Renal Adrenoceptor Mediation of Antinatriuretic and Renin Secretion Responses to Low Frequency Renal Nerve Stimulation in the Dog

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SUMMARY. We evaluated renal adrenoceptor mediation of the renin secretion and antinatriuretic responses to low frequency (1.0 Hz) electrical stimulation of the renal nerves in the dog using renal \( \alpha \)-adrenoceptor blockade with phentolamine (\( \alpha_1/\alpha_2 \)), prazosin (\( \alpha_1 \)), yohimbine (\( \alpha_2 \)), and rauwolscine (\( \alpha_2 \)), and \( \beta \)-adrenoceptor blockade with dl-propranolol (\( \beta_1/\beta_2 \)) and atenolol (\( \beta_1 \)). In all animals studied, renal blood flow and glomerular filtration rate remained constant throughout the experiment. In 11 dogs, low frequency renal nerve stimulation decreased urinary sodium excretion (119 ± 13 to 86 ± 18 \( \mu \)Eq/min) and increased renin secretion (79 ± 22 to 348 ± 73 ng/min). Renal arterial infusion of phentolamine (2–10 \( \mu \)g/kg per min) prevented the antinatriuresis but did not change the response of renin secretion (96 ± 46 to 412 ± 93 ng/min). In six dogs, renal arterial infusion of prazosin (0.7 \( \mu \)g/kg per min) similarly blocked the antinatriuretic but not the renin secretion responses to low frequency renal nerve stimulation. Renal arterial infusion of either yohimbine or rauwolscine did not affect the antinatriuretic or renin secretion responses to low frequency renal nerve stimulation. Intrarenal \( \beta_1 \)-adrenoceptor blockade with low dose atenolol (0.5 \( \mu \)g/kg per min, \( n = 9 \)) had no effect on the antinatriuretic responses to low frequency renal nerve stimulation (~47 ± 12 vs. ~37 ± 8 \( \mu \)Eq/min) but significantly decreased the increment in renin secretion during low frequency renal nerve stimulation (636 ± 249 vs. 305 ± 157 ng/min; \( P < 0.05 \)). Renal arterial infusion of dl-propranolol (0.5 \( \mu \)g/kg per min, \( n = 4 \)) or a high dose of atenolol (5.0 \( \mu \)g/kg per min, \( n = 8 \)) abolished the renin secretion but not the antinatriuretic responses to low frequency renal nerve stimulation. These results demonstrate that: antinatriuresis during 1.0 Hz renal nerve stimulation (where renal blood flow and glomerular filtration rate are unchanged) is mediated by renal \( \alpha_1 \)-adrenoceptors and not by \( \alpha_2 \)- or \( \beta \)-adrenoceptors, that renin secretion elicited by low frequency renal nerve stimulation is mediated by renal \( \beta_1 \)-adrenoceptors and not by \( \beta_2 \)-adrenoceptors, and that the renin secretion response to low frequency renal nerve stimulation is evoked by direct stimulation of juxtaglomerular granular cell \( \beta_1 \)-adrenoceptors and not indirectly by stimulation of the macula densa receptor through decreased urinary sodium excretion. (Circ Res 53: 298–305, 1983)

DIRECT electrical stimulation of the efferent renal nerves at frequencies greater than 2.0 Hz decreases renal blood flow and urinary sodium excretion and increases renin secretion (Coote et al., 1972; Kopp et al., 1981). Under these circumstances of intense renal nerve stimulation, renin secretion may be elicited by a direct neural effect on the juxtaglomerular granular cells, stimulation of a renal tubular macula densa receptor [via decreased sodium chloride delivery to the distal nephron (Churchill et al., 1978)], or by activation of an intrarenal vascular baroreceptor (Blaine et al., 1970).

We recently have separated the neural effects on renin secretion from nonneural stimuli using low frequencies of renal nerve stimulation (i.e., less than 1.0 Hz). Renal nerve stimulation at 0.5 Hz increased renin secretion without altering mean arterial pressure, renal blood flow, glomerular filtration rate, or urinary sodium excretion (Osborn et al., 1981, 1982). We interpreted this to mean that the renin secretion response is elicited by direct neural activation of the juxtaglomerular granular cells. This response was abolished by renal \( \beta_1 \)-adrenoceptor blockade with atenolol but was unaltered by renal \( \beta_2 \)-adrenoceptor blockade with butoxamine (Osborn et al., 1981) or renal \( \alpha \)-adrenoceptor blockade with phentolamine or prazosin (Osborn et al., 1982). Thus, renin secretion during 0.5 Hz renal nerve stimulation resulted from renal \( \beta_1 \)-adrenoceptor stimulation and not from activation of \( \beta_2 \)- or \( \alpha \)-adrenoceptors.

Earlier studies demonstrated that 1.0 Hz renal nerve stimulation increased renin secretion rate and decreased urinary sodium excretion without affecting mean arterial pressure, renal blood flow, or glomerular filtration rate (Slick et al., 1975; Zambraski and DiBona, 1976; Kopp et al., 1980). At this frequency of renal nerve stimulation (1.0 Hz), the increased renin secretion rate may have resulted
from the combination of neural stimuli to the juxtaglomerular granular cells (β₁-adrenoceptor mediated) or from nonneural stimuli to the macula densa receptor mechanism (i.e., decreased sodium chloride delivery to the distal nephron). The first goal of this study was to investigate the contributions of neural (norepinephrine release from nerve terminals on the juxtaglomerular granular cells) and nonneural (decreased sodium chloride delivery to the macula densa receptor) stimuli for renin secretion during 1.0 Hz renal nerve stimulation using renal α₁- or β₁-adrenoceptor blockade.

The antinatriuretic response to 1.0 Hz renal nerve stimulation is probably mediated by renal tubular α₁-adrenoceptors (Zambraski et al., 1976a). Some investigators recently have reported that water reabsorption in the proximal tubule is increased by norepinephrine and that this response is mediated by β₁-adrenoceptors (Besarab et al., 1977; Bello-Reuss, 1980). This finding contrasts strikingly with the observation that the antinatriuresis during 1.0 Hz renal nerve stimulation is abolished by phenoxymethyl-β-adrenoceptor blockade with prazosin (α₁). Selective α₂-adrenoceptor blockade with yohimbine and rauwolscine (α₂), nonselective β₁-adrenoceptor blockade with propranolol (β₁/β₂), and selective β₂-adrenoceptor blockade with atenolol (β₂).

Methods

Experiments were conducted on 45 mongrel dogs of either sex weighing 15–25 kg. Animals were anesthetized with sodium pentobarbital (30 mg/kg, iv). Auffed endotracheal tube was inserted and the animals were artificially ventilated. Catheters were inserted via a femoral artery into the descending aorta for determining systemic arterial pressure and into a femoral vein and jugular vein for the infusion of inulin, isotonic saline, and supplemental doses of anesthetic. Following the bolus intravenous administration of a priming dose of inulin, an inulin solution was infused at 1.0 ml/min to maintain plasma inulin concentration at approximately 30 mg/dl. Isotonic saline was infused at 2.0 ml/min to maintain urine flow rate constant and to replace blood and urine losses. Body temperature was maintained at 35–37°C by external warming.

The left kidney was exposed via a left retroperitoneal flank incision. An electromagnetic flowmeter probe was positioned on the left renal artery and the left ureter was cannulated. A curved 18-gauge needle connected to polyethylene tubing was placed in the left renal vein for the collection of renal venous blood samples. A curved 24-gauge needle connected to polyethylene tubing was positioned in the left renal artery for the intrarenal infusion of drugs and vehicle.

In each dog, the left renal nerves were prepared for electrical stimulation. All visible nerves leaving the aortico-renal ganglion and entering the kidney were isolated and severed so that the only nerve activity passing to the kidney was evoked by electrical stimulation. It has been shown previously that this technique abolishes the renal vasocostrictor response to splanchnic nerve stimulation (Thames and DiBona, 1979). The distal renal nerve bundle was placed on bipolar platinum electrodes for electrical stimulation. At least 1 hour was allowed for stabilization after the completion of surgery.

Systemic arterial pressure was measured with a pressure transducer (Siatham P23Db) and a direct-writing oscillograph (Beckman Dynograph). At the conclusion of each experiment, the flow probe on the renal artery was calibrated in situ with the dog's own blood. Plasma and urinary sodium concentrations were determined by flame photometry. Arterial hematocrit was estimated by a micromethod. Plasma and urinary inulin concentrations were determined colorimetrically (Fuhr et al., 1955). Glomerular filtration rate was calculated as the clearance of inulin from the plasma.

Blood for plasma renin determination was collected in chilled tubes containing ethylenediaminetetraacetic acid (EDTA) to achieve a final concentration of 1 mg/ml. Plasma renin activity of arterial and renal venous samples was determined by radioimmunoassay for angiotensin I generated after 1 hour of incubation at 37°C (Haber et al., 1969). Renin secretion was calculated as the product of the renal venous-arterial plasma renin activity difference and the renal plasma flow.

In each experiment, two control urine collections (of 10 minutes’ duration) were made; arterial and renal venous blood was sampled between the urine collections for the determination of plasma inulin concentration and plasma renin activity. Then the renal nerves were stimulated (Slick et al., 1975) (1.0 Hz, 10 V, 1.0 msec) and, beginning 5 minutes after the onset of renal nerve stimulation, two experimental urine collections were made (10 minutes each). Blood samples again were obtained between the urine collections. Then the renal nerve stimulation was stopped and, after 30 minutes, two recovery urine collections with blood samples (as described above) were made. The renal α₁- or β₁-adrenoceptors were inhibited by continuous renal arterial infusion of:

- phenolamine (α₁/α₂) 2–10 µg/kg per min, n = 11
- prazosin (α₁) 0.7 µg/kg per min, n = 9
- yohimbine (α₂) 0.46 µg/kg per min, n = 7
- rauwolscine (α₂) 0.50 µg/kg per min, n = 7
- propranolol (β₁/β₂) 0.5 µg/kg per min, n = 4
- atenolol (β₂) 0.5 µg/kg per min, n = 9 and 5.0 µg/kg per min, n = 8.

After a 30-minute equilibration period, the protocol was repeated. In six dogs, isotonic saline vehicle, rather than an α₁-adrenoceptor antagonist, was infused into the renal artery.

In each animal, efficacy of postsynaptic α₁-adrenoceptor with phenolamine or prazosin was assessed by determining their influence on the renal vasocostrictor response to 2 µg of norepinephrine injected into the renal artery. In addition, in the yohimbine- and rauwolscine-treated animals, the renal vasocostrictor response to renal nerve stimulation (2–4 Hz) was also measured before and during drug administration. Nonselective (β₁/β₂) β₁-adrenoceptor blockade with dl-propranolol was verified by the abolition of the renal vasodilator response to 2 µg of isoproterenol injected into the renal artery. Selective β₁-adrenoceptor blockade with atenolol was determined by inhibition of the tachycardia but not the depressor response to the intravenous injection of 2 µg of isoproterenol (Osborn et al., 1981).
Values obtained from periods with two urine collections were averaged. All data were evaluated statistically using the Student's procedure for paired comparisons. The control and recovery period values for each parameter were averaged in each experiment for comparison with the renal nerve stimulation period. The 0.05 level of probability was utilized as the criterion of significance.

**Results**

In six dogs, changes in renal hemodynamics, urinary sodium excretion, and renin secretion rate were evaluated in response to low frequency renal nerve stimulation before and during renal artery infusion of isotonic saline vehicle. As noted in prior studies (Slick et al., 1975; Zambraski et al., 1976, 1976a), renal nerve stimulation similarly decreased urinary sodium excretion and increased renin secretion before and during vehicle infusion (Table 1). The increment in renin secretion rate (i.e., RNS value minus average of control and recovery values) during the first phase was 237 ± 112 ng/min and during the second phase was 485 ± 310 ng/min (P > 0.2). The decrease in urinary sodium excretion during the first phase was 22 ± 8 μEq/min and during the second phase was 28 ± 13 μEq/min (P > 0.5). Renal hemodynamics were not altered by renal nerve stimulation. Renin secretion rate and urinary sodium excretion returned toward control after completion of each period of renal nerve stimulation (Table 1). Thus, consistent changes in renin secretion rate and urinary sodium excretion were evoked by two consecutive renal nerve stimulations.

The effect of renal α (α₁/α₂) adrenoceptor blockade with phentolamine on the renal functional responses to 1.0 Hz renal nerve stimulation was studied in 11 dogs (Fig. 1). The first renal nerve stimulation significantly increased renin secretion rate by 283 ± 61 ng/min and decreased renal nerve stimulation before and during renal artery infusion (RNS) before and during renal artery infusion of phentolamine. RNS significantly increased RSR and decreased UN.V (P < 0.05) without altering AP, RBF, or GFR. During renal nerve stimulation, 1.0 Hz RNS similarly increased RSR (P < 0.05), whereas UN.V remained unchanged. C = Control, R = Recovery.

![Figure 1](https://circres.ahajournals.org/content/53/3/134.f1)

**TABLE 1**

**Responses to Renal Nerve Stimulation before and during Renal Artery Infusion of Isotonic Saline**

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>RNS</th>
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<th>C</th>
<th>RNS</th>
<th>R</th>
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<tbody>
<tr>
<td>MAP* (mm Hg)</td>
<td>134 ± 5</td>
<td>135 ± 5</td>
<td>132 ± 5</td>
<td>128 ± 4</td>
<td>129 ± 4</td>
<td>128 ± 5</td>
</tr>
<tr>
<td>RBF (ml/min)</td>
<td>183 ± 24</td>
<td>178 ± 24</td>
<td>184 ± 21</td>
<td>198 ± 22</td>
<td>210 ± 28</td>
<td>202 ± 22</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>39 ± 2</td>
<td>39 ± 3</td>
<td>39 ± 3</td>
<td>39 ± 3</td>
<td>38 ± 4</td>
<td>40 ± 3</td>
</tr>
<tr>
<td>UN.V (μEq/min)</td>
<td>98 ± 42</td>
<td>86 ± 39†</td>
<td>117 ± 50</td>
<td>119 ± 41</td>
<td>101 ± 37†</td>
<td>141 ± 48</td>
</tr>
<tr>
<td>RSR (ng/min)</td>
<td>61 ± 23</td>
<td>364 ± 176†</td>
<td>194 ± 127</td>
<td>55 ± 31</td>
<td>712 ± 496†</td>
<td>298 ± 349</td>
</tr>
</tbody>
</table>

*MAP = mean arterial pressure, RBF = renal blood flow, GFR = glomerular filtration rate, UN.V = urinary sodium excretion, RSR = renin secretion rate. C = control, RNS = renal nerve stimulation, R = recovery. Data are mean ± SE; n = 6.
† P < 0.05.
similarly increased renin secretion rate (334 ± 54 ng/min), whereas urinary sodium excretion was unchanged (8 ± 5 μEq/min—not significantly different from zero and significantly different from first renal nerve stimulation). Prazosin blocked 94 ± 1% of the renal vasoconstrictor response to 2 μg norepinephrine. In the yohimbine experiments (Fig. 3), the first renal nerve stimulation significantly increased renin secretion by 344 ± 82 ng/min and decreased urinary sodium excretion by 13 ± 4 μEq/min. During renal arterial infusion of yohimbine, renal nerve stimulation similarly increased renin secretion rate (268 ± 59 ng/min) and decreased urinary sodium excretion (26 ± 8 μEq/min). Yohimbine did not affect the renal vasoconstrictor response to either 2 μg norepinephrine or renal nerve stimulation at 2–4 Hz. In the rauwolscine experiments (Fig. 4), the first renal nerve stimulation significantly increased renin secretion rate by 335 ± 119 ng/min and decreased urinary sodium excretion by 23 ± 6 μEq/min. During renal arterial infusion of rauwolscine, renal nerve stimulation similarly increased renin secretion rate (411 ± 134 ng/min) and decreased urinary sodium excretion (31 ± 12 μEq/min). Rauwolscine did not affect the renal vasoconstrictor response to either 2 μg norepinephrine or renal nerve stimulation at 2–4 Hz. Renal hemodynamics remained constant throughout each experiment. These experiments indicate that the renal tubular α-adrenoceptor mediating the increase in renal tubular sodium reabsorption produced by low frequency renal nerve stimulation is α1 and not α2.

The effect of selective renal β1-adrenoceptor blockade with atenolol on the renin secretion and antinatriuretic responses to 1.0 Hz renal nerve stimulation are shown in Figure 5. Before renal β1-adrenoceptor blockade renal nerve stimulation significantly increased renin secretion by 636 ± 249 ng/min. During renal arterial infusion of atenolol at 0.5 μg/kg per min, renal nerve stimulation significantly increased renin secretion by 305 ± 157 ng/min. However, these increases in renin secretion rate were significantly different from each other. In contrast, renal nerve stimulation significantly decreased urinary sodium excretion equally before (−47 ± 12 μEq/min) and during (−37 ± 8 μEq/min) renal arterial infusion of atenolol. Renal hemodynamics and glomerular filtration rate remained unchanged throughout each experiment. Adequacy of β1-adrenoceptor blockade was established by the significantly reduced tachycardia response to intra-
Changes in mean arterial pressure (AP), renal blood flow (RBF), glomerular filtration rate (GFR), and urinary sodium excretion (UNV) and renin secretion rate before and during renal artery infusion of atenolol at 0.5 μg/kg per min. Renal nerve stimulation significantly decreased urinary sodium excretion both before and during renal arterial infusion of d,l-propranolol, and these antinatriuretic responses were not different from each other (−31 ± 5 μEq/min vs. −33 ± 8 μEq/min). In contrast, renal β-adrenoceptor blockade with d,l-propranolol abolished the renin secretion rate response to renal nerve stimulation (237 ± 64 ng/min vs. 29 ± 7 ng/min). Thus, renal β-adrenoceptor blockade with atenolol (β₁) or d,l-propranolol (β₁) decreased or abolished the renin secretion rate responses to renal nerve stimulation without altering the antinatriuretic responses.

Discussion

Activation of the renal sympathetic nerves, either by direct electrical stimulation or by activation of cardiovascular reflexes, may selectively increase renin secretion and/or decrease urinary sodium excretion (Slick et al., 1975; Zambraski and DiBona, 1976; Kopp et al., 1980; Osborn et al., 1981) without changing renal hemodynamics or glomerular filtration rate. The antinatriuretic response results primarily from venous injection of isoproterenol (2 μg) during renal arterial infusion of atenolol at 0.5 μg/kg per min.

Although renal arterial infusion of atenolol at 0.5 μg/kg per min reduced the renin secretion rate response without changing the antinatriuretic response to 1.0 Hz renal nerve stimulation, we wondered whether a higher dose of atenolol would exert a similar differential effect (i.e., further reduce the renin secretion rate response and alter the antinatriuresis). Therefore, changes in renal function during renal nerve stimulation were examined before and during renal arterial infusion of atenolol at 5.0 μg/kg per min (Fig. 6). In eight dogs, this 10-fold higher dose of atenolol abolished the increment in renin secretion rate during renal nerve stimulation (297 ± 98 vs. 24 ± 23 ng/min) without significantly altering the antinatriuretic response (−74 ± 12 vs. −54 ± 17 μEq/min). Again, renal hemodynamics and glomerular filtration rate were unchanged throughout each experiment, and urinary sodium excretion and renin secretion rate returned to control values following each period of renal nerve stimulation.

The effect of nonselective renal β-adrenoceptor blockade (β₁/β₂) on the renin secretion rate and antinatriuretic responses to 1.0 Hz renal nerve stimulation was also evaluated. In four dogs, renal nerve stimulation was performed before and during non-selective renal beta adrenoceptor blockade with d,l-propranolol infused into the renal artery (0.5 μg/kg per min). Renal nerve stimulation significantly decreased urinary sodium excretion both before and during renal arterial infusion of atenolol at 0.5 μg/kg per min. During renal artery atenolol infusion, 1.0 Hz RNS similarly decreased UNV (P < 0.05) and increased RSR by 305 ± 157 ng/min (P < 0.05). These increases in RSR were different from each other (P < 0.05). C = Control, R = Recovery.
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Figure 6. Changes in mean arterial pressure (AP), renal blood flow (RBF), glomerular filtration rate (GFR), urinary sodium excretion (UNV), and renin secretion rate (RSR) in response to 1.0 Hz renal nerve stimulation (RNS) before and during renal artery infusion of a high dose of atenolol (5.0 μg/kg per min). RNS decreased UNV (P < 0.05) and increased RSR by 297 ± 98 ng/mm without altering AP, RBF, or GFR. During high dose atenolol infusion, 1.0 Hz RNS equally decreased UNV (P < 0.05) and increased RSR by 24 ± 23 ng/mm. These increases in RSR were different from each other (P < 0.05). C = Control, R = Recovery.

markedly from increased renal tubular sodium reabsorption located, in part, in the proximal tube (Bello-Reuss et al., 1976) and the loop of Henle (DiBona et al., 1982). The response of renin secretion during 1.0 Hz renal nerve stimulation may have resulted from direct sympathetic adrenergic stimulation of the juxtaglomerular granular cells (Osborn et al., 1981) and/or indirectly from a decreased delivery of sodium chloride to the macula densa region of the distal nephron (Churchill et al., 1978). In the present experiments, we have examined the adrenergic mediation of the antinatriuretic and renin secretion responses to 1.0 Hz renal nerve stimulation and evaluated the role of intrarenal mechanisms mediating renin secretion during low frequency renal nerve stimulation.

Direct electrical stimulation of the renal nerves at 1.0 Hz consistently decreased urinary sodium excretion without changing mean arterial pressure, renal blood flow or glomerular filtration rate (Figs. 1–6). Competitive presynaptic/postsynaptic (α1/α2) α-adrenoceptor blockade with phentolamine (Fig. 1) or postsynaptic (α1) α-adrenoceptor blockade with prazosin (Fig. 2) abolished the antinatriuretic responses to 1.0 Hz renal nerve stimulation, whereas α2-adrenoceptor blockade with either yohimbine (Fig. 3) or rauwolscine (Fig. 4) was without effects. These results indicate that increased renal tubular sodium reabsorption evoked by low frequency renal nerve stimulation is mediated by stimulation of postsynaptic α1-adrenoceptors located on the renal tubules; α2-adrenoceptors are not involved.

These observations are consistent with previous reports that antinatriuretic responses to direct electrical renal nerve stimulation at low frequencies (Zambraski et al., 1976a) and reflex activation of sympathetic nerve activity (Zambraski et al., 1976b) were prevented by noncompetitive α1/α2 adrenoceptor blockade with phenoxybenzamine. Others, however, have suggested that β-adrenoceptors may participate in catecholamine induced changes in renal tubular function. In isolated perfused proximal convoluted tubule segments, Bello-Reuss (1980) reported that fluid absorption was stimulated by norepinephrine and isoproterenol and that this increased fluid absorption was prevented by β-adrenoceptor blockade with propranolol but not by α-adrenoceptor blockade with phentolamine. Besarab et al. (1977) demonstrated in isolated perfused rat kidneys that antinatriuretic responses to norepinephrine were prevented by β-adrenoceptor blockade with propranolol but not by α-blockade with phenoxybenzamine. Thus, pharmacologic studies conducted in vitro have implicated a β-adrenoceptor mechanism mediating tubular sodium reabsorption. In view of this in vitro evidence suggesting a potential role for β-adrenoceptor mediation of renal tubular sodium reabsorption during humoral adrenergic stimulation with native and non-native catecholamines, we wondered whether a similar β-adrenoceptor response would be evoked in vivo during renal nerve stimulation.

Our studies evaluated β-adrenoceptor mediated tubular sodium reabsorption in vivo using low frequency renal nerve stimulation (1.0 Hz). Antinatriuretic responses to 1.0 Hz renal nerve stimulation were not altered by renal beta adrenoceptor blockade with d,l-propranolol, or atenolol (Figs. 5 and 6). Taken together with the results utilizing renal α-adrenoceptor blockade with phentolamine prazosin, yohimbine, and rauwolscine, these data demonstrate that, in vivo, antinatriuresis during 1.0 Hz renal nerve stimulation (which presumably represents a physiological stimulus for increased renal tubular sodium reabsorption) is mediated by postsynaptic α1-adrenoceptor activation and not by renal α2- or β1- or β2-adrenoceptors.

In addition to the antinatriuresis, 1.0 Hz renal nerve stimulation increases renin secretion (Zambraski and DiBona, 1976; Kopp et al., 1980). This response of renin secretion may result directly from stimulation of adrenoceptors on the juxtaglomerular granular cells (Kopp et al., 1980; Osborn et al., 1981).
or indirectly from stimulation of the tubular macula densa receptor mechanisms (Churchill et al., 1978) which senses a decreased delivery of sodium chloride from more proximal nephron segments. We have investigated the mechanism of the renin secretion response to 1.0 Hz renal nerve stimulation using renal \( \alpha \) (phenolamine and prazosin) and \( \beta \) (d,l-propranolol and atenolol) adrenoceptor blockade. Renal \( \alpha \)-adrenoceptor blockade with phenolamine (\( \alpha_1/\alpha_2 \)) prazosin (\( \alpha_1 \)), yohimbine (\( \alpha_2 \)), and rauwolfscine (\( \alpha_2 \)) had no effect on renin secretion elicited by 1.0 Hz renal nerve stimulation, although the antinatriuretic response was abolished by phenolamine and prazosin but not by yohimbine or rauwolfscine (Figs. 1–4). In contrast, renal \( \beta \)-adrenoceptor blockade with d,l-propranolol and atenolol significantly decreased or abolished the renin secretion responses to 1.0 Hz renal nerve stimulation without changing the antinatriuretic responses (Figs. 5 and 6). These results indicate that unlike the antinatriuretic response, renin secretion elicited by 1.0 Hz renal nerve stimulation is mediated by renal \( \beta \)-adrenoceptors and not by \( \alpha_1 \)- or \( \alpha_2 \)-adrenoceptors.

Other in vivo and in vitro studies using \( \alpha \)-adrenoceptor agonists and antagonists have suggested that \( \alpha \)-adrenoceptors increase (Powis and Donald, 1979; Blair, 1981; Blair, 1983) or decrease (Pettinger et al., 1976) renin secretion. Recently, we have reported that 0.5 Hz renal nerve stimulation increases renin secretion without changing mean arterial pressure, renal blood flow, glomerular filtration rate, or urinary sodium excretion (Osborn et al., 1981, 1982). The renin secretion response to this frequency of renal nerve stimulation was prevented by renal \( \beta \)-adrenoceptor blockade with atenolol but was unaltered by renal \( \beta_2 \)-adrenoceptor blockade with butoxamine (Osborn et al., 1981) or by \( \alpha \)-adrenoceptor blockade with phenolamine (\( \alpha_1/\alpha_2 \)) or prazosin (\( \alpha_1 \); Osborn et al., 1982). The present data utilizing 1.0 Hz renal nerve stimulation are in agreement with these previous findings, and the results indicate that renin secretion responses to frequencies of renal nerve stimulation which do not change renal blood flow or glomerular filtration rate (i.e., 0.5 or 1.0 Hz) are mediated by renal \( \beta \)-adrenoceptors and not by renal \( \alpha \)-adrenoceptors.

The results of the present study also demonstrate that after renal \( \alpha \)- and \( \beta \)-adrenoceptor blockade, the antinatriuretic responses to 1.0 Hz renal nerve stimulation are dissociated from the renin secretion responses. Renal \( \alpha_1 \)-adrenoceptor blockade prevented the antinatriuretic but not renin secretion responses to 1.0 Hz renal nerve stimulation, whereas renal \( \beta \)-adrenoceptor blockade decreased or abolished renin secretion responses but did not alter the antinatriuretic responses. These observations suggest that the renin secretion response to 1.0 Hz renal nerve stimulation is evoked by \( \beta \)-adrenoceptor activation of the juxtaglomerular granular cells and not by a macula densa receptor mechanism sensing decreased sodium chloride delivery to the distal nephron. Renal artery methoxamine (\( \alpha \)-adrenoceptor agonist) infusion at doses that do not change renal blood flow or glomerular filtration rate but significantly decrease urinary sodium excretion (i.e., doses which are functionally similar to 1.0 Hz renal nerve stimulation) have no effect on renin secretion rate (Osborn et al., 1982). These observations, taken together with those of the present study which demonstrate a dissociation of antinatriuretic and renin secretion responses to 1.0 Hz renal nerve stimulation, indicate that renal \( \alpha \)-adrenoceptor activation at levels which elicit antinatriuresis (i.e., increase renal tubular sodium reabsorption) have no measureable effect on renin secretion via indirect activation of the tubular macula densa receptor mechanism.

Higher frequencies of renal nerve stimulation (2.0 Hz and greater) elicit intense renal vasoconstriction (\( \alpha \)-adrenoceptor mediated), antinatriuresis, and large increases in renin secretion (Coote et al., 1972; Kopp et al., 1981). Under these circumstances, the renin secretion response to renal nerve stimulation may be produced, at least in part, by vascular \( \alpha \)-adrenoceptor activation since renal \( \alpha \)-adrenoceptor blockade inhibits the renal vasoconstrictor, as well as the renin secretion, response. Furthermore, we have shown that renal \( \alpha \)-adrenoceptor stimulation by infusion of methoxamine into the renal artery at doses which decrease renal blood flow, glomerular filtration rate and urinary sodium secretion (i.e., functionally similar to 2.0 Hz renal nerve stimulation) also increase renin secretion (Osborn et al., 1982). The present findings, however, are consistent with the view that low frequency stimulation of the renal nerves (1.0 Hz) decreases urinary sodium excretion by renal tubular \( \alpha_1 \)-adrenoceptor activation and increases renin secretion by activation of \( \beta_1 \)-adrenoceptors on the juxtaglomerular granular cells.

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