A STUDY OF THE ADRENOTROPIC RECEPTORS

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The adrenotropic receptors are those hypothetical structures or systems located in, on or near the muscle or gland cells affected by epinephrine. The concept of a receptive mechanism was introduced by Langley (1, 2) to explain the action of curare on skeletal muscle. Dale was probably the first to make significant use of the receptor concept in connection with the sympathetic nervous system. In his classical paper (3) on the sympatholytic action of the ergot alkaloids, he recognized that what he called the sympathetic myoneural junction could also be called 'the receptive mechanism for adrenaline'; and he used this mechanism to explain the fact that the ergot alkaloids prevented only the motor (excitatory) actions of epinephrine and had no effect on the inhibitory actions of epinephrine or on the excitatory actions of barium or pituitrin.

The adrenotropic receptors have been considered to be of two classes, those whose action results in excitation and those whose action results in inhibition of the effector cells. Experiments described in this paper indicate that although there are two kinds of adrenotropic receptors they cannot be classified simply as excitatory or inhibitory since each kind of receptor may have either action depending upon where it is found. The evidence for these conclusions is, in brief, that a series of six sympathomimetic amines has one order of potency—1, 2, 3, 4, 5, 6—on the following functions: vasoconstriction, excitation of the uterus and ureters, contraction of the nictitating membrane, dilation of the pupil and inhibition of the gut. In contrast, this same series of amines has an entirely different order of potency—2, 4, 6, 5, 3, 1—on the following functions: vasodilation, inhibition of the uterus and myocardial stimulation.

The variations in activity could be due to any or all of three factors: a) quantitative differences in potency, b) qualitatively different effects or c) differences due entirely to the experimental methods used. If the last two factors are controlled as much as possible by the selection of the amines and by using suitable experimental techniques, then the variations in activity are presumably due to actual differences in the receptors involved. Tentatively the first kind of receptor has been called the alpha adrenotropic receptor and the second kind the beta receptor. This concept of two fundamental types of receptors is directly opposed to the concept of two mediator substances (sympathin E and sympathin I) as propounded by Cannon and Rosenblueth (4) and now widely quoted as a 'law' of physiology. Results reported in this paper indicate that conclusions drawn by Cannon and Rosenblueth are open to controversy and that there is no known amine which fulfills the requirements for

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either sympathin E or I. The evidence presented strongly supports the concept that epinephrine is the only sympathetic adrenergic mediator.

The amines used were restricted to those which produced responses in the same dosage range as epinephrine, for which equivalent doses had similar durations of action, and which had qualitatively identical actions on the myocardium. None of them produced tachyphylaxis. The following amines were studied (abbreviations given in italics will be used throughout the remainder of this paper):

I. dl-(3,4-dihydroxyphenyl) ethanolamine. Arterenol, art.
II. dl-(3,4-dihydroxyphenyl) isopropanolamine. Cobefrine, methyl-art.
III. and IV. dl, and l-(3,4-dihydroxyphenyl) methyl ethanolamine. Racemic and levo epinephrine, dl-epi. and l-epi.
V. dl-(3,4-dihydroxyphenyl) methyl isopropanolamine. Methyl-epi.
VI. dl-(3,4-dihydroxyphenyl) isopropyl ethanolamine. N-isopropyl arternol, N-iso-art.

All of these amines have been studied extensively in the past (5-20) and hence there is a voluminous literature concerning them. No previous studies, however, have included all of them together in a quantitative comparison.

PROCEDURE

Dogs, cats, rats and rabbits were used in this study. The amines, in the form of their hydrochlorides, were made up in M/1000 stock solutions using isotonic saline containing 0.1 per cent sodium bisulfite and 0.1 per cent chlorobutanol as the solvent. Higher dilutions were made at the time of use with isotonic saline. The use of other drugs was kept to a minimum. Sodium pentobarbital, 20 to 30 mgm. per kgm., or urethane, 1 gram per kgm., was used as the anesthetic. The dogs and rabbits were usually pretreated with morphine sulfate, 10 mgm. per kgm. Atropine, 0.5 mgm. per kgm., was used as the anticholinergic agent. Three sympatholytic agents were used: ergotoxine, 2 mgm. per kgm., dibenamine (21), 25 mgm. per kgm. and Priscol (22).

Two types of dosage were employed with the amines: equimolar and equivalent. Truly equivalent doses in intact animals were many times unobtainable. For example, in attempting to determine the equivalent dosages necessary to inhibit the intact intestine it was found that the marked cardiovascular effects (some pressor and others depressor) interfered with or in themselves produced changes in the intestinal activity. For this reason equivalent doses were determined chiefly on isolated structures and equimolar doses compared in intact animals. In determining the relative activity of equimolar doses, both the degree and the duration of the response were considered. The amines were administered intravenously unless otherwise stated.

Cardiovascular. There are at least three functions served by adrenotropic receptors in the cardiovascular system: vasoconstriction, vasodilation and myocardial stimulation. Arterial pressure changes in themselves are not suitable for comparing the activity of these amines on these receptors because the arterial pressure represents the resultant of a number of factors such as the cardiac output and venous return, the balance between constriction, dilation and blood viscosity, and the mechanical effects produced by the muscular contractions such as occur in the heart,
intestine or uterus. Therefore in order to study each type of receptor it was necessary to work with more or less isolated parts of the cardiovascular system and then to correlate these results with those obtained from arterial pressure studies.

The arterial pressure was recorded by means of either a mercury manometer or a Hamilton manometer (25) from the carotid or femoral artery. In many of the dogs the aortic pressure pulse was recorded by means of a high frequency Hamilton manometer using a metal sound passed through the left common carotid into the aortic arch. In these latter experiments two recording cameras were used, one running continuously at low speed for a complete record of the amine response, and the other at high speed for pulse contours at appropriate times during the amine response.

The blood flow was measured in the important vascular beds by means of flowmeters introduced into either the venous outflow or the arterial supply. A Shipley optically recording rotameter (24, 25) or a modified Soskin type (26) 'bubble' flowmeter was used. The 'bubble' flowmeter was equipped with a reversing system so that only a single air bubble was needed for any one experiment. Heparin, 10 mgm. per kgm. every two hours, was used as the anticoagulant agent.

The effects of the amines on the vascular receptors were compared by determining their actions on the vasomotor resistance (VR). The VR represents the pressure-flow relationship calculated by the formula (27), VR = \( \frac{P - 20}{F} \) in which P is the arterial pressure in mm. Hg and F is the volume flow in cc. per minute. P - 20 was used since the \( \frac{P}{F} \) ratio changes abruptly at a pressure of about 20 mm. Hg (28), a phenomenon due in part to the presence of the cellular elements in the blood.

The results on the VR of the renal, mesenteric and femoral beds are shown in figure 1 and tabulated in table 1. It will be seen that the increase in VR produced by epi. in these vascular beds bears an inverse relationship to the decrease in VR produced by N-iso-art. In the bed (renal) which shows the least dilation with N-iso-art., dl-epi. is the most active among the racemic amines in producing constriction. In the femoral bed, in which N-iso-art. produces the greatest dilation, the net constrictor effect of dl-epi. is diminished by its own dilator action. These results are interpreted as showing 1) that the ratio of constrictor to dilator receptors varies in the different vascular beds and 2) that dl-epi. is the most active of the racemic amines on the constrictor receptor. Art. on the other hand, produces the greatest constriction in those beds which have the most dilator receptors, since this amine has very little action on the dilators (see below). The remaining two racemic amines show variable amounts of constrictor as against dilator activity.

This same relationship was shown in the arterial pressure responses to these amines as shown in figure 2. In the cat, which appears to have many dilator receptors, art. is the most active pressor agent among the racemic amines, with dl-epi. being third. In the rabbit, which appears to have few dilator receptors, dl epi. is more active than art. Even N-iso-art., which is a depressor in cats and dogs, produces a slight pressor response in rabbits. Blood flow studies showed that this pressor action of N-iso-art. in rabbits was due in part to vasoconstriction.

The comparative effects of these amines on the vasodilator receptors were deter-
mined by measurements of the coronary flow in perfused hearts (see below) and by their depressor effects in intact animals after the administration of the sympatholytic agent Dibenamine. In cats treated with the sympatholytic agent, \( \text{l-epi} \) and \( \text{dl-epi} \).

![Graph showing comparative action of amines on vasomotor resistance in the renal, mesenteric, and femoral vascular beds of dogs.](image)

Fig. 1. **Comparative action of amines on vasomotor resistance** in the renal, mesenteric, and femoral vascular beds of dogs. **Ordinates:** VR plotted logarithmically for convenience only; **abscissae:** time marks at 10 sec. intervals. The amines were injected intra-arterially as 0.1 cc. of the concentration shown. In the case of the renal and mesenteric curves, lower concentrations of methyl-epi. and N-iso-art. had no appreciable effect on the VR.

were both very active depressors. On the other hand, art. and methyl-art. were both poor depressors, with the former being the less active in this respect. The usual depressor effects of Methyl-epi. and N-iso-art. were slightly augmented. In dogs the results were essentially the same, with the exception that art. did not lower the pres-
sure in any animal tested. In rabbits none of these amines produced depressor responses after Dibenamine, with the occasional exception of $N$-iso-art.

The relative order of activity of these amines on the vascular receptors can now be summarized as follows (see table 1). On the dilator receptors $N$-iso-art. is the most active followed in order by $l$-epi., methyl-epi., $dl$-epi., methyl-art. and art. The relative activity on the constrictor receptors must be interpreted by correlating their actions on both the dilator and constrictor receptors with the relative ‘number’ of each of these receptors in the vascular bed or species studies. The dilator activity of $l$-epi. and $dl$-epi. is so great that this effect diminishes the net constrictor or pressor effect in those vascular beds or species having many dilator receptors. Therefore

<table>
<thead>
<tr>
<th>ADRENOTROPIC RECEPTOR AND METHOD OF EVALUATION</th>
<th>ORDER OF RELATIVE ACTIVITY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$l$-epi.</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
</tr>
<tr>
<td>Vasoconstrictor</td>
<td></td>
</tr>
<tr>
<td>Renal vasomotor resistance</td>
<td>1</td>
</tr>
<tr>
<td>Mesenteric “ “</td>
<td>1</td>
</tr>
<tr>
<td>Femoral “ “</td>
<td>1</td>
</tr>
<tr>
<td>Pressor action in cats</td>
<td>1</td>
</tr>
<tr>
<td>Pressor action in dogs</td>
<td>1</td>
</tr>
<tr>
<td>Pressor action in rabbits</td>
<td>1</td>
</tr>
<tr>
<td>Vasodilator</td>
<td></td>
</tr>
<tr>
<td>Renal vasomotor resistance</td>
<td></td>
</tr>
<tr>
<td>Mesenteric “ “</td>
<td></td>
</tr>
<tr>
<td>Femoral “ “</td>
<td></td>
</tr>
<tr>
<td>Coronary dilation</td>
<td></td>
</tr>
<tr>
<td>Depressor after Dibenamine</td>
<td></td>
</tr>
<tr>
<td>Myocardial</td>
<td></td>
</tr>
<tr>
<td>Perfused rabbit and cat</td>
<td></td>
</tr>
<tr>
<td>Intact dog</td>
<td></td>
</tr>
<tr>
<td>Intestinal (inhibitory)</td>
<td></td>
</tr>
<tr>
<td>Isolated rabbit, rat etc.</td>
<td>1</td>
</tr>
<tr>
<td>Intact dog, cat and rabbit</td>
<td>1</td>
</tr>
<tr>
<td>Uterine</td>
<td></td>
</tr>
<tr>
<td>Excitatory</td>
<td></td>
</tr>
<tr>
<td>Isolated rabbit</td>
<td>1</td>
</tr>
<tr>
<td>Intact dog and rabbit</td>
<td>1</td>
</tr>
<tr>
<td>Inhibitory</td>
<td></td>
</tr>
<tr>
<td>Isolated rat, cat, rabbit</td>
<td>2</td>
</tr>
<tr>
<td>Intact dog, cat, rabbit</td>
<td>2</td>
</tr>
<tr>
<td>Ureteral (excitatory)</td>
<td></td>
</tr>
<tr>
<td>Intact rabbit</td>
<td>1</td>
</tr>
<tr>
<td>Dilator pupillae (excitatory)</td>
<td></td>
</tr>
<tr>
<td>Intact cat</td>
<td>1</td>
</tr>
<tr>
<td>Nictitating membrane (excitatory)</td>
<td></td>
</tr>
<tr>
<td>Intact cat</td>
<td>1</td>
</tr>
</tbody>
</table>
l-epi. is considered to be the most active amine on the constrictor receptors followed in order by dl-epi., art., methyl-art., methyl-epi. and N-iso-art.

Fig. 2. COMPARATIVE ACTION OF AMINES on mean arterial pressure of cats, dogs and rabbits. Ordinates: pressure in mm. Hg; abscissae: time marks at 10 sec. intervals. The amines were injected intravenously.

Cats: average results from 12 determinations in 6 cats. Dosage, 0.1 cc. M/1000 solution per kgm. Cats after dibenamine—average results from 3 determinations in 3 cats. Dosage, 0.1 cc. per kgm. of the concentrations shown. Lower concentrations of art. did not produce any depressor responses. Dogs: average results from 12 determinations in 8 dogs. Dosage, 0.05 cc. M/1000 solution per kgm. Rabbits: average results from 10 determinations in 6 rabbits. Dosage, 0.1 cc. M/1000 per kgm. Larger doses of N-iso-art. produced depressor responses.

The relative activity of these amines was determined on both the perfused and intact heart. The isolated heart of the rabbit or cat was perfused with Ringer-Locke solution by the method of Lagendorff. Oxygen containing 5 per cent carbon dioxide was used to aerate the solution and to maintain the perfusion pressure (usually about 100 mm. Hg). Coronary inflow was measured by the rotameter and
the cardiac contractions were recorded with an optical lever system. This method allowed an absolutely simultaneous record of coronary inflow and myocardial activity to be obtained. Figure 3 illustrates the type of record obtained, while table 2 gives the results obtained on 20 rabbit hearts.

![Figure 3. Example of the action of the amines on the perfused rabbit heart. Cardiac contractions (myocard.) recorded with an optical lever. Coronary inflow (cor.) recorded with a rotameter. Time marks at 30 sec. intervals. The measurements listed in table 2 were made at the indicated points: R & A-I, the increased rate and amplitude at the point of maximal effect; R-2, the increased rate at a point about 2 min. after the amine administration (a measure of the duration of action); D.F., the decreased coronary inflow due to the increased myocardial activity; and I.F., the increased coronary flow due to the direct action on the coronary vessels. The amines were injected into the coronary inflow.](image)

**Table 2. Comparative Effects of the Amines on the Perfused Rabbit Heart**

<table>
<thead>
<tr>
<th>AMINE</th>
<th>INCREASE IN RATE AND AMPLITUDE</th>
<th>CORONARY FLOW</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R - 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>A - 1&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>N-iso-art.</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>l-epi.</td>
<td>101</td>
<td>90</td>
</tr>
<tr>
<td>methyl-epi.</td>
<td>75</td>
<td>70</td>
</tr>
<tr>
<td>dl-epi.</td>
<td>62</td>
<td>67</td>
</tr>
<tr>
<td>methyl-art.</td>
<td>57</td>
<td>45</td>
</tr>
<tr>
<td>art.</td>
<td>38</td>
<td>33</td>
</tr>
</tbody>
</table>

<sup>1</sup> Averages obtained from 20 hearts in which each amine was tested in each heart in a dosage of 0.1 cc. M/10,000 solution injected into the coronary inflow. See figure 3.

<sup>a</sup> Increase in rate and amplitude at the time of maximum effect.

<sup>b</sup> Increase in rate about 2 min. after injection.

<sup>c</sup> Decreased coronary inflow measured at point of maximum decrease.

<sup>d</sup> Increased coronary inflow measured at point of maximum increase.

Each of the amines increased the rate and amplitude of the cardiac contractions, the relative order of activity being given in tables 1 and 2. Simultaneous with the myocardial stimulation there was a decrease in the coronary inflow which was probably mechanical in origin (29). The flow then returned to or above the control value. Since the coronary flow in the perfused heart is determined by the balance between the myocardial stimulation and the vasodilation, those amines with the least dilator activity would allow the greatest mechanical decrease in flow. In contrast, those amines with the greatest dilator action would allow the least mechanical effect. The...
relative order of coronary dilator activity in the perfused heart will then be seen to
be the same as described above for the other dilator receptors.

The relative order of activity of these amines on the intact myocardium was
determined by two methods. Wiggers (30), Krop (31) and Remington and Hamilton
(32) have shown that epinephrine shortens the time of systole (T_s) even though the
heart rate may be unchanged. This shortening of T_s which probably results from
the myocardial stimulation was also produced by the other amines studied. The
T_s was measured on aortic pressure pulse contours of dogs from the beginning of
systolic upstroke to the incisura. The apparent order of activity of these amines to
shorten the T_s was found to be the same as their relative order on the isolated myo-
cardium.

The blood pressure effects of these amines in dogs pretreated with ergotoxine
can be used as a measure of their cardiac action since this sympatholytic agent, in
common with dibenamine and Priscol, does not prevent their myocardial actions.
Although ergotoxine unmasks the vasodilator effects of the amines it also produces
enough vasoconstriction in some dogs to diminish the depressor actions of the amines.
This effect allows the amines to produce an increase in arterial pressure in these ani-
mals by myocardial stimulation, an effect confirmed by cardiac output measurements
by the contour method of Hamilton and Remington (33). The comparative activity
of these amines on the myocardium as tested by this method was found to be the same
as found on the perfused heart.

The relative order of activity of these amines as myocardial stimulants will be
seen (table I) to be the same as that found for their vasodilator actions. This in-
dicates that the myocardial receptor is related to the vasodilator receptor rather than
to the vasoconstrictor receptor.

Intestine. The contractions of the isolated ileum of rabbits, cats and rats were
recorded in the usual manner using a 40 cc. muscle chamber and Ringer-Locke solu-
tion. Three types of dosage were used: a) equimolar concentrations applied to the
same segment of the ileum, b) equivalent concentrations to the same segment and
c) equivalent concentrations to different segments from the same animal (only one
amine to each segment). The results were the same for each method and for each
species and are tabulated in table I.

The contractions of the intact ileum of anesthetized dogs, cats and rabbits were
recorded with a sensitive Hamilton manometer by means of a small, water-filled bal-
loon inserted through a stab wound in the intestinal wall. In all of these animals the
arterial pressure was also recorded and in many of them other records such as mesen-
teric or femoral blood flow, or activity of the uterus or nictitating membrane were
also obtained. Only equimolar doses of the amines were compared since the vascular
effects of these amines interfered with their intestinal effects. The order of relative
activity was found to be the same as that found on the isolated ileum. The most
active amine was L-epi., followed in order by dl-epi., art., methyl-art., methyl-epi. and
N-iso-art. This order of activity indicates that the intestinal inhibitory receptor
must be related to the vasoconstrictor receptor rather than to the vasodilator
receptor.

Uterus. This organ presents a peculiar problem because of its well-known varia-
tions of response to epinephrine. The findings in the literature, and those reported herein, indicate that all uteri have two adrenotropic receptors, one excitatory and the other inhibitory in function, and that the response to epinephrine is determined by which receptor is predominant. The cat uterus, for example, is usually inhibited when nonpregnant and excited when pregnant. The isolated rabbit uterus, on the other hand, is always excited. The intact uteri of dogs, rabbits and humans (pregnant or nonpregnant) exhibit a diphasic response, excitation followed by inhibition.

The responses of the isolated nonpregnant rat uterus (inhibitory) and the rabbit uterus (excitatory) were recorded as described above for the isolated intestine. The comparative effects of the amines on these two species are given in table 1. The order of inhibitory action is seen to be the same as found on the vasodilator and myocardial receptors: \( N\text{-iso-art} \) is the most active, followed in order by \( 1\text{-epi.} \), \( methyl\text{-epi.} \), \( dl\text{-epi.} \), \( methyl\text{-art.} \) and \( art. \) The order of excitatory activity is the same as found on the vasoconstrictor and intestinal inhibitory receptors, \( l\text{-epi.} \), the most active, followed by \( dl\text{-epi.} \), \( art. \), \( methyl\text{-art.} \), \( methyl\text{-epi.} \) and \( N\text{-iso-art.} \).

When the isolated rabbit uterus was pretreated with Priscol, a sympatolytic agent, the amines lost their excitatory effects and produced only inhibition, with the order of activity being the same as found on the rat uterus. Due to a limited supply, only 2 virgin cat uteri were tested and these gave results identical to those found on the rat uterus.

The responses of the intact uteri of pregnant and nonpregnant dogs, cats and rabbits were recorded as described above for the intact intestine. The results obtained here were difficult to interpret, not only because of the diphasic effects that occurred but also because the muscular effects were complicated by the vascular effects. This can best be described by the following example. The uterine blood flow and the intrauterine pressure were measured simultaneously in a dog a few days post-partum (34). The intra-arterial injection of 0.1 cc. of \( M/1000 \text{ dl-epi.} \) produced a complete cessation of blood flow lasting about 30 minutes. One uterine contraction was produced and this was followed by complete inhibition also lasting for about 30 minutes (fig. 4.). In contrast to this result, the administration of an equimolar dose of \( N\text{-iso-art.} \) produced a slight increase in flow together with a slight inhibition

![Fig. 4. Effect of intra-arterially injected epinephrine on the uterine activity and blood flow. Calibrations: arterial pressure (A.P.) and intra-uterine pressure (U.P.) in units of 50 mm. Hg; uterine blood flow (F.) in units of 10 cc. per min. Time marks at 10-sec. intervals. During the control period the uterus was contracting every 3 to 4 min. At the signal, 0.1 cc. M/1000 dl-epi. was injected into the uterine artery. Note that during the control contraction the decrease in blood flow occurs simultaneously with the uterine contraction. Following the dl-epi., the flow diminished first, then one uterine contraction appeared, followed by complete inhibition. The zero flow and uterine inhibition persisted for more than 30 min.](http://ajplegacy.physiology.org/)
of activity; these effects lasted only 3 minutes. These results show that the vascular effects so modify the duration of action of the muscular effects (constriction increasing and dilation decreasing) that a true comparison of activity becomes almost impossible. With intravenous injections the arterial pressure changes added still another complicating factor.

The apparent relative activity of these amines on the intact uteri is given in table 1. The order of activity on the uterine inhibitory receptor (derived from the primary effect in the non-pregnant cat and the secondary effect in dogs and rabbits) is seen to be the same as found for the isolated rat uterus. The order of excitatory activity (derived from the primary effect in dogs and rabbits) was the same as described for the isolated rabbit uterus.

Iris and Nictitating Membrane. The comparative effects of the amines on these structures were determined in anesthetized cats. The responses of the dilator pupillae were determined by direct observation, using an ordinary 60-watt lamp at 12 inches for illumination. The movements of the nictitating membrane were recorded with a simple string and lever system. Some of the eyes were acutely denervated by section of the cervical sympathetics but this procedure had no apparent influence on the results. In some of the cats the amines were injected into the common carotid to avoid their blood pressure effects as much as possible.

Equimolar and equivalent doses were tested. The relative order of activity of these amines was found to be the same on both structures as shown in table 1. The most active amine was l-epi., with dl-epi. about one-half as active, art. about one-sixth, methyl-art. one-fifteenth, and methyl-epi. one-fortieth. Only occasionally did N-iso-art. have any effect on these structures and then only when given in a very high dosage directly into the artery.

Ureter. The actions of the amines were compared on the ureter of the anesthetized rabbit. The ureter was exposed at the renal pelvis and cannulated. Saline was perfused under a pressure of about 25 cm. of water, the rate of flow being recorded with a drop counter. The bladder was incised to allow free escape of the perfusate. All of the amines, except N-iso-art., decreased the flow when injected intravenously. The relative order of activity as determined by the amount of flow decrease produced by equimolar doses is shown in table 1. N-iso-art. had practically no effect on the flow except when given in very high dosage at which time it increased the flow rate.

The adrenotropic receptor of the rabbit ureter appears to be mainly excitatory in nature and related to the uterine excitatory and vasoconstrictor receptors.

DISCUSSION

The relative order of activity of these sympathomimetic amines on the various adrenotropic receptors is summarized in table 3. There are at least two distinct general types of these receptors. One type of receptor is associated with most of the excitatory functions and with at least one of the inhibitory functions (intestine). The other type is associated with most of the inhibitory functions and with one important excitatory function (myocardium). The relative order of activity of dl-epi. and art. on the vasoconstrictor receptor is opposite to that previously reported in
the literature. This difference is probably due to the previous methods of comparison, in which the pressor effects only were used as the criteria of activity. The fact that dl-epi. is more active than art. is more in accord with their relative activities on some of the other excitatory receptors. Because of the opposite effects associated with each type of receptor, the customary signs, E (excitatory) and I (inhibitory), cannot be applied. Therefore, for

**Table 3. Summary of the Relative Order of Activity of the Amines**

<table>
<thead>
<tr>
<th>RECEPTOR</th>
<th>Most active</th>
<th>ORDER OF ACTIVITY</th>
<th>Least active</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasoconstrictor</td>
<td>l-epi.</td>
<td>dl-epi. art.</td>
<td>methyl-art.</td>
</tr>
<tr>
<td>Uterine excitatory</td>
<td>l-epi.</td>
<td>dl-epi. art.</td>
<td>methyl-art.</td>
</tr>
<tr>
<td>Nictitating membrane excitatory</td>
<td>l-epi.</td>
<td>dl-epi. art.</td>
<td>methyl-art.</td>
</tr>
<tr>
<td><em>Dilator pupillae</em> excitatory</td>
<td>l-epi.</td>
<td>dl-epi. art.</td>
<td>methyl-art.</td>
</tr>
<tr>
<td>Ureteral excitatory</td>
<td>l-epi.</td>
<td>dl-epi. art.</td>
<td>methyl-art.</td>
</tr>
<tr>
<td>Intestinal inhibitory</td>
<td>l-epi.</td>
<td>dl-epi. art.</td>
<td>methyl-art.</td>
</tr>
<tr>
<td>Vasodilator</td>
<td>N-iso-art.</td>
<td>l-epi. methyl-epi.</td>
<td>dl-epi.</td>
</tr>
<tr>
<td>Uterine inhibitory</td>
<td>N-iso-art.</td>
<td>l-epi. methyl-epi.</td>
<td>dl-epi.</td>
</tr>
<tr>
<td>Myocardial excitatory</td>
<td>N-iso-art.</td>
<td>l-epi. methyl-epi.</td>
<td>dl-epi.</td>
</tr>
</tbody>
</table>

**Table 4. Structures or Functions Containing or Associated with Each of the Two Types of Adrenotropic Receptors**

<table>
<thead>
<tr>
<th>ALPHA RECEPTOR</th>
<th>BETA RECEPTOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasoconstriction</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>Viscera</td>
<td>Skeletal muscle</td>
</tr>
<tr>
<td>Skin</td>
<td>Coronary</td>
</tr>
<tr>
<td>Nictitating membrane</td>
<td>Viscera (few)</td>
</tr>
<tr>
<td>Uterus (excitatory)</td>
<td>Myocardium</td>
</tr>
<tr>
<td>Rabbit</td>
<td>Uterus (inhibitory)</td>
</tr>
<tr>
<td>Dog</td>
<td>Rat</td>
</tr>
<tr>
<td>Human</td>
<td>Cat</td>
</tr>
<tr>
<td>Intestine</td>
<td>Dog</td>
</tr>
<tr>
<td>Ureter</td>
<td>Human</td>
</tr>
<tr>
<td><em>Dilator pupillae</em></td>
<td>Bronchi (20)</td>
</tr>
</tbody>
</table>

1 The following structures or functions have not as yet been completely tested: spleen, *erectores pilorum*, urinary bladder, glands and glycogenolysis.

convenience they have been designated as the *alpha* adrenotropic receptors and the *beta* receptors. Table 4 lists the structures or functions associated with each type of receptor.

This concept of two fundamental types of adrenotropic receptors is directly opposed to the concept of two adrenergic mediators. Epinephrine has all of the chemical and physical properties, and, as shown in table 3, all of the physiological properties necessary to be the only adrenergic mediator. It is the most active substance on the *alpha* receptors and almost the most active on the *beta* receptors. It is, therefore, the one amine which is both the best excitatory agent and the best inhibitory agent
on the effector cells thus far tested. It is fundamentally the most logical substance to be the sympathetic neuro-hormone since all histological and embryological evidence points to the similarity of the adrenal medulla and the adrenergic post-ganglionic nerves.

Cannon and Rosenblueth based their belief in two kinds of sympathin on three fundamental observations (4): a) ergotoxine affects released sympathin and injected epinephrine differently, b) the combined effect of simultaneously released sympathin from two different sources appears to be greater than expected and c) the substance released by the stimulation of the hepatic nerves (liver sympathin) has physiological actions different from those of injected epinephrine. In order to support the theory of a single mediator and two receptors, it is necessary to challenge the validity of the conclusions drawn from these observations.

A comparison of the effects of intravenously injected epinephrine and sympathin released by stimulation of the lower abdominal sympathetics is not valid because of the difference in the manner of delivery of the two substances to the effector cells. A constrictor substance presented intra-arterially, or released directly into a vascular bed by nerve stimulation, tends to hold itself in the periphery by its own constricting action. This can be readily shown by injected epinephrine into the femoral artery while measuring the femoral blood flow. Ergotoxine does not prevent this effect since it, in common with the other known sympatholytics, is not absolute in its sympatholytic or adrenolytic action. Therefore, a large amount of sympathin formed in the periphery by nerve stimulation (the figure reproduced by Cannon and Rosenblueth shows that prolonged nerve stimulation was done) would, even in the presence of ergotoxine, result in contraction of the vessels of that region, which in turn would hold the sympathin and not allow free circulation to other sites. The constriction would therefore be restricted and prolonged. Epinephrine, on the other hand, administered intravenously, would be delivered to all parts of the body, and therefore in low enough concentration to produce vasodilation by selective action upon the adrenotropic dilator receptors.

The apparent difference between sympathins from two sources (the cardioaccelerator and splanchnic nerves) as interpreted by Cannon and Rosenblueth is questionable, since the cardiovascular effects were not considered. The effects (on the nictitating membrane) of the sympathins were separately quantitated against intravenously injected epinephrine. Simultaneous stimulation of the two sources then produced a greater response than expected from the original quantitation. The amount of sympathin delivered to the nictitating membrane is a function of the amount formed at the remote ending and of the blood flow from that region to the membrane. The blood flow was undoubtedly increased during the double stimulation (especially by the cardio-acceleration) and tended to force (against the holding effect described above) more of the splanchnic sympathin to the membrane. This would render the original quantitation invalid. The results may then be explained on the basis of delivery of different amounts of a single substance rather than by a potentiated effect produced by two different substances.

The substance produced by stimulation of the hepatic nerves (liver sympathin) has been the subject of much study. It is evident that liver sympathin is not epine-
phrine. There is, however, no absolute evidence that it is the neuro-hormone (sympathin) or sympathin E. According to Cannon and Rosenblueth, liver sympathin contracts the nictitating membrane, increases arterial pressure, is not 'reversed by ergotoxine' and does not dilate the pupil or relax the pregnant cat's uterus. Further studies by Greer et al. (13), and Gaddum and Goodwin (17) have confirmed, in the main, these observations, but have also shown that it does relax the intestine, and may dilate the pupil and relax the cat's uterus.

Liver sympathin is related to epinephrine, and several investigators (9, 10, 13, 17) have suggested that it might be art. Euler has obtained a sympathomimetic substance by extraction of mammalian hearts and has suggested (19) that it might be the epinephrine isomer, methyl-art. Of the amines used in this study art. appears to be the most similar to liver sympathin.

Cannon and Rosenblueth considered the lack of pupillary dilator action of liver sympathin as a paradox, on the basis that this substance was the hypothetical sympathin E. Actually however, the stimulation of the nictitating membrane by liver sympathin is the paradox, if liver sympathin is art. It has been shown that art. is almost equally effective on the iris and the nictitating membrane. Therefore, an amount of liver sympathin, if it is art. that would contract the membrane, should also dilate the pupil. As Gaddum and Goodwin (17) have pointed out, the nictitating membrane is very responsive to many substances other than sympathomimetic amines. It is possible that stimulation of the hepatic nerves could produce small amounts of histamine or acetylcholine which might account for the marked action of liver sympathin on the nictitating membrane.

Assuming that liver sympathin is art., does this amine possess the necessary qualifications to be called sympathin E? The answer must be no, since the results reported herein (based on the racemic forms) demonstrate conclusively that art. is not the most active agent on any of the excitatory adrenotropic receptors. Just why sympathin from the liver should be chiefly excitatory has never been explained. The source must either be the nerve endings in the liver cells or the endings in the smooth muscle of the hepatic blood vessels. Evidence has been obtained by direct flow studies that epinephrine can produce vasodilation in the hepatic vessels in a manner analogous to its action on other vascular beds (35). Therefore, if there are two kinds of sympathin there is no good reason why an inhibitory substance should not also be formed by hepatic nerve stimulation.

Considering all of the facts available, it is apparent that liver sympathin is a unique product, possibly a modification of the neuro-hormone chemically changed by the liver substance after formation; and that no other substance like it has ever been conclusively demonstrated as being formed by stimulation of other sympathetic nerves. It should therefore be considered as an exception and not be used as the entire basis for the proof of the existence of two kinds of sympathin.

Although little can be said at the present time as to the fundamental nature of the adrenotropic receptor and the difference between the alpha and beta types, this concept should be useful when studying the various actions of epinephrine, the actions and interactions of the sympathomimetic agents, and the effects of sympathetic nerve stimulation. Use of the terms sympathin E and I should be discouraged, and
the term sympathin should be used to distinguish between the neuro-hormone produced by nerve stimulation and exogenous epinephrine. Fortunately in the case of the cholinergic nerves there has never been any suggestion that there might be two mediators, although both excitatory and inhibitory effects are produced. The diverse effects of the cholinergic mediator, acetylcholine, have always been ascribed to differences in the receptors upon which it acts.

**SUMMARY**

There are two distinct types of adrenotropic receptors as determined by their relative responsiveness to the series of racemic sympathomimetic amines most closely related structurally to epinephrine. The *alpha* adrenotropic receptor is associated with most of the excitatory functions (vasoconstriction, and stimulation of the uterus, nictitating membrane, ureter and dilator pupillae) and one important inhibitory function (intestinal relaxation). The *beta* adrenotropic receptor is associated with most of the inhibitory functions (vasodilation, and inhibition of the uterine and bronchial musculature) and one excitatory function (myocardial stimulation). Racemic epinephrine (and therefore levo-epinephrine which is about twice as active) is the one amine which is the most active on both the *alpha* and *beta* receptors.

The results support the theory that there is only one adrenergic neuro-hormone, or sympathin, and that sympathin is identical with epinephrine. The so-called liver sympathin (the sympathin E of Cannon and Rosenblueth) is regarded as a modified form of sympathin, chemically changed by the liver after formation; and liver sympathin is also considered a unique product and should not be regarded as sympathin E or even sympathin.

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