Adrenergic Receptors Within the Cardiovascular System

By Neil C. Moran, M.D.

The concept that drugs react with specific receptors in living tissues to produce pharmacologic effects is believed to have originated with Langley in 1905, although Ehrlich and others had certainly conceived of specific drug-cellular interactions. Today receptors have achieved such status among pharmacologists to be almost commonplace in spite of the fact that their identity has not been established. In undertaking a discussion of adrenergic receptors in the cardiovascular system consideration should be given to what is meant by "receptor."

The definitions which follow are intended to be operational and heuristic: operational in the sense of providing a conceptual framework on which both the experimentalist and the physician can establish a common basis for understanding and classifying sympathomimetic drugs; heuristic in the sense that this framework may provide a basis for further investigation into mechanisms of action of drugs and to the design of more nearly "perfect" drugs. Until more refined techniques lead to precise description of the molecular dynamics of drug-receptor interactions, the definition of receptors must remain general.

Let us first consider a schematic representation of a sympathetic nerve ending and the adjacent effector cell (fig. 1). The chemical transmitter—here labeled "sympathin" (probably norepinephrine*)—is synthesized and bound in the nerve cell. In response to impulses it is released to diffuse to the effector cell and react with a receptor. The transmitter-receptor combination (or combination between sympathomimetic drug and receptor) can be considered as the triggering of a multi-step sequential reaction leading to the cellular response. For example, norepinephrine, either released from the endings of the cardiac sympathetic nerves or of exogenous origin, reacts with receptors in the heart initiating reactions leading to cardiac acceleration and increased contractility. That is, the adrenergic receptor is part of the effector cell. It is not a binding site in either the nerve or the effector cell in which the transmitter or drug is held inactive. In addition to the specific adrenergic receptor there are other types of receptors, depicted in figure 1 as II and III, which react with other drugs.

The structure of the adrenergic receptors is not known, either biochemically or morphologically. What then is the basis for defining the "adrenergic receptor" as distinct from other receptors, as well as for distinguishing at least two types of adrenergic receptors? To elaborate on this question, gross physiologic response of the effector cell may not allow distinction between two types of receptors, e.g., activation of either of the hypothetical receptors I and II in figure 1 leads to augmented muscle contraction. Some distinction between receptors may be made by comparing characteristics of responses such as magnitude, time course, etc., as well as by contrasting the chemical families of drugs producing similar responses, e.g., sympathomimetic amines versus cardiac glycosides. These distinctions, however, are vague and

*Although norepinephrine has the strongest claim to the title of "adrenergic neurohumoral transmitter," the possibility of related compounds acting as transmitters at some sites cannot be dismissed. Consequently, the designation "sympathin" seems most appropriate and least committal for the sympathetic transmitter.
provide little understanding of basic mechanisms.

The most compelling evidence for formulating an answer to our question comes from the use of specific antagonists. The schema in figure 2 exemplifies this approach from a theoretical basis. Activation of receptor I leads to a type of response, depicted here as a muscle contraction, and is antagonized by only one type of blocking drug, e.g., blocking drug I. Activation of receptor II produces a response similar in type to that elicited by I but distinguished from the latter by blockade by still another drug, e.g., blocking drug II. Finally, activation of receptor III produces a response of qualitatively different type, which is blocked by a third type of antagonist. Thus, the distinction of receptor types becomes more discrete by the use of specific antagonists.

From this hypothetical framework it follows that classification and description of receptors in these terms can be a logical and fruitful enterprise for a scientist without his ever 'seeing' a receptor. An analogous operation is the classification of antibodies on the basis of antigen-antibody response, which may be performed without isolation of the antibodies.

The currently popular classification of adrenergic receptors is that of Ahlquist, which names two types—alpha and beta. According to this classification, blood vessel constriction in response to adrenergic stimuli is subserved by alpha receptors in vascular smooth muscle and adrenergic vasodilatation by beta receptors. Cardiac responses are subserved only by beta receptors. An important step in the development and confirmation of this classification came in 1957 with the discovery by Powell and Slater that a chlorinated derivative of isoproterenol, dichloroisoproterenol (DCI), antagonized certain "inhibitory" actions of sympathomimetic amines—actions not blocked by conventional adrenergic blocking drugs. DCI has since been employed extensively in analyses of actions of sympathomimetic amines.

Dichloroisoproterenol selectively antagonizes adrenergically induced vasodilatation. That is, it inhibits the vasodepression induced by epinephrine and isoproterenol but not the vasoconstriction elicited by sympathomimetic amines. Nor does it antagonize the vasodilatation evoked by histamine or acetylcholine. Thus, this evidence supports the classification of Ahlquist that sympathetic vasodilatation and vasoconstriction are subserved by separate receptors.

Moran and Perkins demonstrated the ability of DCI selectively to antagonize the augmentation of cardiac contractile force and the acceleration of heart rate produced by adrenergic stimuli. Blockade of the positive ino-

![Figure 1](image_url)  
*Figure 1*  
*Schematic representation of sympathetic neuro-effector junction.*

![Figure 2](image_url)  
*Figure 2*  
*Schematic representation of concept of specific receptors.*
Figure 3

Blockade of the positive inotropic effect of adrenergic stimuli by dichloroisoproterenol (DCI). Cardiac contractile force recorded via a Walton-Brody strain-gage arch sutured to the right ventricle of an anesthetized, open-chest dog. Upper panels show responses to left cardiac sympathetic nerve stimulation, and intravenous injections of norepinephrine and isoproterenol before administration of DCI. Lower panels demonstrate blockade by 7 mg./Kg. of DCI.

Table 1

Specificity of Cardiac Adrenergic Blockade by Dichloroisoproterenol (DCI)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Change in contractile force</th>
<th>Change in heart rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without DCI</td>
<td>After DCI</td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.15 mg./Kg.</td>
<td>17.9 ± 2.1</td>
<td>28.3 ± 7.2</td>
</tr>
<tr>
<td>Calcium chloride</td>
<td>60.3 ± 3.7</td>
<td>54.0 ± 7.3</td>
</tr>
<tr>
<td>Theophylline</td>
<td>37.8 ± 7.7</td>
<td>35.2 ± 10.3</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>127.2 ± 28.6</td>
<td>9.5 ± 3.1</td>
</tr>
</tbody>
</table>

Cardiac contractile force was measured in anesthetized, vagotomized dogs by means of a Walton-Brody strain gage arch sutured to the right ventricle. All drugs were injected intravenously. Seven mg./Kg. or more of DCI was administered. Values are means ± standard errors. Modified from table 4, reference 6, with permission of Williams & Wilkins Co.

Figure 3

Blockade of the positive inotropic effect of adrenergic stimuli by dichloroisoproterenol (DCI). Cardiac contractile force recorded via a Walton-Brody strain-gage arch sutured to the right ventricle of an anesthetized, open-chest dog. Upper panels show responses to left cardiac sympathetic nerve stimulation, and intravenous injections of norepinephrine and isoproterenol before administration of DCI. Lower panels demonstrate blockade by 7 mg./Kg. of DCI.

Table 1

Specificity of Cardiac Adrenergic Blockade by Dichloroisoproterenol (DCI)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Change in contractile force</th>
<th>Change in heart rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without DCI</td>
<td>After DCI</td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.15 mg./Kg.</td>
<td>17.9 ± 2.1</td>
<td>28.3 ± 7.2</td>
</tr>
<tr>
<td>Calcium chloride</td>
<td>60.3 ± 3.7</td>
<td>54.0 ± 7.3</td>
</tr>
<tr>
<td>Theophylline</td>
<td>37.8 ± 7.7</td>
<td>35.2 ± 10.3</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>127.2 ± 28.6</td>
<td>9.5 ± 3.1</td>
</tr>
</tbody>
</table>

Cardiac contractile force was measured in anesthetized, vagotomized dogs by means of a Walton-Brody strain gage arch sutured to the right ventricle. All drugs were injected intravenously. Seven mg./Kg. or more of DCI was administered. Values are means ± standard errors. Modified from table 4, reference 6, with permission of Williams & Wilkins Co.

Figure 3

Blockade of the positive inotropic effect of adrenergic stimuli by dichloroisoproterenol (DCI). Cardiac contractile force recorded via a Walton-Brody strain-gage arch sutured to the right ventricle of an anesthetized, open-chest dog. Upper panels show responses to left cardiac sympathetic nerve stimulation, and intravenous injections of norepinephrine and isoproterenol before administration of DCI. Lower panels demonstrate blockade by 7 mg./Kg. of DCI.

Table 1

Specificity of Cardiac Adrenergic Blockade by Dichloroisoproterenol (DCI)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Change in contractile force</th>
<th>Change in heart rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without DCI</td>
<td>After DCI</td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.15 mg./Kg.</td>
<td>17.9 ± 2.1</td>
<td>28.3 ± 7.2</td>
</tr>
<tr>
<td>Calcium chloride</td>
<td>60.3 ± 3.7</td>
<td>54.0 ± 7.3</td>
</tr>
<tr>
<td>Theophylline</td>
<td>37.8 ± 7.7</td>
<td>35.2 ± 10.3</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>127.2 ± 28.6</td>
<td>9.5 ± 3.1</td>
</tr>
</tbody>
</table>

Cardiac contractile force was measured in anesthetized, vagotomized dogs by means of a Walton-Brody strain gage arch sutured to the right ventricle. All drugs were injected intravenously. Seven mg./Kg. or more of DCI was administered. Values are means ± standard errors. Modified from table 4, reference 6, with permission of Williams & Wilkins Co.

tropic action has been confirmed by Drese and by Furchgott. Figure 3 shows the nearly complete blockade by DCI of the effects of cardiac sympathetic nerve stimulation, norepinephrine, and isoproterenol on cardiac contractile force in an anesthetized dog. Table 1 illustrates the specificity of this blockade for adrenergic type stimuli.
The cardiac adrenergic blocking effect of DCI gave support to the view proposed by Ahlquist that the cardiac adrenergic receptors are of a different type from those which serve vasoconstriction and are similar to those mediating vasodilation, e.g., beta receptors.

Further supporting evidence comes from the studies of Nickerson and Chan, and of Moran and Perkins, showing that conventional adrenergic blocking agents such as phenoxybenzamine (Dibenzyline) do not have specific cardiac blocking actions. Figure 4 demonstrates a comparison of phenoxybenzamine and DCI. Phenoxybenzamine, given in progressively larger doses to dogs, produces progressive blockade of the vasoconstrictor actions of epinephrine and norepinephrine, leading to a reversal of the vaspessor action of epinephrine and abolition of that of norepinephrine. Even at the highest dose of phenoxybenzamine, however, there is no antagonism of the positive inotropic effect of the two amines, the maximum contractile force produced by epinephrine and norepinephrine after phenoxybenzamine equaling or exceeding that before. In contrast, DCI does not block the vaspessor effect of either epinephrine or norepinephrine but antagonizes both the vasodilator action of isoproterenol and the positive inotropic action of the three amines. Thus, phenoxybenzamine blocks the responses subserved by alpha receptors, e.g., vasoconstriction, but not those subserved by beta receptors. DCI, by comparison, is a beta receptor-blocking compound.

DCI itself has sympathomimetic activity.

Figure 4
Comparison of adrenergic blocking properties of phenoxybenzamine and dichloroisoproterenol (DCI). Upper graphs depict right ventricular contractile force and lower graphs diastolic blood pressure in anesthetized open-chest dogs. Closed circles are "control" measurements immediately before i.v. injection of epinephrine (Epi), norepinephrine (Norepi), or isoproterenol (Isopro). Open circles are maximum responses, the arrows showing the direction and magnitude of change. Left hand part: dogs were given phenoxybenzamine in geometrically progressing doses, the responses to amines being tested after each dose. Right hand part: effect of progressive increase of dose of DCI. (Reproduced with permission of Williams & Wilkins Co. from J. Pharmacol. & Exper. Therap. 133: 194, 1962.)
Table 2

<table>
<thead>
<tr>
<th>Cardiac sympathetic nerve stimulation</th>
<th>Epinephrine 1 mg./Kg. i.v.</th>
<th>Calcium chloride 20 mg./Kg. i.v.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>193 ± 48 (5)</td>
<td>187 ± 19 (11)</td>
</tr>
<tr>
<td>After I.C.I. 38,174</td>
<td>2.4 ± 2.4 (5)</td>
<td>10.9 ± 3.9 (11)</td>
</tr>
<tr>
<td>P</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Experiments were performed on anesthetized, open-chest dogs; right ventricular contractile force measured with strain gage arch. I.C.I. 38,174 was given in divided doses to cumulative dose of 7 or 15 mg./Kg. Results of two dose levels are pooled. I.C.I. 38,174 was supplied by Dr. J. W. Black of Imperial Chemical Industries Limited. P values are for significance of differences by paired t test. Numbers in parentheses are number of animals used.

Initial injections in dogs produce a fall in blood pressure and increased cardiac contractile force and rate. This "intrinsie" activity is a disadvantage, both in terms of experimental and possible clinical use of the compound. Another beta adrenergic blocking drug has recently been described by Black and Stephenson. It is a naphthyl isopropylaminoethanol (I.C.I. 38,174; nethalide). Table 2 illustrates the selective cardiac adrenergic blockade produced by this agent.

It has been stated that alpha adrenergic blocking drugs are able to antagonize cardiac arrhythmias induced by sympathomimetic amines although unable to block the positive inotropic and chronotropic effects. Moore and Swain, Luechesi and Hardman, and Moran et al. have recently shown that DCI antagonizes several types of ventricular arrhythmias produced by catecholamines. It is not definitely established, however, that this antagonism is entirely explained on the basis of specific blockade; that is, DCI may have an antiarrhythmic action distinct from its adrenergic blocking action. The antagonism of catecholamine-induced arrhythmias by alpha adrenergic blocking agents is probably nonspecific and related to the antagonism of the vasopressor effect of amines by these blocking drugs.

Another effect of adrenergic stimuli which is antagonized by DCI and not by phenoxybenzamine is the activation of glycogen phosphorylase in the dog heart. The relatively specific activation of this enzyme system, which catalyzes the first step of glycogenolysis, by adrenergic stimuli and the selective blockade of this effect by DCI suggests that a beta type receptor subserves this adrenergic action.

The adrenergic receptors in blood vessels, as indicated above, are either alpha or beta. It is presumed that adrenergic vasoconstriction in the systemic circulation is alpha, in that isoproterenol has negligible arteriolar constricting action and DCI does not block the vasoconstrictions induced by potent amines. Adrenergic vasodilatation in the systemic circulation, mostly in skeletal muscle, is subserved by beta receptors since isoproterenol is the most potent amine and DCI blocks the effect. Mohlme-Lundholm and Lundholm have postulated that adrenergic vasodilation in skeletal muscle is secondary to the lactic acid released in response to the glycogenolytic effect of adrenergic stimuli. If this hypothesis is correct, one need not assume a beta receptor specific to adrenergic amines in the vascular smooth muscle. Furchgott, however, has presented evidence that adrenergically induced relaxation of smooth muscle may occur without increase in tissue lactic acid.

The available evidence suggests the existence of both alpha and beta receptors in the pulmonary circulation, that is, vasoconstriction mediated by alpha and vasodilatation mediated by beta receptors.
The concept of two types of adrenergic receptors in the circulatory system is summarized in table 3. Four sympathomimetic amines are considered: isoproterenol, which has predominantly beta action; epinephrine, which has both alpha and beta actions; norepinephrine, which is primarily an alpha stimulant but possesses potent beta actions on the heart; and finally, methoxamine (Vasoxyl), which is predominantly an alpha receptor antagonist. The spectrum of actions of these four amines indicates the overlapping effects one encounters in sympathomimetic drugs. The two adrenergic blocking drugs, DCI and phenoxybenzamine are shown selectively to block beta and alpha receptors, respectively.

The concept of two receptors in the circulatory system has obvious implications to the experimental pharmacologist. Does it, however, have value to the physician? I believe it does. One, a classification of the type presented in table 3 might enable the physician to select more rationally a sympathomimetic amine for specific therapeutic effects. For example, if one desires a vasoconstrictor amine devoid of cardiac stimulant actions one would choose a predominantly alpha agent. Drugs with varying degrees of dual action are available and finally a "pure" beta stimulant is found in isoproterenol with its profound cardiac stimulant action. Two, the therapeutic potential of beta type adrenergic blocking agents remains to be assessed. DCI, because of its marked intrinsic activity, produces tachycardia and, therefore, has little therapeutic promise. I.C.I. 38,174, (nethalide) which has less intrinsic activity than does DCI, would theoretically not have this side effect to as prominent a degree. In fact, Dornhorst and Robinson 22 have reported that I.C.I. 38,174 (nethalide) increases the exercise tolerance and reduces exercise tachycardia in patients with angina pectoris. The rationale of therapy of angina pectoris with beta adrenergic blocking compounds is based upon their ability to antagonize the tachycardia, augmented contraction, and increased metabolic activity brought about through sympathoadrenal discharge, thereby moderating the myocardial hypoxia resulting from stress. Whether beta adrenergic blocking drugs are of importance in therapy of angina pectoris or of other circulatory conditions is not established at present.

References
1. Langley, J. N.: On the reaction of cells and of nerve-endings to certain poisons, chiefly as regards the reaction of striated muscle to nicotine and to curare. J. Physiol. 33: 374, 1905.
SYMPOSIUM—ADRENERGIC CARDIOVASCULAR CONTROL

Adrenergic Receptors Within the Cardiovascular System

NEIL C. MORAN

Circulation. 1963;28:987-993
doi: 10.1161/01.CIR.28.5.987

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1963 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/28/5/987.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/