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Review Article

The Adrenergic Receptor

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At this moment in time it is appropriate to review briefly the status of the adrenergic receptor.

The nomenclature of α and β receptors introduced by this laboratory in 1948 (1) is now used internationally (27, 37, 48, 70, 77, 105).

A new class of drugs having potential therapeutic value, the β adrenergic blocking agents, has appeared (23, 24, 26, 44, 70, 77, 115, 117, 118, 125).

In the study of receptors the biological approach based on observations of tissue and organ response is yielding to a biochemical approach based on studies of binding, membranes, and enzyme kinetics. Therefore, this review will attempt only to summarize the biological studies of the adrenergic receptor. Some biochemical views will be found in papers by Ariens (12, 13), Belleau (19), Burn (34), Furchgott (64–67), Volle (139), and Bloom (26).

For purposes of this review the adrenergic receptor is defined as the specific molecular site or structure in or on effector cells with which molecules of adrenergic agonists (epinephrine, etc.) react in order to elicit the characteristic response of the cell (67). There is some tendency to call any and all sites of uptake or binding receptors (85). However, the receptor is usually considered to be the site of drug-effector interaction that produces an observable response.

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It is the opinion of this reviewer that the adrenergic receptor is the most important link in the adrenergic neuroeffector transmission chain. Effector cells without adrenergic receptors, the ciliary muscle of the eye, for example, cannot respond to adrenergic agonists. This is true whether the agonist is administered by a pharmacologist, a nerve end, or the adrenal medulla. Although this is obviously circular reasoning (the response depends on a receptor and the receptor is defined by the response) it is, however, the way in which all receptors have originated. Regardless of the exact chemical structure of the adrenergic transmitter the effector response is controlled by the receptor and by the natural function of the effector cell.

There are others, however, that do not place much importance on the receptor. For example, Euler puts most emphasis on structure, synthesis, storage release, and uptake of the transmitter (60).

There are two classic ways to characterize biologically the adrenergic receptors; Sir Henry Dale pioneered both methods. One is to compare responses to structurally different but chemically related agonists (16). The other is to compare responses to specific receptor blocking agents (47). This review will consider both views of the adrenergic receptor.

As previously pointed out by this reviewer (4), experimental design, deliberate or unconscious, favors results that best support the experimenter's currently held notions. Reviewers, including the

present one, are not immune to this phenomenon. Therefore, comparative potencies assigned to various agonists are not necessarily the same as those assigned by the authors of the quoted papers. In some cases the authors made no estimates of comparative potency although their published results give sufficient information to allow these estimates to be made. In other cases, older papers have been reinterpreted in the light of newer ideas.

HISTORICAL VIEW

Ehrlich proposed the basic ideas of receptor theory (52). He considered chemicals as having two functional parts: a selective group that governs distribution in the body, tissues, and cells, and a pharmacophore group that evokes the specific effect produced by the chemical. In modern terms, affinity and intrinsic activity (13) could be substituted for Ehrlich's terms.

Dale was the first to make significant use of the receptor concept in connection with the sympathetic nervous system (47). He recognized that the sympathetic neuromyal junction could be viewed as "the receptive mechanism for adrenaline," and he used this concept to explain the differential blocking effect of the ergot alkaloids.

Initiated by the work and ideas of Cannon (38), theories of differential activity based on the chemical structure of the transmitter started to develop. Cannon's sympathins E and I were followed by sympathins A (from adrenal) and N (from adrenergic nerves) (14, 58, 59); sympathin A was thought to be epinephrine and N norepinephrine.

In the course of a search for a compound to prevent the myometrial stimulation induced by vasopressin some unexpected (to this experimenter) observations were made. These were: phenylephrine, a potent vasoconstrictor, *relaxed* the smooth muscle of the gut while a methyl derivative of epinephrine, a potent depressor agent, did not as readily relax the gut; isoproterenol in high dosage *contracted* rabbit uterus; and arterenol was *less* potent than epinephrine as a vasoconstrictor. These findings suggested a more thorough comparison of closely related catecholamines. The relative potencies of five amines, including epinephrine, were studied on a variety of effectors. The conclusions drawn from the results were as follows (1, 4, 5, 7).

1. There are two distinct types of adrenotropic (adrenergic) receptors as determined by their relative responsiveness to closely related sympathomimetic amines.

(*a*) The α receptor is associated with most of the excitatory functions (vasoconstriction, and contraction of the smooth muscle of the uterus, nictitating membrane, ureter, and pupillary dilator) and one important inhibitory function (intestinal relaxation).

(*b*) The β receptor is associated with most of the inhibitory functions (vasodilation, and inhibition of the uterine and bronchial smooth muscle) and one excitatory function (myocardial stimulation).

2. Epinephrine is the one amine that is most active on both α and β receptors; the adrenergic receptor seems to be designed to fit best with the molecular shape of epinephrine (5).

Two of the catecholamines used in this study, the l-methyl derivatives of arterenol and epinephrine, were dropped from the experimental procedures because of questionable purity and optical activity. Furthermore, the *levo*-rotatory isomer of arterenol (levarterenol) became commonly available. Therefore, for testing adrenergic receptors by the comparative potency method only epinephrine,[1] levarterenol,[1] and isoproterenol[1] are usually considered.

Two other adrenergic receptor theories have been proposed. Lands (86), on the basis of responses to a large variety of sympathomimetic amines, suggested receptors A c (excitatory), A r (inhibitory), and A cr (undifferentiated). The undifferentiated receptor was to be found in the heart and presumably the intestine, and responded equally to almost all sympathomimetic amines. Furchgott (65) added two receptors. The γ receptor for glycogenolysis and the δ receptor for intestinal inhibition. As will be described below the receptor blocking agents seem to have clarified partly the cardiac and intestinal receptor. However, catecholamine metabolic effects, including glycogenolysis, may require a different receptive mechanism.

ALPHA ADRENERGIC RECEPTORS

The α receptor is characterized by being most responsive to epinephrine and least responsive to isoproterenol. In terms of comparative potency the order of activity is, epinephrine is more potent than levarterenol which is more potent than isoproterenol.

Eye.—There is no doubt that epinephrine is the most potent catecholamine on the adrenergically controlled smooth muscle of the eye. This is true whether the racemic or *levo* forms of epinephrine and norepinephrine are com-

[1] In discussing comparative potencies of the catecholamines it should be understood that epinephrine and levarterenol are *levo* rotatory compounds and that isoproterenol is a racemic mixture. These are the forms compared unless otherwise specified. In some of the older studies, prior to 1948, racemic epinephrine was compared to racemic norepinephrine (arterenol). In some more recent studies *levo* isoproterenol has been used.

pared. This is shown by mydriasis produced by intra-arterial injection in the intact cat (1, 58, 78), by intraocular injection in the dog or rabbit (21), or in the isolated eye of the rat (18).

The smooth muscle controlling the nictitating membrane, usually studied in the cat, has long been used to show the difference in potency between epinephrine and levarterenol (1, 33, 134, 142). On the isolated membrane of the cat, epinephrine is five times more potent than levarterenol (133). The chronically denervated or cocaine pretreated nictitating membrane becomes supersensitive to both epinephrine and levarterenol (33, 134). The increase in sensitivity to the latter exceeds that to the former so that the potency difference between these amines becomes smaller. However, epinephrine remains the more potent.

The smooth muscle of the orbit of the eye seems to be more sensitive to epinephrine than to levarterenol (personal observation). However, a quantitative study has apparently been done only in the rat; epinephrine was found to be about twice as potent as levarterenol (68).

What is the effect of isoproterenol on the iris dilator and the nictitating membrane? On intraocular administration, this amine produces mydriasis by causing contraction of the radial muscle (62); this is an α receptor response as shown below by tests with specific blocking agents. A similar result is obtained in the isolated eye of the rat (18). In the intact eye of the cat mydriasis is obtained only with very large doses of isoproterenol (1). On the isolated nictitating membrane of the cat isoproterenol in a concentration of 1 mcg./ml. produces relaxation if the muscle is in spasm (123); a concentration of 10 mcg./ml. produces only contraction (133). In summary, isoproterenol activates the α receptors associated with the eye, and its potency is a tenth to a hundredth that of epinephrine, depending on the test method used to compare the drugs.

Spleen.—The smooth muscle of this organ is contracted by the catecholamines. Epinephrine is more potent than levarterenol. This has been determined using measurements of whole spleen size in anesthetized dogs (9, 41), contraction of isolated strips of cat spleen (22), and by hematocrit increases in sheep (135). Isoproterenol in relatively high dosage also produces splenic contraction in the dog or cat (22, 102).

Seminal Vesicles.—When tested on isolated preparations from the rat, epinephrine is more potent than levarterenol in causing contraction (42, 126).

Retractor Penis.—The smooth muscle of this canine structure *in situ* is contracted by catecholamines. Epinephrine is more potent than levarterenol (91, 95). Occasionally, high doses of isoproterenol will produce contraction.

Myometrium.—It has long been known that the myometrial response to epinephrine varies from species to species and depends on the hormonal status at the time of experiment (72). Rabbit or dog uterus, *in situ* or isolated, contracts in response to epinephrine or levarterenol; the former is the more potent (1, 3, 58, 142). Results similar to those obtained in the rabbit have recently been found in the sloth (*Choloepus hoffman* Peters) (114). Isoproterenol produces both relaxation and contraction, the latter occurring only with high concentrations (1). The uterus of the pregnant cat also responds to epinephrine and levarterenol with contraction, but the latter is now the more potent (142). This is due to the fact that the inhibitory receptor is dominant over the excitatory receptor. The dominance between receptors varies from the rabbit, in which the excitatory is predominant, to the rat, in which the inhibitory is dominant. In the human female both receptors are apparently present since epinephrine can produce either relaxation or contraction depending on dosage, and levarterenol produces contraction (43, 81, 116, 145).

Arterial Pressure (Pressor Response).—The acute transient rise in mean arterial pressure in the anesthetized animal is the classic hallmark of sympathomimetic activity. Levarterenol under ordinary circumstances, administered intravenously, is a more potent pressor agent than epinephrine (1, 16, 42, 58, 78, 94, 95, 142). However, epinephrine is the more potent agent in eviscerated dogs (42), in dogs anesthetized with ether (131), and in rabbits (1).

Isoproterenol produces a depressor response in most species of animals. In the rabbit a pressor response may occur (1).

While it is true that arterial blood pressure responses give clues as to how drugs effect the peripheral resistance and cardiac action, other more direct measurements are needed. Arterial pressure can be elevated by either vasoconstriction or cardiac stimulation. Reflex effects initiated by pressure changes can conceal or even reverse the responses due to direct drug action.

Vasoconstriction.—Epinephrine is the most potent adrenergic vasoconstrictor. This has been demonstrated in dogs in the renal circulation (1, 9, 124), in the skin (75), in the mesenteric circulation (1, 73), and in the femoral

circulation (9). Epinephrine is more potent than levarterenol as an intracutaneous vasoconstrictor (42, 78, 95). It is also more potent in the perfused rabbit ear (95) and perfused frog (142).

Levarterenol is more potent than epinephrine as a vasoconstrictor in the canine skeletal muscle vascular bed (74). This is due to the fact that epinephrine is a more potent vasodilator than is levarterenol (see below).

Coronary blood flow is increased by the catecholamines. There is, however, little conclusive evidence that this is a direct relaxing effect on coronary smooth muscle. Changes in heart rate, ventricular contractile force, and diastolic pressure can markedly change coronary flow by mechanical or metabolic means. These effects complicate and obscure attempts to measure the direct coronary effects of the catecholamines. It is possible that epinephrine and levarterenol are direct coronary vasoconstrictors.

Aortic Muscle.—The smooth muscle in rabbit aorta is contracted by the catecholamines. Epinephrine is equipotent with levarterenol, and isoproterenol is the least potent (63, 64, 144). These studies include blocking agents, and the results are consistent with existence of a single receptor (α).

Intestinal Smooth Muscle.—On the two standard experimental preparations for testing drugs on the gut, isolated rabbit ileum and intact canine intestine, *all catecholamines and all sympathomimetics*, produce an inhibitory effect. In comparing epinephrine and levarterenol the majority of studies show epinephrine to be the more potent (1, 9, 33, 37, 58, 142). Isoproterenol is sometimes the least potent of the three catecholamines, and sometimes the most potent. And in intact animals, isoproterenol often produces stimulation of the ileum instead of inhibition. Although an α receptor could be assigned to intestinal smooth muscle, it will be shown below that this would not be a complete explanation.

BETA ADRENERGIC RECEPTOR

The β receptor is most responsive to isoproterenol and epinephrine and in general is least responsive to levarterenol. In terms of potency: isoproterenol > epinephrine > levarterenol. Only two smooth muscle inhibitory responses seem unequivocally to be controlled by a β receptor. These are: the bronchial smooth muscle and the rat myometrium. All other smooth muscle adrenergic responses are best described as being controlled by a balance between α and β activity.

Bronchial Smooth Muscle.—The relative potencies of the catecholamines on this muscle are, isoproterenol > epinephrine > levarterenol (42, 78, 95). This relationship is the same whether the test method used is protection against histamine asthma in guinea pigs, perfusion of the isolated lung, or mechanical response of tracheal ring chains.

Myometrium.—The isolated uterus of the rat is relaxed by all of the catecholamines and, indeed, by all sympathomimetic compounds tested. The relative potencies of the catecholamines are: isoproterenol > epinephrine > levarterenol (1, 95, 142). As stated above, the myometrium of other species appears to have both α and β receptors. As will be described below the myometrium can be used to detect the specific blocking agents of these receptors.

Arterial Pressure (Depressor Response).—Isoproterenol injected intravenously produces a transient but well marked fall in pressure in most species (1, 87, 114). There is no unequivocal evidence that epinephrine or levarterenol can produce a similar depressor response. However, after an α adrenergic blocking agent (see below) epinephrine evokes a depressor response. This change from a pressor response to a depressor response is termed epinephrine reversal. This is considered to be due to an unmasking of a vasodilator action that is normally concealed by a predominant vasoconstricting effect. In addition, epinephrine and levarterenol evoke special depressor reflexes (2, 76).

Vasodilation.—Intra-arterial injections of epinephrine produce vasodilation in the vascular bed of skeletal muscle of dog and man (15, 74, 121). Epinephrine is said to increase hepatic blood flow in man (17).

Isoproterenol produces vasodilation when injected intra-arterially in the femoral and mesenteric vascular beds (1). In the renal vascular bed isoproterenol has either no significant effect (1) or produces some vasoconstriction (124).

Although there have been few detailed comparative studies of the potency of the three principal catecholamines the information available shows isoproterenol > epinephrine > levarterenol as direct vasodilators.

Heart.—Isoproterenol is the most potent of the three catecholamines in producing a positive chronotropic effect on the heart (1, 80, 87). Epinephrine is probably more potent than norepinephrine (11), but reflexes due to pressure changes can obscure the positive chronotropic effect. For example, in animals with intact buffer reflexes, vagal bradycardia may

completely overshadow any tachycardia. Levarterenol in this case produces more bradycardia (less positive chronotropic effect) than epinephrine (9).

In man, levarterenol produces reflex bradycardia while epinephrine produces sinus tachycardia (71, 145).

The relative potency for producing a positive inotropic cardiac effect is isoproterenol > epinephrine = levarterenol (46, 61, 78, 87, 120). In certain amphibia epinephrine is definitely more potent than levarterenol (142) and the same is true in isolated rabbit hearts under some experimental conditions (1).

Intestinal Smooth Muscle.—The potency of isoproterenol as compared to epinephrine and levarterenol is difficult to determine. On isolated strips of rabbit ileum the response seems to depend on the order of administration. Using equimolar doses, if isoproterenol is applied first, and applied only once to each strip, it is the least potent catecholamine in producing cessation of movement. On the other hand, if isoproterenol is applied repeatedly or after the other two amines, it appears to be the most potent. If the strip is pretreated with atropine its response to isoproterenol becomes more uniform, but the relative potency is still variable. The evidence makes it difficult to assign either an α or a β receptor on the basis of relative response to the catecholamines. Furchgott (64) assigned a δ receptor. However, an alternative explanation will be presented below under β adrenergic blocking agents.

ALPHA RECEPTOR BLOCKADE

The classical adrenergic blocking agents such as dibenamine, phenoxybenzine, and phentolamine have long been known to block most of the excitatory responses to epinephrine and other catecholamines. The excitatory responses that are not blocked are the positive inotropic and chronotropic effects on the heart. This class of drugs has been reviewed extensively (110, 111). Green and co-workers have published extensively on adrenergic block in skeletal muscle vascular bed (74), mesenteric bed (73), and skin (75). The iris has been studied by Bennet *et al.* (21), the spleen by Bickerton (22), and the isolated seminal vesicles by Stone and Loew (126).

Levy and Ahlquist (91) have described a general method for examining adrenergic blocking agents. This consists of recording arterial pressure, heart rate, intestinal contraction, and contractions of the retractor penis in the anesthetized dog. Four test amines are administered before and after the unknown blocking agents. These are: epinephrine and ethylnorepinephrine (α and β activators), phenylephrine (a relatively pure α activator), and isoproterenol (the most potent β activator). An α blocking agent diminishes or prevents the effect of epinephrine and phenylephrine on the retractor penis, blocks the pressor action of phenylephrine, reverses the pressor action of epinephrine, and does not essentially alter the responses to isoproterenol.

It was found that these blocking agents also blocked the inhibitory effect of phenylephrine on the intestine (8).

It is fair to say that all responses described above as being controlled by α receptors are blocked by the agents known as classic adrenergic blocking agents. This includes vasoconstriction and contraction of iris dilator, seminal vesicle, spleen, and retractor penis.

BETA ADRENERGIC BLOCKADE

In 1958 Powell and Slater described the actions of the dichloro analog of isoproterenol, DCI (114). This compound had effects that could only be described as due to blockade of the β adrenergic receptors (122). Moran (106) suggested that the term "*beta* adrenergic blocking agent" was most appropriate. This was the start of a continuing search for new β adrenergic blocking agents for possible therapeutic use in cardiac arrhythmias.

It is of historical interest that at least two compounds preceded dichloroisoproterenol as β blocking agents. Ethylnorepinephrine, to be described in greater detail below, in large doses had β adrenergic blocking activity. The first dose of this compound administered intravenously produced a transient pressor response followed by a more prolonged depressor response. If the dose was immediately repeated the pressor response increased and the depressor response decreased. After three or four doses of about 0.5 mg./Kg., ethylnorepinephrine produced only a pressor response (132). The reason for this "reversal" was not found until 25 years later (90).

Butylsympatol blocked the depressor response to isoproterenol and increased the pressor response to epinephrine (41, 113).

Many substances have been found to have β adrenergic receptor blocking properties. At the present time the principal compounds are as follows.

Dichloroisoproterenol, DCI (88, 90, 115).

Naphthylisoproterenol, 1-(2-naphthyl)-2-isopropylaminoethanol, nethalide, pronethalol (24).[2]

[2] Trademarked as Alderlin.

1 - Isopropylamine - 3 - (1 - naphthyloxy) - 2-propanol, propranolol (23).[3]

4 - (2 - Isopropylamino - 1 - hydroxyethyl) methanesulfanilide, MJ1999 (51, 125).

4 - (2 - Methylamino - 1 - hydroxypropyl) methanesulfonanilide, MJ1998 (51, 125).

Arterial Pressure.—The β adrenergic blocking agents diminish or block the depressor response to isoproterenol (91). This effect can serve as a basic indicator for these compounds. A more sensitive screening test has been described; this is known as the "ethylnorepinephrine reversal" test (90). This catecholamine in a dose of 50 mcg./Kg. in anesthetized dogs treated with atropine consistently produces a small pressor response followed by a more prolonged depressor response. Blood flow studies show this to be due to vasoconstriction followed by vasodilation. Following an effective dose of a β blocking agent, ethylnorepinephrine produces only a pressor response due to peripheral vasoconstriction. Many vasoconstrictors of prolonged action also produce ethylnorepinephrine reversal by obscuring the dilator effect of this catecholamine. Therefore, to be certain only β receptor blockade is involved, blood flow studies should be done. Isoproterenol block *but not reversal* must also be present.

The β blocking agents also potentiate the pressor action of epinephrine (6). This is consistent with the idea that the pressor response to epinephrine is reduced by the vasodilating action of this catecholamine.

Bronchial Smooth Muscle.—The bronchodilation produced by epinephrine, norepinephrine, or isoproterenol is blocked by β adrenergic blocking agents (100). Epinephrine and levarterenol now produce a contraction that is blocked by α adrenergic blocking agents.

Myometrium.—Inhibition of the feline myometrium *in situ* produced by epinephrine is blocked by β adrenergic blocking agents (122). Inhibition of isolated uteri by epinephrine is also blocked by these agents (65, 92, 115). All of the β blocking agents have some intrinsic activating effect on the β receptors. This renders the assessment of blockade of inhibitory adrenergic effects difficult (137). For example, isolated strips of rat myometrium, are persistently relaxed by the β blocking agents.

Intestinal Smooth Muscle.—The inhibitory effect of isoproterenol on the canine intestine *in situ* is blocked by a β blocking agent (4, 87). In the same experiments the inhibitory effect of phenylephrine was blocked by an α blocking agent. When it became apparent that the inhibitory effect of epinephrine was blocked only by a combination of an α and a β blocker the conclusion was drawn that the intestine has both types of receptors and that both control inhibition. Confirmatory results have been obtained using isolated intestine (96, 143).

Myocardium.—Cotton *et al.* (45) found evidence that led them to believe that the α blocking agents, phenoxybenzamine and phentolamine, blocked the positive inotropic effect of epinephrine in the open-chest dog. Following the description of the blockade of the myocardial actions of epinephrine by dichloroisoproterenol (49, 50, 106) the effect of blocking agents was re-examined. It was found that the relative increase in force of contraction produced by epinephrine was reduced by phenoxybenzamine. However, the α blocking agent had by itself markedly increased the force of contraction. This increase in control level resulted in the decrease in relative response to epinephrine. The absolute increase, however, was not reduced. Therefore, the suggestion that α blocking agents prevent the cardiac effects of the catecholamines was withdawn (107, 112).

DCI blocks the effects of catecholamines in dog heart-lung preparations (62) and blocks action of epinephrine to increase automaticity in isolated hearts (50).

Pronethalol blocks positive inotropic and chronotropic effects of catecholamines (24, 83, 84). This substance also prevents hydrocarbon-epinephrine fibrillation (108), fibrillation due to cardiac glycosides (138), and blocks catecholamine induced heart rate increases in man (40). It also blocks the effects of catecholamines on the heart-lung preparation (48).

Propranolol is somewhat more potent in blocking action than pronethalol and is said to have practically no intrinsic β activating effect (23). It also acts as an antifibrillatory substance (20). In man propranolol decreases heart rate, cardiac output, arterial pressure, and cardiac work (57).

Any agent that blocks the positive chronotropic effects of catecholamines should be a potential antiarrhythmic drug. Propranolol is now undergoing extensive clinical testing (70, 77, 117, 118). There is some question, however, whether the demonstrable antiarrhythmic effect is due to β blockade or to some other effect (69, 93).

A modification of the ethylnorepinephrine reversal test (see above) based on the blockade of the positive chronotropic effect has been suggested (130). In anesthetized dogs with intact buffer reflexes, slight, transient direct, and reflex tachycardia is produced by ethylnorepinephrine.

[3] Trademarked as Inderal.

Following β blocking agents this response is converted to one of reflex bradycardia. This test is sensitive enough to detect the β blocking activity of 10–50 mcg./Kg. of pronethalol.

METABOLIC EFFECTS OF CATECHOLAMINES

In addition to the effects on smooth and cardiac muscle, epinephrine and related compounds produce a variety of metabolic effects. This includes hepatic glycogenolysis, lipolysis in adipose tissue, and an increase in blood lactic acid. It is tempting to assign an α or β receptor for each of these actions. However, as will be pointed out, this is not possible at the present time.

Comparative Potencies of Catecholamines.—As far as these metabolic effects are concerned the only consistent finding reported is that epinephrine is the most potent catecholamine when all effects are considered. This has been found for hyperglycemia in rabbits (42), hyperglycemia in rats (136), hepatic glycogenolysis (54, 140), increase in hepatic active phosphorylase in rabbit liver slices (127), lipolysis from adipose tissue (141, 146), and increased blood lactic acid (54, 99).

It is the lack of uniformity of the comparative potency of isoproterenol to epinephrine that prevents a clear assignment of a receptor. In some cases isoproterenol is the least potent. In some cases it is even inactive, for example, in producing hepatic glycogenolysis (82). Only in the case of increasing active phosphorylase in the heart (101) and the increase in cyclic 3-5-AMP (128) is isoproterenol the more potent.

On the basis of comparative potencies it is not possible to assign a single receptor, although it seems that a β type receptor would be appropriate.

Blocking Agents.—The β adrenergic receptor blocking agents have been found to block epinephrine induced hyperglycemia in cats (53, 55), myocardial and skeletal muscle glycogenolysis (82), increase in active phosphorylase in the dog heart (101), rat diaphragm and liver (10), increase in plasma free fatty acid (35), and free fatty acid release from adipose tissue (28).

Many of the same effects are also blocked by α blocking agents (10, 28, 29, 39, 53). In addition, the compound isopropylmethoxamine which is not a β blocking agent (89, 129) blocks these effects too. And most recently, the compound *N*-tertiary butyl methoxamine, another substance with no β blocking properties has been shown to block these metabolic effects (36). However, there is some evidence that methoxamine itself may have some β blocking properties (25).

In the opinion of the reviewer the adrenergic metabolic actions do not seem to be controlled by a receptor that fits with the smooth or cardiac muscle effects. Celander's (39) idea that the sympathetic adrenergic nerves and the adrenal medulla have two different general controlling effects seems most attractive. In his view epinephrine from the adrenal should be regarded solely as a metabolic hormone. The theory set forth by the Lundholms (97, 98) that the vasodilator and inhibitory actions of the catecholamines are secondary to metabolic changes deserves further study. Furchgott's original suggestion of a γ adrenergic receptor (65) for metabolic effects appears to be useful.

CONCLUSIONS

1. How valid is the adrenergic receptor concept? It is as valid as any other receptor mechanism. It would be better to define a site of drug or hormone action by the actual enzyme or enzymes involved. However, if these are not known, some other way to characterize sites of action is needed.

The receptor concept correctly describes the site of drug-effector interaction as belonging to the effector cell. The effector responds to the drug (or hormone). Drugs do not act on just any cell.

2. What is the usefulness of the adrenergic receptor concept? In the first place it allows prediction of drug action. For example, the β receptor blocking agents were characterized before any such compounds were recognized. Dale (47) and Rothlin *et al.* (119) suggested that ergot alkaloids could block the effects of epinephrine on the heart and on the gut. However, the predominant α adrenergic blocking actions of these alkaloids strongly interfered with early definitive studies of β blockade. Holzbauer and Vogt (79) tested 27 different substances, including classical adrenergic blocking agents, on the rat uterus without finding a single β blocker.

It also follows that different kinds of chemicals than previously thought to be adrenergic blocking agents should be sought to block the metabolic effects of catecholamines.

Prediction of drug response is also necessary in determining what are the active parts of a given chemical structure. Biochemical studies of drug-enzyme interactions have usually been based on structure-response studies.

3. Can adrenergic receptor studies determine the nature of the adrenergic neuro-transmitter? Considering all adrenergic responses, epinephrine is the most potent catecholamine. Therefore, if potency is a measure of drug-receptor interac-

tion, the adrenergic receptor seems to be designed to "fit" epinephrine. However, potency can also reflect changes in metabolism, binding to inactive sites, membrane penetration, and other things beside drug-receptor interaction. However, epinephrine is the most potent, *in vivo* or *in vitro*, and under many different circumstances. From this we must assume that the superior potency of epinephrine is a true drug-receptor property.

Until definitive evidence to the contrary is obtained there is no reason for this reviewer to discard his assumption that epinephrine is the ultimate adrenergic neuro-hormone. Epinephrine is the end product of the catecholamine biosynthetic pathway (30). It is the receptor that determines the effector response. The reviewer has no information on the exact mechanism of the transmitter-receptor interaction. Therefore, it can be assumed that although adrenergic transmission is based on epinephrine as the transmitter the receptor would allow precursors such as levarterenol or even dopamine to affect transmission if necessary.

4. On the basis of relative responsiveness to sympathomimetic amines, and on the basis of specific blockade, the α receptor is associated with all adrenergic excitatory smooth muscle responses and with intestinal relaxation.

On the same basis the β receptor is associated with all adrenergic inhibitory effects on smooth muscle and with the adrenergic positive inotropic and chronotropic cardiac effects.

On the basis that epinephrine is usually the most potent catecholamine metabolically, and that a specific class of blocking agents for these effects has not yet been found, a γ receptor could be assigned to the adrenergic metabolic effects.

5. The adrenergic receptor concept should not interfere with or negate other studies or findings in regard to the cellular responses to catecholamines. The biophysical changes as described by Bulbring (31), for example, are a step beyond the drug-receptor interaction.

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