AGENTS WHICH BLOCK ADRENERGIC β-RECEPTORS[1]

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The adrenergic β-receptor blocking agents are new compounds that are useful as pharmacologic tools and potentially valuable as therapeutic agents. Several recent symposia and reviews have extensively covered the literature on at least one compound of this type, propranolol (1–4). A New York Academy of Science Conference (5) has presented the general subject in depth. It is the purpose, therefore, of this review to examine critically the pharmacodynamics of this group of drugs in terms of the concept of the adrenergic β-receptor proposed by this laboratory (6–8).

The receptor concept of drug-effector interaction is a useful device in studying pharmacodynamics, but the limitations of this concept ought to be understood and appreciated. By definition, the adrenergic receptor is that part of certain effector cells that allows them to detect and respond to epinephrine and related compounds. The receptor can be described only in terms of effector response to drug application.

The adrenergic receptor was originally conceived by Sir Henry Dale (9). He noted that ergot alkaloids blocked only some effects of epinephrine. In further studies, Barger & Dale (10) again noted the two separate sets of responses to catecholamines. In 1948, the now widely used nomenclature for two different adrenergic receptors was originated (6). This differentiation was based on the observation that only two sets of structure-activity relationships seemed to exist within a small group of related catecholamines[2] (11). Moran & Perkins (12, 13) are credited with the first use of the terms, adrenergic α-receptor blocking agents and adrenergic β-receptor blocking agents.

Pharmacodynamically, the β-receptor blocking agents are substances that specifically block catecholamine-evoked responses stated to be associated with β-receptors. An extension of this definition includes the statement that β-receptor blocking agents do not block adrenergic responses associated with α-receptors, or responses to substances, such as digitalis, calcium ions, acetylcholine, 5-hydroxytryptamine, or histamine.

To review briefly, the adrenergic α-receptor is associated with vasoconstriction, myometrial contraction, retraction of the third eyelid, contraction

[1] The survey of the literature pertaining to this review was concluded in June 1967.

[2] The term catecholamine as used in this review refers specifically to primary or secondary 3,4-dihydroxyphenyl-ethanolamines in which the permissible substituents on the 1-carbon are methyl or ethyl and on the nitrogen are methyl or isopropyl.

of dilator muscle of the pupil, contraction of splenic smooth muscle, and relaxation of intestinal muscle. The β-receptor is associated with vasodilation, relaxation of the smooth muscle of bronchi, intestine, and uterus, and the adrenergic-positive cardiac inotropic and chronotropic effects. The adrenergic receptor seems to be designed to fit best with epinephrine, the most potent catecholamine when all adrenergic responses are considered. The specific agonist for α-receptors is phenylephrine; for β-receptors, isoproterenol (14).

For this review, adrenergic α-receptor blocking agents are substances that specifically block responses to phenylephrine, block part of the responses to epinephrine, and have no effect on responses to isoproterenol. Adrenergic β-receptor blocking agents specifically block the responses to isoproterenol, block part of the responses to epinephrine, and have no effect on the responses to phenylephrine.

Historical

In 1958, Powell & Slater (15, 16) described some experiments with the dichloro analogue of isoproterenol (DCI). This agent blocked the depressor responses to isoproterenol or epinephrine, blocked myometrial relaxation produced by epinephrine in the intact cat, blocked or diminished the bronchial smooth muscle relaxation produced by epinephrine *in vivo* or *in vitro*, and diminished femoral vasodilation produced by isoproterenol in the dog. The inhibitory effect of isoproterenol on isolated rabbit intestine was diminished, but relaxation by isoproterenol of the isolated rat uterus was apparently not blocked or diminished. In addition, the stimulant effect of epinephrine on the isolated heart frog was not blocked. Moran & Perkins (13) demonstrated conclusively in the dog the specific blocking effect by DCI of the positive cardiac chronotropic and inotropic actions of the catecholamines.

Although DCI may be regarded as the first adrenergic β-receptor blocking agent, a retrospective study shows that in actuality the catecholamine, ethylnorepinephrine, was found to have this type of action 20 years earlier. Cameron et al. (17–19) studied this amine extensively. They found that although it produced a depressor response when administered intravenously to an intact cat, it usually produced vasoconstriction when injected into the artery of the perfused cat leg. Ethylnorepinephrine was also found to increase markedly cardiac output in the heart-lung preparation. A more remarkable finding was that the response to intravenously administered ethylnorepinephrine changed from depressor to pressor with repeated doses. When it was later found that ethylnorepinephrine was only a pressor agent when administered to a dog pretreated with DCI, a relatively simple explanation of the actions of this catecholamine in terms of adrenergic receptors was offered (14). Ethylnorepinephrine is a potent agonist for both α-receptors and β-receptors. When applied to structures having more α-receptors, this response predominates as on the nictitating membrane or the pupillary dilator, for example. On responses controlled by a balance between the receptors such as the blood pressure, a β-receptor effect is produced by the first dose. The first dose, if of sufficient size (more than **0.25** mg/kg), also blocks the β-receptor.

Subsequent doses then produce only the α-receptor effects. Another retrospective finding was that a substance known as butylsympatol is a β-receptor blocking agent. This compound blocks the depressor responses to isoproterenol and increases the pressor response to epinephrine (4).

Black & Stephenson (21) described the β-receptor blocking agent, pronethalol, in 1962. However, since pronethalol seemed to induce metastatic thymic lymphosarcomas and reticulum cell sarcomas and adenomas (22), it was not further studied clinically, and a related compound, propranolol, was selected for trial. Propranolol has been extensively studied, and at the time this review was prepared, was available for clinical use in England, Japan, Spain, and West Germany. In the United States, it was still classified as an investigational drug.

Characteristics of β-Receptor Blockade

According to the original description of the adrenergic β-receptor, blockade should result in the following: (*a*) reduction or block of usual responses to isoproterenol, including stimulant effects on heart and inhibitory effects on bronchi, intestine, uterus, and blood vessels; (*b*) reduction or block of the above responses produced by any catecholamine, any adrenergic nerve stimulation (electrical or chemical), and any sympathomimetic agent; (*c*) no direct effect on responses associated with α-receptors or histamine, bradykinin, serotonin, and similar compounds, even if the responses are similar to those evoked by isoproterenol.

Based on the above, the responses to an adrenergic β-receptor blocking agent per se will be the following: (*a*) decrease in heart rate unless there is no significant ongoing adrenergic influence on the heart; (*b*) some decrease in force of myocardial contraction unless there is no significant ongoing adrenergic influence; (*c*) a possible increase in intestinal and myometrial activity; (*d*) a possible depressor response in intact animals due to the effects on the heart. There should be no other significant or measurable effects, because there is no other significant ongoing β-receptor controlled activity.

The β-receptor blocking agents have other important pharmacodynamic effects which may or may not be directly related to their effects on adrenergic receptors.

(*a*) Many have intrinsic β-receptor activating effects. DCI, as a primary effect, produces typical adrenergic tachycardia, and intestinal and myometrial inhibition (14). These effects make the study of β-receptor blocking agents on smooth muscle difficult. However, since DCI blocks itself, repeated small doses may evoke the blockade, and thereby minimize the intrinsic effect.

(*b*) Several compounds have effects on the heart similar to those produced by local anesthetics or by quinidine. Impulse transmission is modified and a variety of arrhythmias may be modified or corrected. In view of the proposed use of β-receptor blocking agents in arrhythmias, this may be an important side effect.

(*c*) Epinephrine and related catecholamines produce a variety of meta-

bolic effects, such as hepatic glycogenolysis, lipolysis in adipose tissue, and lactic acidemia. There are divergent views on the relationship of these metabolic effects to the other adrenergic effects. Some consider the metabolic effects to be controlled by an adrenergic receptor; the β-receptor seems to be the more likely, since β-receptor blocking agents interfere with the adrenergic metabolic effects (23). Others consider the metabolic effect to be the sole β-receptor controlled effect, and the muscular effects to be the result of the metabolic changes (24). There are, however, reasons to believe that these relationships are not so simple. This aspect will be considered later in this review.

Screening Tests

Broom & Clark (25) first described the test for adrenergic blocking agents, which is now known as epinephrine "reversal." This test consists of blocking some of the responses (α-receptor) to epinephrine, and thereby allowing the other responses (β-receptor) to be manifest or exaggerated. Traditionally, the isolated rabbit uterus or the blood pressure of the anesthetized dog or cat have been the test object. A screening test for β-receptor blocking agents, conversely, would allow α-receptor responses to appear more readily. For example, in the original study of DCI (15), it was noted that this blocking agent potentiated the pressor response to epinephrine.

Using ethylnorepinephrine, a specific screening test for adrenergic β-receptor blockade has been devised (20). This catecholamine, in a dosage of 0.05 mg/kg, consistently produces vasodilation, tachycardia, and a diphasic pressure response consisting of a depressor effect, followed by a pressor response and reflex bradycardia. Following β-receptor blockade, ethylnorepinephrine produces vasoconstriction, a pressor response, and reflex bradycardia. This test, and a more sensitive variation (26), have been termed the ethylnorepinephrine reversal test for β-receptor blockade.

Another screening test consists of reducing or blocking the effects of isoproterenol on the heart (27). Using either the positive chronotropic or inotropic response, dose-response curves for β-receptor blocking agents can be constructed. Whenever a β-receptor blockade is invoked to explain some drug action, proof of this kind of blockade must be provided. In man this should consist minimally of a demonstration of the diminution or block of isoproterenol-induced tachycardia. In other species, more extensive evidence should be produced.

Drugs That Are Not β-Receptor Blocking Agents

Ethylnorepinephrine reversal, or prevention of isoproterenol-induced tachycardia is not absolute proof of adrenergic β-receptor blockade. Consider the following drugs:

Veratramine.—The studies of Krayer and associates (28) have demonstrated that veratramine and related alkaloids specifically prevent catecholamine-induced tachycardia. However, there is no evidence that any

other adrenergic effects are blocked. Therefore, by definition, veratramine cannot be an adrenergic β-receptor blocking agent.

Phenylephrine.—This α-receptor agonist reverses the depressor and vasodilator responses to isoproterenol (29). It also produces ethylnorepinephrine reversal. However, an examination of these effects shows that the positive chronotropic effect of catecholamines is not blocked, and that blockade of α-receptors will completely prevent the so-called β-receptor block by phenylephrine. A more reasonable explanation of this phenomenon is that phenylephrine produces excessive vasoconstriction. Although blood pressure may return to normal levels, vascular resistance continues very high. The administration of isoproterenol, or ethylnorepinephrine, then produces an increase in cardiac output. Since vasodilation is prevented by the phenylephrine vasoconstriction, blood pressure must increase (30). Any long-acting vasoconstrictor would produce the same effect. This phenomenon should be considered a physiological antagonism rather than β-receptor blockade.

Methoxamine.—This adrenergic α-receptor agonist was shown to restore the epinephrine pressor response after the response had been reversed by phenoxybenzamine (31). Methoxamine, isopropyl-methoxamine, dimethyl-isopropyl-methoxamine, and butoxamine block some of the metabolic effects of the catecholamines (32). Detailed studies show that these drugs have β-receptor effects as defined in this review only on the isolated rat uterus (33–36).

Ergotamine.—This vasoconstrictor may produce isoproterenol reversal in addition to α-receptor blockade. There is no evidence that this alkaloid is a β-receptor blocking agent. However, the halogenated ergot alkaloids are both α- and β-receptor blocking agents (14).

Chemistry of β-Receptor Blocking Agents

Several series of compounds having β-receptor blocking action have been reported. In general, the screening tests employed have included blockade of catecholamine effects on the myocardium, tracheal smooth muscle, or myometrium. The structure-activity comparisons have usually included an appraisal of the intrinsic β-receptor agonist effects, and the specificity of blockade. Most of the β-receptor blocking agents are chemical relatives of isoproterenol. At the present time, the only absolute structural requirement is a hydroxyl group on the second carbon atom from the amino nitrogen (the aminoethanol side chain).

The first series described consisted of halogenated derivatives of isoproterenol (14, 15) prepared in a search for a clinically effective bronchodilator. The *o*-chloro derivative of isoproterenol, isoprophenamine, has considerable intrinsic β-receptor agonist activity. The 3,4-dichlorophenyl derivative (DCI) was the most potent of the derivatives of this series studied. The 2,4-dichlorophenyl derivative seemed to have the least intrinsic β-receptor effect, while having considerable β-receptor blocking activity. The substitution of halogen for the alcoholic hydroxyl group produced α-receptor blocking

agents of the alkylating type. In addition, the similar dichloro derivatives of epinephrine and norepinephrine have practically no β-receptor blocking actions (36).

In another series that included methyl, ethyl, and halogen derivatives of isoproterenol, Corrodi et al. (37) showed that the 3,4-dimethylphenyl derivative of isoproterenol was somewhat more active than DCI as a β-receptor blocking agent. In addition, methylation of the first carbon atom of the side chain in DCI and related compounds reduced potency but seemed to increase selectivity. For example, α-methyl DCI (38) apparently blocks vascular β-receptors, more selectively than cardiac β-receptors.

The first clinically effective β-receptor blocking agent was pronethalol. In this particular series (N-alkyl-2-amino-1-2-naphthyl ethanol hydrochlorides), the alkyl group was varied (39). The isopropyl compound and others, such as the tertiary butyl derivative, were relatively potent. It was also found that the (−) form of pronethalol is 40 times more potent than the (+) form. (The compound reported in the literature is the racemic mixture unless specifically stated otherwise.)

Propranolol, 1-isopropylamine-3-(1-naphthyloxy)-2-propanol, was introduced as a less toxic compound than pronethalol (40, 41). A similar compound has been described by Stock & Westerman (42): N-isopropyl-1-amino-3-(*m*-tolyloxy)-2-propanol (Kö-592). Two related methanesulfanilide compounds have been described (43–45). These are 4-(2-isopropylamino-1-hydroxyethyl)-methanesulfanilide (MJ-1999) and 4-(2-methylamino-1-hydroxyethyl)-methanesulfanilide (MJ-1998).

A report by Karim (46) describes methoxamine as a typical adrenergic β-receptor blocking agent. However, as noted above, this reviewer does not think that methoxamine and its derivatives fit the criteria for this type of action.

There is no reason to assume that the "best" β-receptor blocking agent has been found. Many already synthesized compounds have not yet been adequately studied, and probably many active agents have not yet been synthesized.

Actions of β-Receptor Blocking Agents

At the time of this writing, the principal agents are DCI, pronethalol, propranolol, MJ-1999, and Kö-592. As far as can be determined, the β-receptor blocking actions of all are similar but they differ in terms of potency and other actions.

Heart.—The β-receptor blocking agents slow heart rate in the intact experimental animal or human. In practically every reference cited that includes heart rate measurements, bradycardia is mentioned. All of the agents block the positive chronotropic actions of catecholamines, exogenous or endogenous.

Using isolated, spontaneously beating right atrial preparations from the rabbit, it was found that DCI increased rate, propranolol decreased rate, and

others had no significant effect on rate (47). All of the blocking agents prevented the positive inotropic response to isoproterenol. Using the electrically driven rabbit atrium, it was found that Kö-592, DCI, and propranolol were equi-potent; pronethalol and MJ-1999 were less potent; in each case the (−) isomer was more potent than the racemic mixture. In this same study, only propranolol and pronethalol produced significant depression of contractile force. Ledsome et al. (48) showed that pronethalol or propranolol prevented reflex heart rate changes that are controlled through the sympathetic motor system. They also showed that these agents did not affect reflex heart rate changes controlled by the vagus. Blinks (49) studied the chronotropic and inotropic effects of some of these agents on the atria and papillary muscles of kittens. Propranolol was potent, specific, and blocked inotropic responses to isoproterenol at concentrations that did not depress contractile force. MJ-1999 blocked responses only in concentrations that directly depressed contraction. Pronethalol was in between. Using the maximal rate of development of left ventricular pressure in intact cats, Benfey et al. (50) compared these blocking agents against isoproterenol. Propranolol, pronethalol, and Kö-592 were effective; propranolol was more potent than Kö-592. All blocked isoproterenol without great direct depression of myocardium.

Myometrium.—In the original presentation of the current concept of adrenergic receptors (6), the myometrium was described as having both α- and β-receptors. The α-receptor evoked contraction, the β-receptor, relaxation. The response to agonists is determined by which receptor is dominant; the dominance is related to species and hormonal influence. The uterus of the nonpregnant rat seems to have only β-receptors; all catecholamines and relatives evoke relaxation, with isoproterenol the most potent. Although Powell & Slater (15) were unable to demonstrate block of isoproterenol relaxation by DCI in the isolated rat uterus, they did show this block in intact nonpregnant cats.

As stated earlier in this review, the intrinsic β-receptor agonist effect of some β-receptor blocking agents interferes with this type of study. Levy & Tozzi (51) have shown that this effect can be overcome on isolated tissues by repeated additions of the blocking agent; the agent blocks its own intrinsic effect.

In their definitive study, Levy & Tozzi (51) showed that epinephrine, isoproterenol, or phenylephrine inhibits rat myometrium. This inhibition was not prevented by α-receptor blocking agents and was specifically blocked by propranolol. The rat uterus should, therefore, be one of the test systems for specificity of new β-receptor blocking agents.

Tothill (52) has described another problem related to the study of isoproterenol on the isolated rat uterus. Isoproterenol resistance was induced by adding the catecholamine and then allowing time for motor activity to return even though the isoproterenol was still in the muscle bath. The inhibitory effect of epinephrine or phenylephrine in induced estrus was reversed to stimulation during this isoproterenol resistance. This stimulant response

could be blocked by α-receptor blockade (phentolamine), mixed α- and β-receptor blockade (dihydroergotamine), or by 5-hydroxytryptamine blockade (bromolysergic acid). Tothill concluded that the rat uterus had, in addition to adrenergic β-receptors, another receptor (E), which controls a general excitatory response.

Miller (53) has thoroughly reviewed the work from his laboratory and from the literature in regard to myometrial adrenergic receptors. Evidence is presented to show that all β-receptor blocking agents are effective in preventing adrenergic myometrial relaxation.

In the human uterus at term, the inhibitory effect of isoproterenol (2 to 8 μg/min) can be blocked by intravenous administration of propranolol (1 to 4 mg) (54). Eskes et al. (55) studied the effect of pronethalol and propranolol on the intact human pregnant uterus. These agents blocked the inhibitory effects of an experimental sympathomimetic drug, *p*-hydroxyphenyl isopropylethanolamine.

Intestine.—All sympathomimetics relax the isolated ileum of the rabbit. However, it was early noted that this smooth muscle has a special response to isoproterenol. In some instances on isolated intestine, this catecholamine is less potent than epinephrine or norepinephrine, and isoproterenol often produces a contractile response on intact intestine.

Originally, an α-receptor evoking relaxation was assigned to the intestinal smooth muscle on the basis that epinephrine was most potent and isoproterenol the least potent. When β-receptor blocking agents became available, it was found that a two-receptor concept fitted best. Administration of α-receptor blocking agents prevented the inhibitory effect of phenylephrine. Administration of a β-receptor blocking agent prevented isoproterenol relaxation. A combination of α- and β-receptor is necessary to prevent the inhibitory response to epinephrine (56, 57). Confirming evidence for this concept has been obtained by Furchgott (58, 59), Lum & Kermani (60), and Wilson (61). Using strips of human taenia coli, Bucknell & Whitney (62) have demonstrated both receptors.

This idea that two different receptors subserve the same function has stimulated a search for a similar phenomenon in other effectors controlled by adrenergic receptors. There is as yet no good evidence that this occurs in any other structure.

Blood vessels.—Shanks (63) has recently studied the effect of propranolol, pronethalol, DCI, and MJ-1999 on iliac and renal arterial blood flow in dogs. All increased blood flow when injected into the artery. MJ-1999 was least active as a vasodilator. This dilator response was not considered the result of β-receptor activation, since it occurred equally in the iliac and renal vascular beds. In addition, it was not affected by skinning the leg or by the administration of α-receptor blocking agents, or other β-receptor blocking agents. In this same study, propranolol blocked the vasodilation produced by isoproterenol, and that produced by epinephrine or norepinephrine following phenoxybenzamine. The (+) isomer was less potent than the (−) isomer or

racemic mixture. Propranolol did not block the vasodilation produced by bradykinin.

Bohr (64, 65) has demonstrated only β-receptors in small coronary arteries. Catecholamine relaxation of these is blocked by β-receptor blocking agents: propranolol > pronethalol > MJ-1999. Brick et al. (66) have shown that propranolol blocked the dilator response to catecholamines in the human forearm. The dilator response to histamine is not affected. Lundholm & Svedmyr (67) have also shown this effect with pronethalol but believe it is secondary to the block of metabolic responses. Hughes & Vane (68) have found both receptors in veins. The β-receptors, subserving relaxation, are blocked by propranolol, pronethalol, and *p*-nitrophenyl-isoproterenol.

Quinidine-like action.—Pronethalol has an antifibrillatory action against several types of experimental arrhythmias (69–71). Not all of this effect is due to β-receptor blockade. For example, digitalis arrhythmias were equally prevented by (+) or racemic pronethalol. However, (+) pronethalol had very little β-receptor blocking action. Standaert & Roberts (72) found that while pronethalol had a direct depressant effect on neural tissue, MJ-1999 did not seem to have this action. It would be tempting to ascribe these non-β-receptor blocking antifibrillatory effects to local anesthesia. However, this is not the whole explanation (73). Since arrhythmias, definitely associated with β-receptor activity, are completely prevented by β-receptor blocking agents (74), it seems appropriate to conclude that these agents can act as antiarrhythmic drugs through several mechanisms: β-receptor blockade, local anesthesia, quinidine-like action, or direct myocardial depression (75).

Metabolic action.—It is tempting to assign a β-receptor for the metabolic actions of catecholamines, but this reviewer does not consider it possible at this time. The β-receptor blocking agents do block some of these actions and the following articles can be cited in support of this: Burns et al. (32), Wenke et al. (76), Fain (77), Ellis et al. (23), Levy (33–35), Heim & Hull (78), and Estler & Ammon (79). A difficult point to resolve is the contradictory evidence given in the literature. For example, Barrett (80) states that the increase in serum free fatty acid produced by adrenergic agents is not due to β-receptor activation. On the other hand, Harrison & Griffin (81) think that free fatty acid is controlled by a β-receptor. It is the lack of uniformity of the potency of isoproterenol compared to the other catecholamines that prevents the simple β-receptor assignment. Although the rat seems the most different (23) as far as the catecholamine metabolic effects are concerned, the myocardial and smooth muscle responses to catecholamines are essentially the same in all species. Even the sloth (4) has the same smooth muscle adrenergic receptors as other mammals.

A more basic problem is the relationship between the metabolic effects and the mechanical responses to catecholamines. For example, Brody & Diamond (82) have described relaxation of the myometrium of the rat and an associated phosphorylase activation. However, they felt that they could not tell whether these were causally related. The phosphorylase activation could

have been the cause or the result of the relaxation, or not even directly related. Øye (83) and Valadares & Friesen (84) found that although the time courses of epinephrine-induced positive inotropic response and phosphorylase activation were similar, they were not related as a cause and effect, or vice versa. Mayer et al. (85) are of the opinion that phosphorylase activation and the catecholamine-induced positive inotropic effect are causally related.

The biochemical explanation for the pharmacological actions of catecholamines will shortly displace the receptor concepts. Therefore, this field deserves a separate review. A probable first biochemical explanation will include adenyl cyclase. The enzyme catalyzes the conversion of adenosine triphosphate to adenosine 3′, 5′-phosphate (cyclic AMP) (86). A number of different cellular processes are known to be changed by the level of cyclic AMP (87, 88), and there is evidence that the metabolic effects of catecholamines are mediated by cyclic AMP.

Other effects.—Bray (89) has found that propranolol or DCI will specifically block the enlargement of salivary glands produced by isoproterenol in the rat. Ingram & Vaughn Jones (90) found that the intravenous administration of epinephrine increased clotting factor VIII in man. Pronethalol prevented this response but phentolamine did not.

Clinical Pharmacology

The adrenergic β-receptor blocking agents have been studied in man. Although in most cases the blocking agents were given for some therapeutic purpose, direct information concerning their pharmacological effects has been obtained.

Pheochromocytoma.—This catecholamine-secreting tumor produces effects that are similar to catecholamine overdosage. If epinephrine is the principal amine secreted, increased cardiac rate and force predominate. If norepinephrine is the principal amine, vasoconstrictive hypertension predominates. An α-receptor blocking agent is the drug of choice to prevent the peripheral vascular actions; in some cases, phenoxybenzamine by mouth may completely correct the symptoms. Pritchard & Ross (91) have shown that a β-receptor blocking agent given with the α-receptor blocking agent may produce two different types of response. A type I response consists of a rise in systolic and diastolic pressures, and a decrease in heart rate. This response is consistent with an epinephrine-secreting tumor. The well-known epinephrine depressor effect in humans is prevented by the β-receptor block, thereby allowing the not-completely blocked constrictor effects to appear. A type II response is a fall in systolic and rise in diastolic pressure, and a fall in the heart rate. This is consistent with a norepinephrine secreting tumor. Without question, the effects of adrenergic blockade in pheochromocytoma are consistent with the known effects of the catecholamines in man.

Jose (92) has used propranolol in combination with atropine to determine the "intrinsic heart rate." This rate, as measured by this method of complete pharmacologic cardiac denervation, averages 104 in the normal individual.

In hypotensive anesthesia for ear surgery (produced by partial ganglionic blockade), propranolol reduces the usual reflex tachycardia (93).

Exercise.—Simplified, the effects of exercise on the human cardiovascular system are: increased heart rate, increased mean arterial pressure, and increased cardiac output. All of these effects are diminished by β-receptor blockers (94–98). Three explanations have been offered for lack of complete blockade of these cardiovascular effects: (*a*) The response to exercise is only partly mediated through adrenergic nerves. (*b*) Inadequate doses of the blocking agent were used. (*c*) It is more difficult to block neurogenic catecholamines than exogenous catecholamines. The last two explanations seem unlikely.

Idiopathic hypertrophic subaortic stenosis.—In this condition, ventricular outflow obstruction is increased by any mechanism that increases cardiac contractability (99). Exercise or isoproterenol increases the outflow obstruction. While pronethalol (99) or propranolol do not usually modify this obstruction during rest, they do prevent the intensification of obstruction by isoproterenol, and diminish that produced by exercise.

Hyperdynamic circulatory state.—Frohlich et al. (100) described a new syndrome called "hyperdynamic β-adrenergic circulatory state." This consisted of severe tachycardia as an exaggerated response to emotional stimuli. The patients also showed an exaggerated response to isoproterenol. Pronethalol was effective in preventing the tachycardia.

Bronchial asthma.—Propranolol, 5 to 10 mg, given intravenously to patients with bronchial asthma evoked a marked fall in forced expiratory volume (101, 102). Some of these patients were using isoproterenol at the time. This is the expected result, as demonstrated by the studies of Ariëns (103) on the isolated tracheal rings of guinea pigs.

Therapeutic Uses

It is not the purpose of this review to cover this point. However, it can be categorically stated that any disorder caused by "excessive" adrenergic β-receptor activity will be benefited or modified by a β-receptor blocking agent. The effects in angina pectoris, cardiac arrhythmias, myocardial infarction, and hypertension are not completely predictable. This means, in the reviewer's opinion, that the relationship of adrenergic drive to these disorders is not uniform or completely elucidated.

Conclusions

At the present moment, adrenergic receptors can be described only in terms of effector response to the administration of certain chemical agents. The adrenergic β-receptor, as originally described, responds best to isoproterenol and is associated with cardiac stimulation, vasodilation, and inhibition of smooth muscle in the bronchi, myometrium, and intestine. When the β-receptor is restricted to this description, it can be uniformly found in practically all mammalian species, and in frogs and turtles.

The adrenergic β-receptor blocking agents, as exemplified by propranolol, competitively and specifically blocked the responses of the β-receptor to isoproterenol, other endogenous or exogenous catecholamines, and all other sympathomimetic agents.

The relationship between the β-receptors and the metabolic responses to the catecholamines is not clearly defined. Isoproterenol is not the most potent catecholamine; in fact, in some cases, it is inactive as compared to epinephrine. Adrenergic β-receptor blocking agents prevent the metabolic responses to epinephrine, but so do several adrenergic α-receptor blocking agents, and several methoxamine derivatives. The latter do not qualify as adrenergic β-receptor blocking agents.

At the present time, it would be too restrictive to consider that adrenergic metabolic responses are controlled by adrenergic β-receptor blocking agents. A third receptor may need to be considered, or the muscular responses may be due to the metabolic changes. This area is not settled and requires further study.

The adrenergic β-receptor blocking agents will have therapeutic use in any condition in which adrenergic β-receptor activity is excessive or undesirable.

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