

# Effect of Beta Adrenergic Blockade on Renin Response to Renal Nerve Stimulation

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**ABSTRACT** The ability of *d,l*-propranolol to block renin secretion in response to various extrarenal stimuli, such as hemorrhage and hypoglycemia, has been interpreted to indicate the presence of an intrarenal beta receptor regulating renin release. However, two problems complicate this interpretation: (a) the stimuli have effects outside the kidney, and (b) *d,l*-propranolol has a local anesthetic, as well as a beta adrenergic blocking, action. In the present study, the effects of a purely intrarenal stimulus, in the form of renal nerve stimulation (RNS), on renin secretion was examined. The effects of *d,l*-propranolol (anesthetic and beta-blocking activity), *l*-propranolol (beta-blocking activity only), and *d*-propranolol (local anesthetic activity only) on the renin response to RNS were examined. In a control group of animals, two sequential RNS increased mean renin secretion from 401 to 1,255 U/min ( $P < 0.25$ ) and from 220 to 2,179 U/min ( $P < 0.01$ ). In a second group the first RNS increased renin secretion from 201 to 1,181 U/min ( $P < 0.01$ ), but after *d,l*-propranolol was given RNS did not significantly alter renin secretion (33 to 55 U/min). In a third group the initial RNS increased renin secretion from 378 to 1,802 U/min ( $P < 0.025$ ), but after *l*-propranolol was given RNS had no significant effect on renin secretion (84 to 51 U/min). A fourth group of dogs showed a rise in renin secretion from 205 to 880 U/min ( $P < 0.001$ ) in response to the first RNS, while the second RNS, given after an infusion of *d*-propranolol, caused a rise in renin secretion from 80 to 482 ( $P < 0.005$ ). The nature of the electrical stimulus was consistent in all groups and caused no detectable changes in renal or systemic hemodynamics or in urinary electrolyte excretion. The results, there-

fore, indicate that renin secretion can be stimulated through intrarenal beta receptors independent of changes in systemic or renal hemodynamics or in tubular sodium reabsorption. Hence, the effect of beta stimulation on renin secretion would appear to result from a direct action on the renin-secreting cells of the juxtaglomerular apparatus.

## INTRODUCTION

There is a great deal of evidence that the adrenergic nervous system plays an important role in renin release. Maneuvers which provide a generalized stimulus to the adrenergic system such as hemorrhage (1, 2), electrical stimulation of the brain stem (3, 4), hypoglycemia (5, 6), intravenous catecholamine infusion (7-9), and vasodilating antihypertensive drugs (10-12) result in increased renin secretion. The increase in renin secretion brought about by such means can be inhibited by the administration of *d,l*-propranolol (6, 7, 10, 11, 13, 14). Furthermore, electron microscopy (15) and histochemical fluorescence methods have demonstrated that the juxtaglomerular cells of both rat (16) and dog (17) kidneys are richly supplied with adrenergic nerve endings. These observations, therefore, suggest that there are intrarenal beta adrenergic receptors and that *d,l*-propranolol acts at these sites to block renin release. In each of the examples cited, however, the adrenergic stimulus was general throughout the body and not confined to the kidney. It is, therefore, possible that propranolol inhibits renin release not by direct action within the kidney but rather by blocking some extrarenal adrenergic mechanisms. That such an extrarenal mechanism might exist is suggested by the observation that the beta adrenergic agonist, isoproterenol, is a much more potent stimulator

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of renin release when administered intravenously than when infused directly into the renal artery (9).

One experimental method by which extrarenal adrenergic influences on renin secretion can be eliminated is through direct renal nerve stimulation. Previous experiments of this type have shown that renal nerve stimulation does cause renin release (8, 18, 19). However, in these studies the effect of nerve stimulation on renal hemodynamics and sodium excretion either were not reported or were so profound that they might have accounted for the observed changes in renin secretion. If this were the case, then the inhibitory effect of *d,l*-propranolol on renin release might have resulted from the effects of the drug on renal hemodynamics or sodium excretion. Moreover, the *d*-isomer of propranolol, which is devoid of beta adrenergic inhibitory properties, is a potent membrane stabilizer (20, 21). The possibility exists, therefore, that this property of *d,l*-propranolol accounted for its ability to impair renin release. Therefore, we felt that the many previous studies had not firmly established whether or not renin release is influenced directly by intrarenal beta receptors and whether propranolol inhibits renin release by its action upon such receptors.

Our experiments were designed to reexamine this question by using: (a) renal nerve stimulation of a frequency and intensity which enhanced renin release but altered neither hemodynamics nor sodium excretion and (b) three different preparations of propranolol (*d,l*-, *d*-, and *l*-propranolol) to block the increase in renin release induced by renal nerve stimulation.

## METHODS

The experiments were performed on 25 mongrel dogs of either sex weighing 20–35 kg. Food was withheld for 18 h before the experiment but water was allowed ad libitum. Anesthesia was induced with intravenous pentobarbital (30 mg/kg) and maintained by the intermittent administration of small doses of phenobarbital. All animals received 5 mg of deoxycorticosterone acetate in oil intramuscularly before the experiments.

The dogs were intubated and ventilated with a Harvard respirator (Harvard Apparatus Co., Inc., Millis, Mass.). Polyethylene catheters were placed in the aorta, one via the femoral artery for continuous measurement of blood pressure with Statham transducers (Statham Instruments, Inc., Oxnard, Calif.) and another catheter via the brachial artery for collection of arterial blood samples.

The kidneys were exposed through bilateral flank incisions with a retroperitoneal approach, and catheters were placed in both ureters and both renal veins. The renal nerves supplying the left kidney were carefully isolated from the left renal artery and vein. They were cut as near the aorta as possible after having been tied with a silk ligature. The electrodes of a Grass electric stimulator (model SD 9 Square Wave Stimulator, Grass Instrument Co., Boston, Mass.) were placed around the renal nerve bundle at a point where there could be no contact with the renal artery. The right kidney was not stimulated and served as

control. An oscilloscope connected to the Grass stimulator continuously monitored the frequency, intensity, and duration of nerve stimulation.

An intravenous infusion of 0.9% sodium chloride was started during surgery. Each animal received 600 ml of this saline solution during the surgery and 3 ml/min after completion of surgery and throughout the study.

1 h after completion of surgery, an intravenous infusion of 0.9% saline (0.5 ml/min) was started with sufficient inulin and *p*-aminohippuric acid (PAH)<sup>1</sup> to maintain blood levels of these substances between 15–25 and 1–3 mg/100 ml, respectively. Clearance of inulin and PAH were measured by standard methods (22). The experiments were begun 1½–2 h after completion of surgery. The experiments were carried out according to the following protocols.

*Renal nerve stimulation without propranolol-group I.* In these experiments, urine was collected in three successive 5- to 10-min control periods and the results are expressed as the mean of these three periods. Blood was drawn from both renal veins and the brachial artery at the middle of the first and third urine collection periods. The total blood withdrawn during the experiment was 400 ml and the saline replacement was 700 ml. Biphasic renal nerve stimulation (10 V, frequency 0.33 Hz, duration 0.5 ms) was then started. In the preliminary experiments this degree of electrical stimulation was found to induce a significant increase in the rate of renin secretion without changing renal blood flow (RBF) or glomerular filtration rate (GFR). This degree of electrical stimulation was used in all experiments. Three 5-min clearance periods were taken during the last 15 min of a 45-min stimulation period. Blood was withdrawn during the first and third periods. 45 min after stopping the nerve stimulation, three recovery clearance periods were made. Stimulation then was performed again and for the same length of time to establish that the stimulated kidney responded to a second stimulation in a manner similar to the first. The urine and blood collections were the same during the second stimulation and the recovery periods as during the first nerve stimulation.

*Renal nerve stimulation and d,l-propranolol-group II.* In the first part of these experiments, a sequence similar to group I dogs was followed (control, first stimulation, and recovery periods). Then *d,l*-propranolol (Inderal, Ayerst Laboratories, New York) was administered (1 mg/kg bolus followed by 0.5 mg/kg per h maintenance). After 30 min, three urine collection periods with blood collections were performed, followed by the second renal nerve stimulation and recovery collection periods as in the group I experiments.

*Renal nerve stimulation and l-propranolol-group III.* The sequence in these experiments was the same as in group II except that *l*-propranolol (Ayerst Laboratories) was administered before the second nerve stimulation.

*Renal nerve stimulation and d-propranolol-group IV.* In these studies *d*-propranolol (Ayerst Laboratories) was administered before the second nerve stimulation. Otherwise, the sequence of events was the same as in group II. The loading and maintenance doses of either *d*- or *l*-propranolol were 1 mg/kg and 0.5 mg/kg per h.

The analytical procedures used in these studies have been referred to elsewhere (22). Statistical analysis was per-

<sup>1</sup> Abbreviations used in this paper: GFR, glomerular filtration rate; PAH, *p*-aminohippuric acid; RBF, renal blood flow; RVR, renal vascular resistance;  $U_{Na}V$ , urinary sodium excretion.

formed by the analysis of variance with Scheffe's analysis of multiple comparisons within groups and by unpaired *t* test for comparison between groups.

Plasma renin activity was measured by using an immunoassay for angiotensin I and expressed as nanograms angiotensin I formed per milliliter of plasma during a 3-h incubation (23). Renin secretion rate was calculated from the renal arteriovenous difference in plasma renin activity and renal plasma flow and is expressed as units per minute. Isoproterenol was infused intravenously (0.05 µg/kg per min) to test efficacy of beta adrenergic blockade. The chronotropic, ionotropic, and peripheral vasodilation of this dose of isoproterenol was blocked by *d,l*- and *l*- but not *d*-propranolol.

## RESULTS

**Effects of renal nerve stimulation in absence of propranolol-group I.** The effects of renal nerve stimulation on renin secretion rate are shown in Fig. 1. In the kidney undergoing stimulation there were significant rises in renin secretion rate in response to both the first and second nerve stimulations. The mean response of renin secretion rate with the second stimulation was actually slightly greater than to the first stimulation but this difference was not statistically significant. The rises in renin secretion rate induced by nerve stimulation were rapidly reversible when the stimulus was stopped. The renin secretion was slightly lower ( $P < 0.05$ ) in the second control period as compared to the first control period. In the subsequent groups II–IV there was, however, no such statistically significant difference in first and second control renin secretion.

In the contralateral kidney, not receiving nerve stimulation, renin secretion rate actually fell during stimulation of the other kidney. This fall in renin secretion rate, however, was not statistically significant.

In Table I are presented the RBF, GFR, renal vascular resistance (RVR), urinary sodium excretion ( $U_{Na}V$ ), and plasma potassium concentration and mean arterial blood pressures in the stimulated kidney. None of these parameters showed a significant response to either the

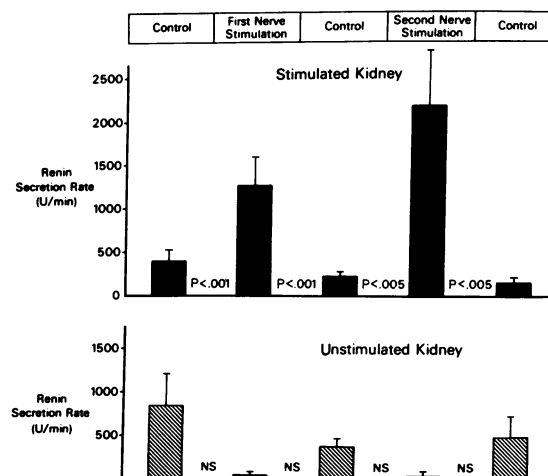


FIGURE 1 Effect of unilateral renal nerve stimulation on renin secretion. In this control group no medication was given between the first and second stimulations.

first or the second stimulation. These parameters also were not different when first and second control periods, first and second stimulation, and first and second post-control periods were compared. The one exception was that  $U_{Na}V$  was lower ( $P < 0.05$ ) in the second control period when compared to the first control period.

**Effects of *d,l*-propranolol on the response to renal nerve stimulation group II.** In this protocol, unilateral renal nerve stimulation was performed on two consecutive occasions as in the previous protocol. However, before and during the second stimulation the animals received *d,l*-propranolol. The effects of the renal nerve stimulations on renin secretion rate for these group II experiments are presented in Fig. 2. As in the previous protocol, the first stimulation caused a significant rise in renin secretion rate in the stimulated kidney and a fall in renin secretion rate in the contralateral kidney. The administration of *d,l*-propranolol then caused a sig-

TABLE I  
Effect of Renal Nerve Stimulation on RBF, GFR, RVR,  $U_{Na}V$ , Plasma Potassium Concentration, and Arterial Pressure in the Stimulated Kidney

	RBF	GFR	RVR	$U_{Na}V$	Plasma potassium	Blood pressure
	ml/min	ml/min	mm Hg/ml·min	µeq/min	meq/liter	mm Hg
Control	295±33.7	55.0±7.58	0.492±0.059	318±110	2.90±0.16	133±5.3
First stimulation	244±43.7	51.7±9.31	0.627±0.092	134±47	3.00±0.20	131±8.7
First postcontrol	274±55.3	53.4±10.21	0.530±0.076	96±28	3.15±0.19	122±9.9
Second stimulation	261±60.2	54.5±9.86	0.548±0.101	82±23	3.22±0.23	116±11.1
Second postcontrol	253±72.0	47.6±10.0	0.673±0.161	103±27	3.09±0.13	121±8.9

None of the values were significantly different.

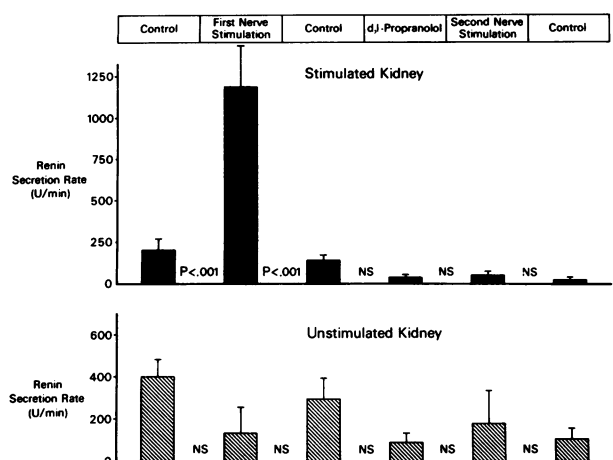


FIGURE 2 Effect of *d,l*-propranolol on the response of renin secretion to unilateral renal nerve stimulation.

nificant decrease in the control levels of renin secretion rate in both kidneys. When unilateral stimulation was repeated in the presence of *d,l*-propranolol there was no significant change in renin secretion rate in either kidney.

The results in Table II demonstrate that neither the first nor the second nerve stimulation significantly altered RBF, GFR, RVR,  $U_{Na}V$ , plasma potassium concentration, or mean arterial pressures. These parameters were also not different for the first and second control and postcontrol periods.

*Effects of l-propranolol on the response to renal nerve stimulation group III.* This protocol was identical to the group II studies except that *l*-propranolol was given

instead of *d,l*-propranolol. The responses of renin secretion rate to unilateral renal nerve stimulation are shown in Fig. 3. During the first stimulation renin secretion rate increased in the stimulated kidney and decreased in the contralateral kidney. As with *d,l*-propranolol the control levels of renin secretion rate in both kidneys decreased when *l*-propranolol was given. After *l*-propranolol administration the second nerve stimulation caused no change in renin secretion rate in either kidney.

Table III shows that neither the first nor the second stimulations significantly altered RBF, GFR, RVR,  $U_{Na}V$ , plasma potassium concentration, or mean arterial pressure. These parameters were also not different for the first and second control and postcontrol periods.

*Effects of d-propranolol on the response to renal nerve stimulation-group IV.* The effects of *d*-propranolol on the response of renin secretion rate to unilateral renal nerve stimulation is shown in Fig. 4. As in all previous protocols, the first stimulation was in the absence of propranolol and caused a rise in renin secretion rate in the stimulated kidney as renin secretion rate fell in the contralateral kidney. Administration of *d*-propranolol caused a fall in renin secretion rate but this effect was only statistically significant in the stimulated kidney.

The second nerve stimulation, which was after *d*-propranolol administration, caused a significant rise in renin secretion rate in the stimulated kidney. This rise, however, was not significantly different from that evoked by the first stimulation.

As shown in Table IV, neither the first nor second nerve stimulation was associated with significant effects on RBF, GFR, RVR,  $U_{Na}V$ , plasma potassium concentration, or mean blood pressure. These parameters were

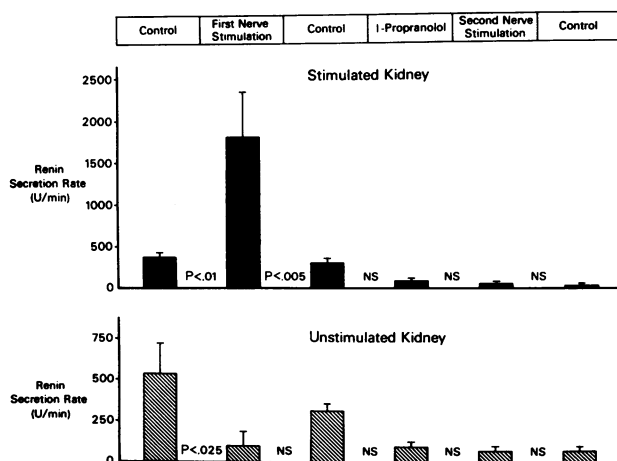


FIGURE 3 Effect of *l*-propranolol on the response of renin secretion to unilateral renal nerve stimulation.

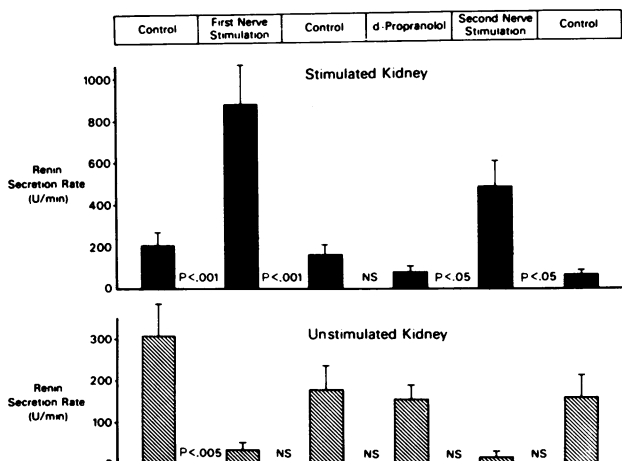


FIGURE 4 Effect of *d*-propranolol on the response of renin secretion to unilateral renal nerve stimulation.

TABLE II  
*Effect of Renal Nerve Stimulation on RBF, GFR, RVR, U<sub>Na</sub>V, Plasma Potassium Concentration, and Arterial Pressure before and after d,l-Propranolol*

	RBF		GFR		RVR		U <sub>Na</sub> V		Plasma potassium	Blood pressure
	Stimu- lated	Unstimu- lated	Stimu- lated	Unstimu- lated	Stimu- lated	Unstimu- lated	Stimu- lated	Unstimu- lated		
	<i>ml/min</i>		<i>ml/min</i>		<i>mm Hg/ml·min</i>		<i>μeq/min</i>		<i>meq/liter</i>	<i>mm Hg</i>
Control	296 ± 31.9	283 ± 32.8	48.8 ± 6.27	45.6 ± 5.31	0.541 ± 0.08	0.552 ± 0.07	203 ± 38.3	126 ± 33.6	2.98 ± 0.06	144 ± 3.06
First stimulation	290 ± 14.9	266 ± 11.9	50.3 ± 5.66	47.1 ± 4.31	0.521 ± 0.03	0.562 ± 0.04	176 ± 25.3	105 ± 27.5	3.01 ± 0.07	147 ± 4.87
First postcontrol	233 ± 13.1	229 ± 13.6	48.8 ± 5.87	44.6 ± 4.55	0.644 ± 0.04	0.664 ± 0.06	116 ± 10.6	75 ± 11.2	3.10 ± 0.08	148 ± 6.15
d,l-Propranolol	239 ± 16.6	230 ± 25.9	47.9 ± 6.58	47.3 ± 6.82	0.634 ± 0.06	0.684 ± 0.08	118 ± 11.0	74 ± 11.2	3.16 ± 0.10	147 ± 6.28
Second stimulation	232 ± 40.5	214 ± 35.5	49.2 ± 7.50	45.2 ± 5.78	0.753 ± 0.13	0.774 ± 0.10	134 ± 21.3	88 ± 12.2	3.19 ± 0.09	147 ± 4.65
Second postcontrol	228 ± 35.6	229 ± 37.3	49.1 ± 7.94	46.7 ± 5.94	0.774 ± 0.13	0.755 ± 0.11	180 ± 37.0	120 ± 24.0	3.20 ± 0.06	153 ± 6.06

None of the values were significantly different.

also not different for the first and second control and postcontrol periods.

### DISCUSSION

There is considerable evidence that generalized adrenergic stimulation by various maneuvers, including hemorrhage (1, 2), hypoglycemia (5, 6), carotid occlusion (1), and electrical stimulation of the brain stem (3, 4) is associated with increased renin secretion. It has been attractive to suggest that this effect of sympathetic stimulation is mediated by the direct effect of increased renal sympathetic tone on renin release from juxtaglomerular cells. The above systemic maneuvers, however, could activate extrarenal mechanisms which stimulate renin secretion independent of any direct intrarenal influence.

In support of a direct intrarenal effect on renin release is the morphological finding that adrenergic nerve endings are located near the juxtaglomerular cells of both dog (17) and rat (16). Direct stimulation of renal nerves, therefore, has been used in an effort to document an intrarenal effect of sympathetic stimulation of renin release. Several investigators have shown that renal nerve stimulation causes a consistent rise in renin secre-

tion. This rise in renin secretion, however, has been associated consistently with diminutions in GFR, RBF, and/or U<sub>Na</sub>V which could activate intrarenal baroreceptor or macula densa mechanisms.

The nonfiltering kidney model has been used to examine whether renal nerve stimulation will increase renin secretion in the absence of changes in sodium delivery to the macula densa. The observed rise in renin secretion with renal nerve stimulation in this experimental model, however, was associated with a fall in RBF which could activate a baroreceptor mechanism for renin release independent of a macula densa mechanism or any direct effect of renal nerve stimulation on juxtaglomerular cells. Although papaverine blocked the renal vasoconstrictor effect of renal nerve stimulation in this nonfiltering kidney model, the concomitant hypotensive effect of this vasodilator could have accounted for the persistent increase in renin secretion (24).

Vander (8) has demonstrated that the effect of renal nerve stimulation to increase renin secretion could be reversed by the infusion of an osmotic diuretic. Specifically, when the decrease in RBF and sodium excretion were reversed by the infusion of an osmotic diuretic,

TABLE III  
*Effect of Renal Nerve Stimulation on RBF, GFR, RVR, U<sub>Na</sub>V, Plasma Potassium Concentration, and Arterial Pressure before and after l-Propranolol*

	RBF		GFR		RVR		U <sub>Na</sub> V		Plasma potassium	Blood pressure
	Stimu- lated	Unstimu- lated	Stimu- lated	Unstimu- lated	Stimu- lated	Unstimu- lated	Stimu- lated	Unstimu- lated		
	<i>ml/min</i>		<i>ml/min</i>		<i>mm Hg/ml·min</i>		<i>μeq/min</i>		<i>meq/liter</i>	<i>mm Hg</i>
Control	262 ± 42	256 ± 38	52.4 ± 6.93	47.8 ± 7.46	0.680 ± 0.094	0.828 ± 0.109	256 ± 85	173 ± 62	3.08 ± 0.13	153 ± 5.89
First stimulation	234 ± 47	227 ± 40	51.2 ± 7.65	48.8 ± 9.11	0.772 ± 0.118	0.785 ± 0.100	180 ± 55	151 ± 49	3.12 ± 0.11	157 ± 5.85
First postcontrol	225 ± 45	233 ± 37	54.7 ± 8.09	54.8 ± 10.03	0.808 ± 0.122	0.766 ± 0.104	126 ± 33	130 ± 37	3.16 ± 0.12	158 ± 5.44
l-Propranolol	210 ± 32	196 ± 37	54.3 ± 7.58	51.9 ± 9.71	0.806 ± 0.104	0.824 ± 0.109	125 ± 41	109 ± 35	3.19 ± 0.12	151 ± 5.76
Second stimulation	207 ± 120	250 ± 64	47.7 ± 7.83	56.4 ± 14.84	0.826 ± 0.114	0.751 ± 0.118	139 ± 36	193 ± 74	3.14 ± 0.10	151 ± 4.95
Second postcontrol	217 ± 123	262 ± 89	52.0 ± 13.48	65.0 ± 24.97	0.905 ± 0.161	0.792 ± 0.126	187 ± 47	219 ± 77	3.11 ± 0.08	152 ± 3.17

None of the values were significantly different.

TABLE IV  
Effect of Renal Nerve Stimulation on RBF, GFR, RVR,  $U_{Na}V$ , Plasma Potassium Concentration,  
and Arterial Pressure before and after *d*-Propranolol

	RBF		GFR		RVR		$U_{Na}V$		Plasma potassium	Blood pressure
	Stimulated	Unstimulated	Stimulated	Unstimulated	Stimulated	Unstimulated	Stimulated	Unstimulated		
	ml/min		ml/min		mm Hg/ml·min		μeq/min		meq/liter	mm Hg
Control	279 ± 37.1	261 ± 28.1	44.8 ± 4.9	41.3 ± 5.8	0.554 ± 0.10	0.576 ± 0.11	201 ± 56.5	117 ± 32.5	3.06 ± 0.13	137 ± 11.3
First stimulation	245 ± 33.9	240 ± 31.7	48.7 ± 6.8	45.0 ± 7.8	0.605 ± 0.09	0.647 ± 0.11	200 ± 94.6	95 ± 32.6	3.07 ± 0.19	139 ± 10.5
First postcontrol	220 ± 27.3	211 ± 25.3	48.3 ± 5.3	42.1 ± 4.9	0.731 ± 0.13	0.751 ± 0.13	209 ± 91.6	84 ± 26.3	3.18 ± 0.21	142 ± 8.4
<i>d</i> -Propranolol	201 ± 23.1	228 ± 33.7	49.9 ± 7.0	47.5 ± 8.2	0.729 ± 0.16	0.669 ± 0.10	220 ± 94.9	88 ± 24.7	3.23 ± 0.22	136 ± 7.0
Second stimulation	206 ± 30.6	220 ± 37.8	47.3 ± 6.9	44.4 ± 8.4	0.780 ± 0.18	0.737 ± 0.16	264 ± 93.1	102 ± 25.6	3.37 ± 0.23	136 ± 8.8
Second postcontrol	195 ± 26.9	200 ± 33.9	46.5 ± 7.1	42.7 ± 7.4	0.799 ± 0.18	0.788 ± 0.14	292 ± 87.5	127 ± 37.6	3.44 ± 0.15	135 ± 10.1

None of the values were significantly different.

continued renal nerve stimulation no longer increased renin secretion (8). This finding was interpreted to suggest that an indirect effect of renal nerve stimulation on RBF or sodium excretion was responsible for the resultant rise in renin secretion. An alternative interpretation, however, is that some consequence(s) of the osmotic diuresis obscured the direct effect of renal nerve stimulation on juxtaglomerular cells to increase renin secretion.

The present studies, therefore, were undertaken to examine further the effect of renal nerve stimulation on renin secretion. A degree of renal nerve stimulation was found which stimulated renin but did not alter GFR, RBF, or  $U_{Na}V$ . This degree of renal nerve stimulation was similar to that reported by LaGrange et al. (25) in which renin secretion increased in the absence of changes in GFR or RBF. In this previous study (25), however, renal nerve stimulation was associated with a decrease in sodium excretion in the stimulated kidney. This may have been because most of the experiments were performed at stimulation rates higher than the 0.33 Hz which we used. The infusion of mannitol during the experiments of LaGrange et al. (25) may also have contributed to the difference in sodium excretion observed in their study.

The present results, therefore, support the hypothesis that renal nerve stimulation may directly increase renin release independent of any secondary activation of baroreceptor or macula densa mechanism. These results, however, do not exclude the likely possibility that with more potent renal nerve stimulation either or both baroreceptor and macula densa mechanisms may be activated and contribute to the resulting rise in renin secretion. Such effects would be expected to be additive to any direct effect of renal nerve stimulation on juxtaglomerular cells.

The next question examined in the present study was whether the effect of renal nerve stimulation on renin release is mediated by alpha or beta adrenergic receptors.

Previous studies have shown that the administration of *d,l*-propranolol blocks or attenuates the effect of systemic adrenergic stimulation secondary to hypoglycemia (6), midbrain stimulation (13), or renal nerve stimulation (26). It is, however, not possible to interpret these results with respect to an intrarenal beta adrenergic receptor influencing renin release, since these systemic stimuli are associated with extrarenal alterations. Moreover, the duration of action of *d,l*-propranolol is such that selective intrarenal blockade cannot be achieved.

These objections to previous studies are particularly important since systemic beta adrenergic stimulation with isoproterenol has been shown to stimulate renin secretion over and above any intrarenal effect of this beta agonist. Specifically, the same dose of isoproterenol (0.09–0.36 μg/kg per min) was found to stimulate renin secretion when administered intravenously but not intrarenally (9). While other studies using larger doses of isoproterenol infused into an isolated rat kidney have shown a renin-stimulating effect, the physiologic versus pharmacologic importance of these results is not known (27). Moreover, the infusion of the beta agonist, isoproterenol, may not be comparable to any beta adrenergic properties of renal nerve stimulation. Lastly, previous studies claiming to support the existence of an intrarenal beta adrenergic receptor influencing renin release have not considered the membrane stabilizing (anesthetic) property of *d,l*-propranolol (20, 21).

The present experimental protocol was designed to avoid these above objections. As already discussed, renal nerve stimulation was chosen as the mode of sympathetic stimulation so as to avoid any extrarenal alterations which might increase renin secretion. In addition, the effect of beta adrenergic blocking doses of *d,l*-propranolol and *l*-propranolol were compared with the same dose of *d*-propranolol which is not a beta blocking agent. This *d*-isomer of propranolol is responsible for the membrane stabilizing effects of *d,l*-propranolol (20, 21). The results demonstrated that administration of either *l*- or

*d,l*-propranolol blocks the effect of renal nerve stimulation to increase renin, while *d*-propranolol has little effect on this response.

In summary, the present results demonstrate that adrenergic stimulation by renal nerve stimulation can increase renin secretion in the absence of changes in GFR, RBF, and  $U_{Na}V$ . This effect can be blocked by *d,l*-propranolol or *l*-propranolol, both agents possessing potent beta adrenergic blocking properties. The membrane stabilizing effect of *d*-propranolol does not abolish the effect of renal nerve stimulation to increase renin secretion. These results, therefore, provide strong support for the presence of an intrarenal beta receptor which influences renin secretion.

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