptor does not fit with the demonstration of Ahlquist and Levy (3) of *alpha* and *beta* receptors in the small intestine. The suggestion that *gamma* receptors mediate glycogenolysis, a suggestion recently repeated by Nickerson (17), does not fit with present day evidence.

Characterization of adrenergic receptors by pharmacologic methods is feasible and rational, but it should depend upon rigorous analyses of orders of potencies of agonists, of specificity of blockade, and of continuous search into the sequential steps of drug action. New information, such as that discussed above with respect to α-methyl DCI, suggests the possibility of using modifying designations to describe the receptors, such as the tissue involved, *e.g.*, $beta_{heart}$ and $beta_{blood\ vessels}$ to differentiate the cardiac and vasodilator *beta* receptors. Although this terminology is cumbersome, evidence does not justify adding to the complexity of classification by introducing completely new types whenever a new drug is found which interferes with an adrenergic response.

Lest we take ourselves too seriously in the search for the adrenergic receptor we should recall Robert Frost's couplet, quoted at the beginning of this paper, especially when paraphrased:

> We dance round the cell and suppose
> But the Receptor sits inside and knows.

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