

Comparison of the Effects on Renin Release of Beta Adrenergic Antagonists with Differing Properties

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ABSTRACT Continuous 6-h infusions of the beta adrenergic blockers *d,l*-propranolol or oxprenolol significantly reduced plasma renin activity (PRA) and mean blood pressure in the resting rabbit and prevented the stimulatory effects of isoproterenol on renin release and heart rate. These actions were due to blockade of beta receptors, for the inactive isomer, *d*-propranolol, had no effect. Despite sustained high plasma concentrations of *d,l*-propranolol (0.2 µg/ml) in the unstimulated animal, PRA did not fall below 36% of control values, suggesting that basal renin secretion is maintained partly by factors other than beta adrenergic mechanisms.

Prindolol, another beta blocker, also abolished the effects of isoproterenol on renin and on the heart, and reduced blood pressure in the resting animal. However, prindolol increased resting PRA and heart rate, and in animals already receiving *d,l*-propranolol, it raised PRA and heart rate without further altering blood pressure. This suggests that the effect on PRA of prindolol was due to its intrinsic sympathomimetic activity and not hypotension-mediated mechanisms. The observation that the blood pressure-lowering effect of prindolol was associated with a rise in PRA, while another beta antagonist, H 35/25, lowered PRA but had no effect on blood pressure, indicates that the hypotensive action of beta blockers is unrelated to their effects on renin release.

In both unstimulated and isoproterenol-challenged animals, only blockers possessing beta-1 receptor affinity (*d,l*-propranolol, oxprenolol, prindolol, practolol, and metoprolol) affected heart rate, while effects on PRA were more prominent with agents possessing beta-2 activity (*d,l*-propranolol, oxprenolol, prindolol, and H 35/25). Thus, the changes in PRA caused by the beta adrenergic blockers appear to be dependent upon the summation of their direct effects, antagonistic or sympathomimetic, on beta-2 adrenergic receptors regulating renin release.

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INTRODUCTION

Sympathetic mechanisms are known to have a role in the regulation of renin release. Renin secretion is increased by renal nerve stimulation (1) and by either intravenous administration or endogenous stimulation of catecholamines (1, 2). These stimuli appear to be mediated by beta adrenergic receptors, for the stimulatory effect on renin release of catecholamines (3), isoproterenol (4), or medulla oblongata stimulation (5) is prevented by the beta blocker propranolol, but not the alpha blocker phenoxylbenzamine.

We have recently reported that single doses of *d,l*-propranolol or oxprenolol produced an acute fall in plasma renin activity (PRA),¹ but prindolol, a beta blocker with sympathomimetic activity, increased PRA (6). It was not clear whether these effects of beta antagonists on renin were direct or dependent upon reflex mechanisms activated by changes in blood pressure.

To clarify the mechanism of action of beta blocking agents on the renin-angiotensin system, we studied in the rabbit the effects on PRA, blood pressure, and heart rate of infusions of several such agents, given separately, during both resting conditions, and graded isoproterenol challenges. In further experiments, propranolol and prindolol were given concurrently to dissociate their direct effects on PRA from those secondary to changes in blood pressure. Also, an attempt was made to elucidate the specificity of the receptors regulating renin release.

METHODS

Animals. Using local anesthesia alone, arterial and venous catheters were inserted into the ear of male New Zealand white rabbits, weighing 2.2–3.3 kg, as described previously (6). After a 90-min recovery period, the experiments were carried out in a quiet room in which external stimuli were minimized.

Infusion studies (series A). In a control group of four animals (group A1), 2.5% dextrose in water was infused

¹Abbreviations used in this paper: HR, heart rate; MBP, mean blood pressure; PRA, plasma renin activity.

TABLE I
Dosage Regimens of Beta Adrenergic Antagonists
Administered to Rabbits during 6-h
Infusion Studies

Group	Beta blocker	Priming dose	Sustaining infusion
		mg/kg	mg/kg/h
A2	<i>d,l</i> -Propranolol	1.0	0.5
A3	<i>d</i> -Propranolol	1.0	0.5
A4	Prindolol	0.125	0.063
A5	Oxprenolol	1.0	0.5
A6	H 35/25	2.5	1.25
A7	Metoprolol	2.5	1.25
A8	Practolol	2.5	1.25

for 360 min at a rate of 0.04 ml/min by constant infusion pump (Sage 351, Sage Instruments Div., Orion Research, Inc., Cambridge, Mass.). Arterial blood samples were withdrawn every 30 min. In each of seven groups of six animals (groups A2-A8) a beta adrenergic blocking agent was administered as an i.v. bolus immediately followed by a sustaining infusion given in 2.5% dextrose in water employing the same protocol as in group A1. The dosages are shown in Table I. In six further animals (group A9), *d,l*-propranolol was given for the first 180 min of the 6-h period, then *d,l*-propranolol and prindolol were infused simultaneously for the second 180 min using the same initial and sustaining dosages as in Table I.

Isoproterenol challenge studies (series B). In six animals (group B1) treated as in group A1, isoproterenol, administered in 2.5% dextrose in water at 0.04 ml/min, was infused for 30-min periods immediately after withdrawal of the blood samples at 120, 210, and 300 min. The isoproterenol was administered in three dosages (0.004, 0.01, and 0.04 µg/kg/min in a randomized sequence) to each animal. In each of seven further groups of six animals, group B2-B8, isoproterenol was infused as in group B1, and the same beta adrenergic blocking agents given as in groups A2-A8.

Techniques. PRA was measured in arterial blood samples collected by free flow into glass tubes containing EDTA placed in a crushed ice bath. A radioimmunoassay method (7) was employed, angiotensin I being generated by plasma incubation at 37°C for 3 h at pH 7.4 in the presence of angiotensinase inhibitors (dimercaprol and 8-OH-quinoline). Results were expressed in nanograms angiotensin I/ml/h.

The possibility that the presence of beta blocking drugs in the plasma may have affected the generation or measurement of angiotensin I was excluded as follows: six untreated rabbit plasma samples were each divided into 3 aliquots. Aliquot 1 of each sample was a control; to aliquot 2 was added propranolol, 500 ng/ml, and to aliquot 3, prindolol 200 ng/ml. Comparison of PRA after incubation and assay of the aliquots showed that there was no difference between the controls, 10.4±1.0 (SE) ng/ml, the propranolol samples, 11.0±1.0 (SE) ng/ml, and the prindolol samples, 10.7±1.0 (SE) ng/ml.

To prevent the increase in PRA caused by minor hemorrhage in the rabbit (8), each 1 ml of blood sampled for biochemical analysis during the experiments was replaced immediately by 0.6 ml of a protein-saline mixture composed of 25 g stable human plasma protein (86% albumin, 14% globulin) in 500 ml buffered physiological saline containing 4-6 meq/liter potassium (Commonwealth Serum Laboratories, Melbourne, Australia).

Plasma propranolol concentrations were measured in the six animals in group A2 by a spectrofluorimetric method (9) after extraction of the propranolol from plasma by *n*-heptane. Plasma prindolol levels were measured in the six animals in group A4 by the fluorimetric method of Pacha (10) in which the fluorescent intensity of the prindolol, extracted from plasma by diethyl ether, is enhanced by ortho-phthalaldehyde.

Plasma sodium and potassium concentrations were measured by flame photometry, and plasma glucose levels were measured by a Technicon AutoAnalyzer (Technicon Instruments Corp., Tarrytown, N. Y.) using the potassium ferricyanide method of Hoffman (11). Packed cell volume was measured by the microcentrifuge technique. Data were evaluated using Student's *t* test for comparisons between groups of animals and the paired *t* test for analysis within groups.

RESULTS

Infusion studies (series A). In the control group (group A1), continuous infusion of 2.5% dextrose in water did not change PRA or heart rate (HR). There was a small, but not significant, fall in mean blood pressure (MBP) during the 360-min experimental period (Table II).

The effects of infusing various beta adrenergic blocking drugs into the normal resting animal are shown in Fig. 1. Administration of *d,l*-propranolol (group A2) resulted in a fall in PRA from 14.1 to 5.1 ng/ml

TABLE II
Mean Values±SEM for PRA, MBP, and HR in Four Rabbits Receiving i.v. Infusion
of 2.5% Dextrose in Water 0.04 ml/min

Time, min....	0	30	60	90	120	150	180	210	240	270	300	330	360
PRA, ng/ml	10.3 ±1.2	10.6 ±1.5	10.3 ±1.5	9.9 ±1.7	10.3 ±1.5	10.5 ±1.5	10.4 ±1.6	10.5 ±1.6	11.0 ±1.5	10.6 ±1.6	10.7 ±1.6	10.8 ±0.6	10.7 ±1.6
MBP, mm Hg	80 ±2.0	80 ±1.8	81 ±1.9	82 ±1.8	80 ±1.8	80 ±1.9	79 ±1.7	79 ±1.8	78 ±2.1	79 ±2.9	77 ±2.9	76 ±3.5	77 ±3.2
HR, per min	212 ±11	211 ±12	210 ±14	206 ±14	211 ±12	211 ±13	212 ±14	217 ±14	214 ±15	213 ±15	209 ±15	214 ±15	214 ±15

within 90 min ($P < 0.001$); MBP fell from 75 to 65 mm Hg ($P < 0.005$) and HR from 225 to 190/min ($P < 0.001$). *D*-Propranolol (group A3) produced no significant change in PRA, MBP, or HR. Prindolol (group A4) increased PRA from 10.9 to 37.3 ng/ml by 150 min ($P < 0.001$); HR was also increased ($P < 0.02$) but MBP fell from 80 to 65 mm Hg ($P < 0.001$). Oxprenolol (group A5) produced a fall in PRA, more gradual than that caused by propranolol, from 12.0 to 5.2 ng/ml by 150 min ($P < 0.01$); MBP fell from 81 to 70 mm Hg ($P < 0.001$). H 35/25 (group A6) lowered PRA from 10.8 to 7.0 ng/ml by 120 min ($P < 0.01$) but did not affect MBP. Oxprenolol and H 35/25 each increased HR ($P < 0.005$). Metoprolol (group A7) lowered PRA from 11.2 to 7.7 ng/ml ($P < 0.025$) and MBP from 80 to 76 mm Hg ($P < 0.05$) by 60 min. Practolol (group A8) caused no change in MBP and a small change in PRA ($P < 0.05$). Metoprolol and practolol each reduced HR ($P < 0.005$).

Thus, with the exceptions of prindolol and *d*-propranolol, each of the agents used caused the resting PRA to fall, the maximal effects of *d,l*-propranolol and oxprenolol each being greater than those of H 35/25 ($P < 0.05$), metoprolol ($P < 0.05$), or practolol ($P < 0.02$). Of the groups in which PRA fell, only in group A8 (practolol) was the reduction not significant in relation to the PRA values observed in the control group (group A1).

In group A9 (Fig. 2), PRA fell from 9.8 to 3.5 ng/ml ($P < 0.001$) during infusion of *d,l*-propranolol alone, but reverted to the control level when *d,l*-propranolol and prindolol were infused simultaneously. Mean HR also fell during *d,l*-propranolol administration ($P < 0.001$) but returned to control during the combined treatment. MBP, which fell during the propranolol infusion, was not further influenced by prindolol.

Plasma sodium, potassium, and glucose concentrations, measured at the beginning and end of each experiment in groups A1–A8, did not alter significantly. Blood packed cell volumes fell uniformly in each of the groups by a mean of 5% ($P < 0.005$). Plasma concentrations of propranolol and prindolol, measured in groups A2 and A4 at intervals after the first 30 min of infusion, did not vary significantly during the 360-min infusions. Plasma concentration of propranolol was between 186 ± 17 (SE) and 203 ± 17 (SE) ng/ml and that of prindolol was between 44 ± 12 (SE) and 61 ± 12 (SE) ng/ml.

Isoproterenol challenge studies (series B) (Fig. 3). In a control group of six animals (group B1), 30-min infusions of isoproterenol (0.004, 0.01, or 0.04 $\mu\text{g/kg/min}$) caused significant increases in PRA of 4.3 ± 0.5 (SE), 11.0 ± 1.6 , and 18.8 ± 2.9 ng/ml, respectively ($P < 0.001$). Similarly, there were significant rises in HR of 11 ± 2 ($P < 0.005$), 24 ± 4 ($P < 0.001$), and 44 ± 4 ($P < 0.001$)/min.

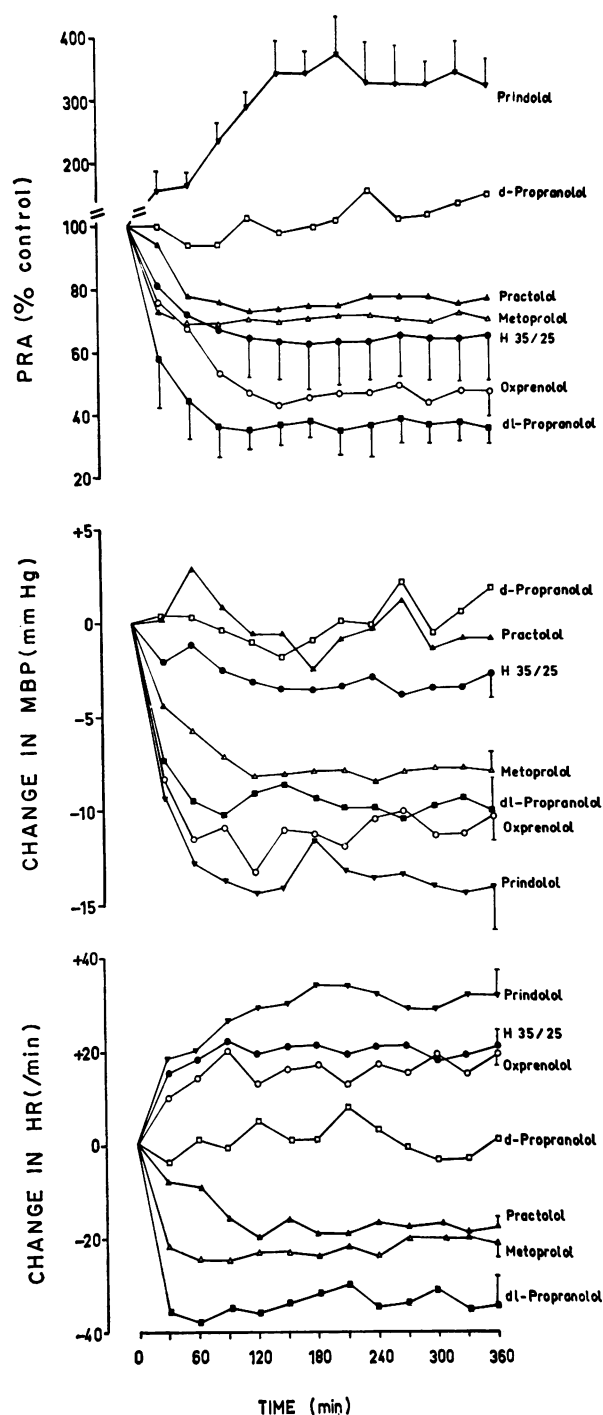


FIGURE 1 Effects of beta adrenergic blocking agents on PRA, MBP, and HR in the unstimulated rabbit. These agents, infused in comparable dosages during a 6-h period, were each administered separately to a group of six animals. Points shown are the mean \pm SEM of six observations.

In animals which received isoproterenol during *d,l*-propranolol infusion (group B2), there was no change in PRA; HR rose by 8 ± 2 /min ($P < 0.05$) during

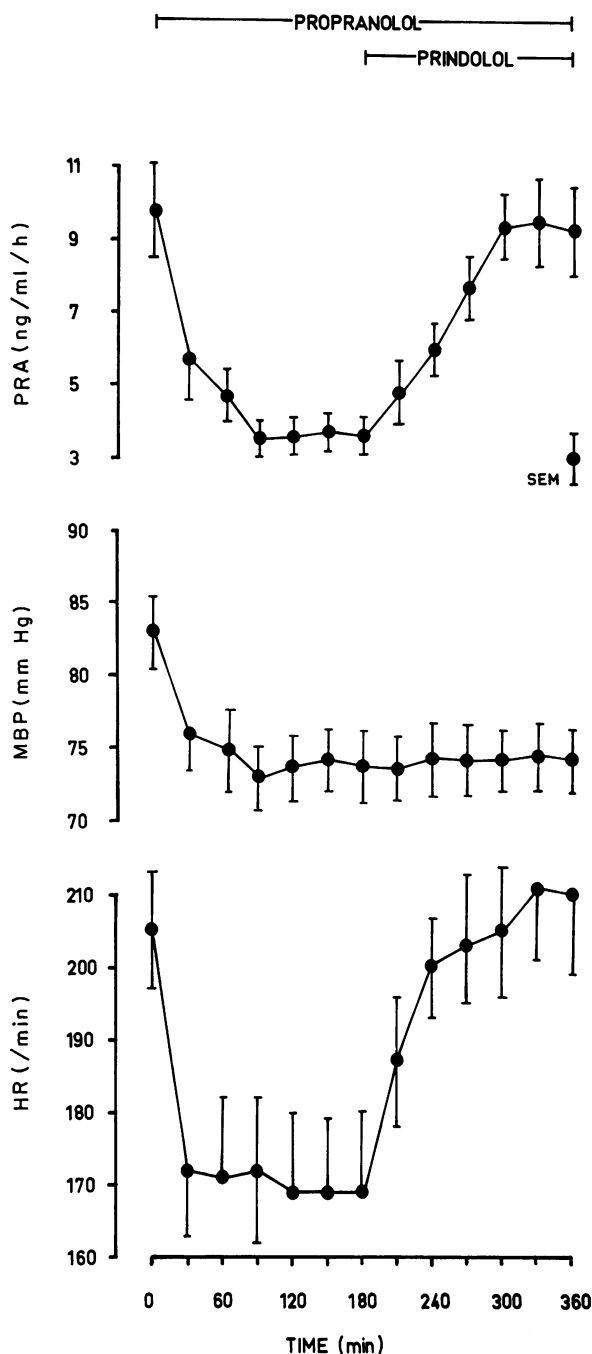


FIGURE 2 Effects of infusions of *d,l*-propranolol (0.5 mg/kg/h) alone, and of *d,l*-propranolol plus prindolol (0.063 mg/kg/h), on PRA, MBP, and HR in the conscious rabbit. Each point shown is the mean \pm SEM of six observations.

administration of the highest dose of isoproterenol. In group B3 (*d*-propranolol), PRA and HR rose significantly during infusion of isoproterenol in low dosage ($P < 0.02$), medium dosage ($P < 0.001$), and high dosage ($P < 0.001$). In group B4 (prindolol), PRA

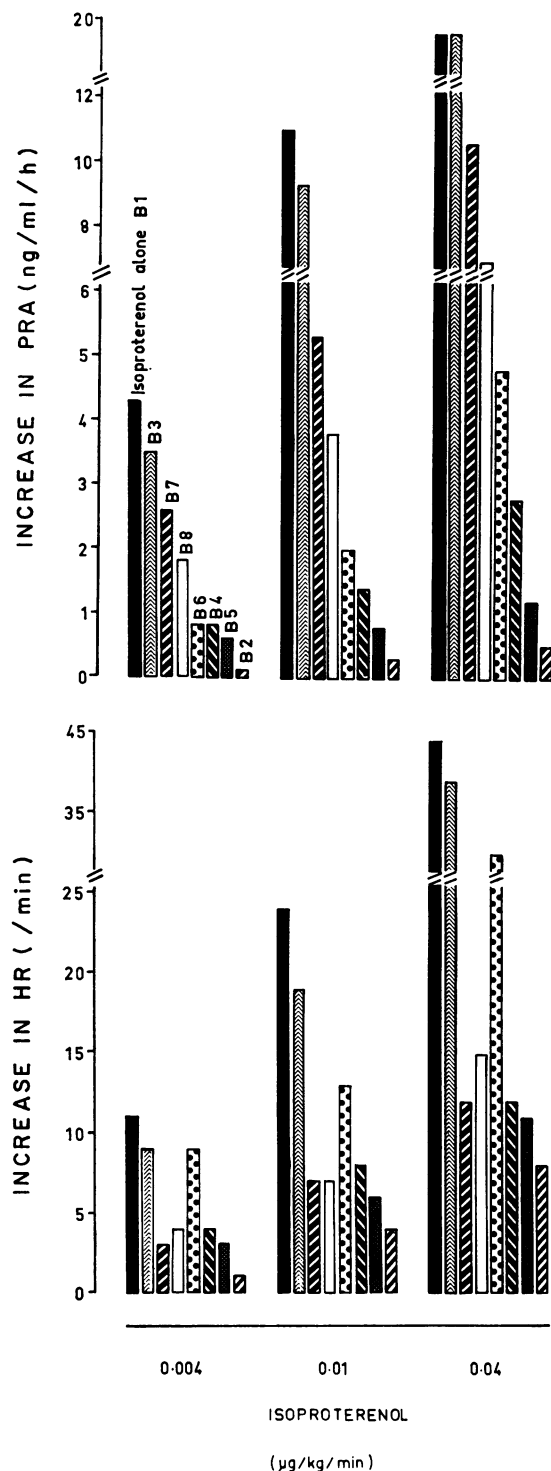


FIGURE 3 Effects of 30-min infusions of isoproterenol in three separate dosages on PRA and HR in rabbits being infused with beta adrenergic blocking agents. The animals received either dextrose (group B1), *d,l*-propranolol (B2), *d*-propranolol (B3), prindolol (B4), oxprenolol (B5), H 35/25 (B6), metoprolol (B7), or practolol (B8). Each column represents the mean of six observations.

and HR rose only during the high dose of isoproterenol ($P < 0.01$). In group B5 (oxprenolol), PRA rose slightly during the high dose ($P < 0.05$) but HR rose during both the medium ($P < 0.02$) and high ($P < 0.005$) doses. In group B6 (H 35/25), PRA rose only during the high dose of isoproterenol ($P < 0.01$) but there were pronounced increases in HR during the low ($P < 0.01$), medium ($P < 0.001$), and high ($P < 0.001$) dose infusions. In groups B7 (metoprolol) and B8 (practolol) there were highly significant increases in PRA, greater than those observed with the other blockers, after each of the isoproterenol challenges. HR rose only with the high dose challenge in group B7 ($P < 0.01$) and with the medium ($P < 0.05$) and high ($P < 0.01$) doses in B8.

There were no significant changes in MBP caused by isoproterenol in the doses used in either the control or the treatment groups.

Plasma sodium, potassium, and glucose concentrations were measured immediately before the beginning and the end of the 30-min isoproterenol 0.04 $\mu\text{g/kg/min}$ infusions (Table III). There were no significant changes in plasma sodium concentrations in any of the groups. Plasma potassium fell in animals infused with isoproterenol alone (group B1) ($P < 0.005$), and in those also receiving *d*-propranolol ($P < 0.01$), metoprolol ($P < 0.05$), or practolol ($P < 0.02$) but there were no changes in the other groups. Plasma potassium concentration was also reduced ($P < 0.02$) by infusion of isoproterenol 0.01 $\mu\text{g/kg/min}$; the influence of the beta adrenergic blockers upon this action was not studied. The low dose isoproterenol challenge caused no significant change in plasma potassium. Plasma glucose levels rose in the 0.04 $\mu\text{g/kg/min}$ isoproterenol control animals (group B1) ($P < 0.01$) and also in those receiving *d*-propranolol ($P < 0.02$) and H 35/25 ($P < 0.05$).

DISCUSSION

It is well established that propranolol prevents the rise in renin secretion caused by experimental adrenergic stimuli (3, 5, 12) and lowers PRA in hypertensive patients (13–15). In the present study, it was shown that oxprenolol, like *d,l*-propranolol, could prevent the rise in PRA caused by the beta adrenergic agonist, isoproterenol. Further, it was demonstrated that in the unstimulated rabbit, constant infusion of either propranolol or oxprenolol produced a sustained fall in PRA.

Prindolol markedly diminished the stimulatory effects of isoproterenol on the heart and on renin release, but in the resting animal, in which it had a strong hypotensive effect, prindolol caused significant rises in PRA and HR. However, when this agent was given

TABLE III
Effects of 30-min Infusions of Isoproterenol* on Plasma Sodium,† Potassium,§ and Glucose|| Concentrations in Rabbits Receiving Beta Adrenergic Blocking Agents

	Control			30 min		
	Na +	K +	Glucose	Na +	K +	Glucose
Isoproterenol alone	146 \pm 1	3.7 \pm 0.1	89 \pm 4	144 \pm 2	2.9 \pm 0.1	104 \pm 3
<i>d,l</i> -Propranolol	144 \pm 1	3.6 \pm 0.1	91 \pm 4	144 \pm 1	3.7 \pm 0.1	92 \pm 5
<i>d</i> -Propranolol	144 \pm 1	3.5 \pm 0.2	88 \pm 6	142 \pm 1	2.9 \pm 0.2	101 \pm 6
Prindolol	143 \pm 2	3.7 \pm 0.1	93 \pm 6	144 \pm 2	3.6 \pm 0.1	90 \pm 6
Oxprenolol	144 \pm 1	3.7 \pm 0.1	91 \pm 5	144 \pm 1	3.6 \pm 0.1	95 \pm 4
H 35/25	145 \pm 1	3.7 \pm 0.2	90 \pm 3	146 \pm 2	3.5 \pm 0.2	101 \pm 4
Metoprolol	144 \pm 1	3.7 \pm 0.1	91 \pm 6	143 \pm 1	3.3 \pm 0.1	91 \pm 5
Practolol	144 \pm 2	3.5 \pm 0.1	88 \pm 6	144 \pm 1	3.0 \pm 0.1	86 \pm 8

For dosages, see Table I; values given are mean \pm SEM, $n = 6$.

* 0.04 $\mu\text{g/kg/min}$.

† meq/liter.

§ meq/liter.

|| mg/100 ml.

to animals already receiving propranolol, these increases occurred in the absence of changes in blood pressure. Thus, the hyperreninemic and chronotropic effects of prindolol are probably direct and not dependent upon reflex mechanisms initiated by hypotension. The observation that prindolol stimulates beta adrenergic receptors in the resting animal, while preventing the agonist effects of isoproterenol, is consistent with its known intrinsic sympathomimetic properties (16).

Although beta blockers possess quinidine-like or local anesthetic properties (17), their effects on PRA appear to be due to their actions on beta adrenergic receptors. *D*-Propranolol, which has the quinidine-like but not the beta antagonist properties of *d,l*-propranolol, failed to prevent the increase in PRA caused by isoproterenol, a finding which is in agreement with studies in the isolated kidney (18) and in man (19).

The results in the unstimulated animal indicate that beta adrenergic receptors also have a role in sustaining resting levels of PRA. However, during the 6-h infusions of *d,l*-propranolol, a blocker which is devoid of intrinsic sympathomimetic properties (16), plasma renin, which has a circulating half-life of only 10–30 min (20, 21), was not reduced below 36% control. Thus, despite sustained blood levels of propranolol considerably greater than those required for effective beta blockade (22, 23), some renin release still occurred. This suggests that basal renin secretion is maintained, in part, by nonadrenergic mechanisms.

The beta adrenergic receptors, as defined by Ahlquist (24), have been classified as two types: beta-1, which includes receptors mediating cardiac stimulation and lipolysis, and beta-2, including receptors situated in the

pulmonary bronchi and in the peripheral vasculature (25). In the doses used in the present study, the non-specific beta blockers, propranolol, oxprenolol, and prindolol, which have affinity for both beta-1 and beta-2 receptors, abolished the increases in PRA and HR caused by all but the highest doses of isoproterenol.

H 35/25, a beta-2-specific antagonist (26) also inhibited renin release in both the resting and the isoproterenol-challenged animals, but did not inhibit the chronotropic effect of isoproterenol. Conversely, practolol and metoprolol, blockers with predominantly beta-1 receptor affinity (27, 28), inhibited the chronotropic action of isoproterenol without preventing its stimulatory effect on PRA. In the resting animal, practolol had little effect on PRA, a result which is similar to findings with beta-1 blockers in man (29, 30). Metoprolol caused a larger reduction in PRA, but this agent possesses a lesser degree of beta-1 specificity than practolol (28) and its effect on renin release could have reflected partial blockade of beta-2 receptors. These data are consistent with the concept that the action of the beta adrenergic blockers on HR is related to their beta-1 receptor activity whereas their effects on PRA depend upon their affinity for beta-2 receptors (30).

The difference between the two classes of beta receptors was emphasized by the differing metabolic effects of the blockers. The known hypokalemic action of isoproterenol (31) was prevented only by antagonists possessing beta-2 receptor affinity, whereas the hyperglycemia which is caused by isoproterenol (32), was blocked only by agents with beta-1 receptor activity.

A fall in plasma potassium concentration may stimulate renin release (33, 34). Therefore, it is possible that the increase in PRA caused by isoproterenol may have been due to its potassium-lowering effect. Moreover, the beta adrenergic blockers which best prevented the stimulatory effect of isoproterenol on renin release were those which abolished its hypokalemic action. However, it should be emphasized that during the beta blocker studies in which isoproterenol was not given, significant increases or decreases in PRA occurred in the absence of alterations in plasma potassium.

It is difficult in a study of this kind to ensure that dosages of the pharmacologic agents used are comparable. The doses (per kilogram) of propranolol, oxprenolol, prindolol, and practolol which were employed were similar to those found to have an anti-hypertensive effect in clinical practice or in previous investigations in the rabbit (6, 35, 36). The doses of metoprolol and H 35/25 were based on those used in studies in which their antagonism to chronotropic stimuli of the heart was compared with that of propranolol (28, 37). We were not able to measure the plasma

concentrations of all the beta blockers used because of methodological difficulties. However, plasma levels of propranolol and prindolol, which are readily assayed by spectrofluorimetric methods, were measured at intervals during the 6-h infusions in the resting animal and were shown not to vary significantly during the experiments. Thus, at least as far as these two agents were concerned, constant blood levels were achieved by the method of administration used in these studies.

Because of the suspected participation of the renin-angiotensin system in the development of certain types of clinical and experimental hypertension (38, 39), it has been suggested that the antihypertensive activity of propranolol may depend upon its PRA-lowering properties (40). Further, in a recent study in hypertensive patients, it was concluded by Bühler et al. (41) that the antihypertensive action of propranolol involves a fall in renin secretion associated with a reduction in renin-induced vasoconstriction. However, such a mechanism does not appear to apply to the beta blockers as a class, for in the present study, H 35/25 reduced PRA without affecting blood pressure, while prindolol lowered blood pressure but increased PRA. Moreover, in previously reported work (42) we showed that when prindolol was substituted for propranolol in the treatment of hypertensive patients, blood pressure remained low despite a significant rise in PRA.

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