Intrarenal Site of Action of Calcium on Renin Secretion in Dogs

BARRY E. WATKINS, PH.D., JAMES O. DAVIS, M.D., PH.D.
THOMAS E. LOHMEIER, PH.D., AND RONALD H. FREEMAN, PH.D.

SUMMARY We studied the effects of intrarenal calcium infusion on renin secretion in sodium-depleted dogs in an attempt to elucidate the major site of calcium-induced inhibition of renin release. Both calcium chloride and calcium gluconate reduced renal blood flow and renin secretion while renal perfusion pressure was unchanged. These data indicate that calcium inhibition of renin secretion did not occur primarily at the renal vascular receptor; decreased renal blood flow is usually associated with increased renin secretion. Calcium chloride infusion increased urinary chloride excretion without affecting sodium excretion, and calcium gluconate failed to increase either sodium or chloride excretion. Also, the filtered loads of sodium and chloride were unchanged during the calcium infusions. These results give no indication that calcium inhibited renin secretion by increasing the sodium or chloride load at the macula densa. The effects of intrarenal calcium infusion on renin release were also assessed in dogs with a nonfiltering kidney in which renal tubular mechanisms could not influence renin secretion. The observation that calcium still suppressed renin release in these dogs provides additional evidence that the major effect of calcium involved nontubular mechanisms. Thus, it appears likely that calcium acted directly on the juxtaglomerular cells to inhibit renin secretion.

The present study was conducted to determine the intrarenal site of action of calcium to suppress renin secretion. The effects of intrarenal calcium infusion on renal hemodynamics and electrolyte excretion were evaluated in an attempt to determine whether the primary renin inhibition occurred at a renal vascular or tubular site or in the juxtaglomerular cells. Also, calcium was infused intrarenally into dogs with a nonfiltering kidney in which tubular control of renin secretion had been eliminated.

Methods

Twenty-three experiments were conducted on 15 female hounds weighing 19.0 ± 1.5 (SEM) kg; range, 14–23 kg. To augment the rate of renin secretion, the dogs were sodium-depleted before the acute experiment. The dogs were fed a low sodium diet containing less than 5 mEq of sodium per day (Riviana Foods) and given intramuscular injections of metaraminol (Mercuhydrin), 2 ml, on days 2 and 3 before the experiment. The average net loss of sodium was 138 ± 12 mEq as determined from the daily sodium balance measurements.

On the morning of the acute experiment each dog was
anesthetized with intravenous sodium pentobarbital (30 mg/kg). Catheters were placed in a femoral artery and vein for measuring arterial blood pressure and collection of blood samples. Arterial pressure was recorded on a Statham model 7700 recorder in series with a Statham model P23Db pressure transducer. The left kidney was then exposed by retroperitoneal blunt dissection from a flank incision to assure the presence of a single renal artery. Following such confirmation, the right kidney was excised through a contralateral flank approach. If the left kidney had a double renal artery, the right kidney was used and the left kidney removed. A polyethylene catheter (PE 90) was inserted into the ureter to collect urine samples for determination of creatinine and urinary electrolyte excretion. An electromagnetic flow probe (Carolina Medical Electronics) was placed around the renal artery near its origin at the aorta for measurement of renal blood flow as displayed on a Statham model 7700 recorder. After placement of the flow probe, a 25-gauge needle was inserted into the renal artery for the intrarenal infusions. Renal venous blood samples were withdrawn through an 18-gauge needle connected to a length of Silastic tubing which was inserted into the renal vein so that the needle tip rested near the hilus.

The dogs were left undisturbed for 60 minutes after completion of the surgical preparation while heparinized saline was infused intravenously at 0.59 ml/min. In several experiments a priming solution coupled with a sustaining infusion of creatinine (36 mg/ml at 0.59 ml/min) was also given intravenously during this time. Following 60 minutes of equilibration, urine was collected during two consecutive 15-minute control renal clearance periods. Blood samples for plasma creatinine were obtained at the midpoint of each collection period. Creatinine was determined by colorimetry, and urinary sodium and potassium were measured by flame photometry. Chloride was analyzed with a chloridometer and calcium was measured on an atomic absorption-emission spectrophotometer. At the end of each period, peripheral and renal venous blood samples were obtained for determination of plasma electrolytes by the methods just described and of plasma renin activity (PRA) by a bioassay technique.4 Processing of plasma samples for determination of PRA included 22 hours of dialysis through cellulose tubing with pores less than 4.8 nm in diameter. Materials with a molecular weight greater than 12,000 are retained and molecules with a weight lower than proteins are dialyzed out and cannot influence the bioassay. Renin secretion was calculated as the product of renal plasma flow and the difference between renal venous and peripheral PRA. In all instances equal volumes of donor blood were transfused to replace blood removed for sampling. After the second control period, calcium was infused intravenously for 45 minutes at a dose of 0.25 mg/kg per min. Calcium was administered as calcium chloride or calcium gluconate in saline and infused at a rate of 0.59 ml/min. During the 45 minutes of calcium infusion, three consecutive 15-minute renal clearance periods were obtained and at the midpoint of each period blood was drawn for measurement of plasma creatinine. Following the infusion of calcium, intrarenal saline infusion at 0.59 ml/min was resumed for 45 minutes to allow the dogs to recover from the effects of calcium infusion. Samples were then collected during two 15-minute periods for measurement of creatinin and PRA. An equivalent dose of the other calcium compound was then infused intravenously for 45 minutes with three additional 15-minute periods for determinations of creatinine and PRA. Following this second experimental infusion, intrarenal saline was given for 45 minutes. At the end of this recovery interval, final sample collections were made for two 15-minute periods. In this series of experiments, five dogs received calcium chloride first and calcium gluconate as the second infusion. The remaining three dogs were given calcium gluconate before calcium chloride.

In an additional group of seven dogs, the left kidney was made nonfiltering under sterile conditions by the method of Blaine et al.6 As in the first series of animals, the dogs were sodium-depleted by maintenance on the low sodium diet and by daily intramuscular injections of 2 ml of Mercuhydrin at 24 and 48 hours after production of the nonfiltering kidney; the net loss of sodium was 144 ± 5 mEq, which was essentially the same as in the dogs with intact kidneys. The acute experiment was performed 48 hours after the last injection of the diuretic. In these studies, 2 hours of equilibration were allowed after excision of the intact kidney and the surgical procedure in preparation for measurement of renin secretion in the nonfiltering kidney. The experimental design in these studies was the same as described for the dogs with an intact kidney, with the exception that only one 45-minute experimental infusion of calcium chloride was used. The dose of calcium chloride for intrarenal infusion in the dogs with a nonfiltering kidney was calculated to produce the same increase in renal venous calcium concentration as occurred in dogs with a filtering kidney. Thus, the dose of calcium chloride was decreased in proportion to the measured suppression of renal blood flow in the dogs with a nonfiltering kidney compared to that in dogs with a filtering kidney. At the end of each experiment Lissamine green dye was injected into the aorta above the kidney and the surface renal tubules were viewed with a dissecting binocular to determine the absence of glomerular filtration. The existence of a nonfiltering kidney was verified by failure of the dye to appear in the renal tubules.

Data on all experiments were analyzed by use of the Student's paired t-test, critical to a 5% significance level. Between-experiment analysis was accomplished using Student's t-test for group comparisons.

Results

EFFECTS OF INTRARENAL CALCIUM CHLORIDE INFUSION IN DOGS WITH AN INTACT KIDNEY

The intrarenal infusion of calcium chloride at 0.25 mg Ca++/kg per min resulted in slight reduction of renal blood flow at 30 and 45 minutes (Fig. 1). Renal blood flow was still suppressed during the two recovery periods at 60 and 75 minutes after the end of calcium chloride infusion. Renin secretion was reduced significantly from the control
CALCIUM ON RENIN SECRETION/Watkins et al.

Effects of intrarenal calcium chloride infusion (shaded bars) on renal blood flow and renin secretion in dogs with a filtering kidney. Bars indicate mean values ± SEM.

Level during the first and third experimental periods, but returned to the control value by the time the recovery measurements were made.

Intrarenal calcium chloride infusion did not alter peripheral plasma or renal venous plasma concentrations of sodium or potassium. However, the calcium infusion induced hypercalcemia by 1.7–2.9 mEq/liter in peripheral plasma and by 2.3–4.6 mEq/liter in renal venous plasma (group I, Table 1). Plasma calcium concentration remained elevated slightly during the recovery periods at 60 and 75 minutes after cessation of calcium infusion. The slightly elevated control values for calcium of 4.9 and 5.2 mEq/liter for peripheral and renal venous plasma, respectively, in group I (Table 1) are the result of the prior infusion of calcium gluconate in three of the eight dogs. This slight elevation is evident by comparison of the control values in groups I and II (Table 1); in group II the control values of 4.6 and 4.6 mEq/liter were obtained before infusion of calcium chloride as the first calcium infusion. Similarly, calcium chloride infusion elevated peripheral plasma calcium concentration from 113.3 ± 1.9 mEq/liter to 115.3 ± 2.1 mEq/liter, while raising renal venous chloride concentration from the control level of 115.2 ± 1.4 to an average of 117.8 ± 1.4 mEq/liter. However, both peripheral and renal venous plasma chloride concentrations had returned to control levels when measured during the subsequent recovery periods.

Creatinine clearance was measured in four of the eight dogs in this series but it did not change significantly. The intrarenal infusion of calcium chloride did not alter the rate of the renal excretion of water or sodium (Fig. 2). However, calcium chloride did produce a transient slight kaliuresis, significant only during the first 15-minute interval when potassium excretion was 40.7 ± 7.6 μEq/min compared to a control value of 29.4 ± 6.3 μEq/min. Calcium chloride increased urinary calcium excretion slightly throughout the experimental period (Fig. 2). Urinary chloride excretion also increased slightly from a control level of 8.4 ± 3.0 μEq/min to 18.3 ± 6.8 μEq/min during calcium chloride infusion. In addition, chloride excretion remained higher than control during the recovery phase. Mean arterial pressure was stable at 140 ± 3 mm Hg until after the end of the calcium chloride infusion, when a slight decrease to 132 ± 5 mm Hg occurred during the final recovery measurements. Hematocrit also decreased from the control level of 53.1 ± 1.7% to an average of 51.5 ± 1.4% (P < 0.05) during the infusion of calcium chloride.

EFFECTS OF INTRARENAL CALCIUM GLUCONATE INFUSION IN DOGS WITH AN INTACT KIDNEY

The intrarenal infusion of calcium gluconate (0.25 mg Ca/kg per min) in eight dogs produced a progressive reduction of renal blood flow (Fig. 3). The low rate of renal

Table 1 Effects of Intrarenal Calcium Infusion on Plasma Calcium Concentrations in Dogs with an Intact Kidney

<table>
<thead>
<tr>
<th>Groups</th>
<th>Control</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Calcium chloride (n = 8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral plasma</td>
<td>4.9 ± 0.3</td>
<td>6.6 ± 0.8</td>
<td>6.8 ± 0.6</td>
<td>7.8 ± 0.7</td>
<td>6.0 ± 0.3</td>
</tr>
<tr>
<td>Renal venous plasma</td>
<td>5.2 ± 0.3</td>
<td>7.5 ± 0.6</td>
<td>8.7 ± 0.6</td>
<td>9.8 ± 0.9</td>
<td>5.6 ± 0.4</td>
</tr>
<tr>
<td>II. Calcium chloride (administered first; n = 5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral plasma</td>
<td>4.6 ± 0.2</td>
<td>5.4 ± 0.4</td>
<td>6.5 ± 0.6</td>
<td>7.0 ± 0.8</td>
<td>5.4 ± 0.2</td>
</tr>
<tr>
<td>Renal venous plasma</td>
<td>4.6 ± 0.2</td>
<td>7.8 ± 0.8</td>
<td>8.2 ± 0.8</td>
<td>9.0 ± 0.9</td>
<td>5.9 ± 0.3</td>
</tr>
<tr>
<td>III. Calcium gluconate (n = 8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral plasma</td>
<td>5.3 ± 0.2</td>
<td>7.0 ± 0.4</td>
<td>7.8 ± 0.5</td>
<td>8.2 ± 0.6</td>
<td>6.3 ± 0.1</td>
</tr>
<tr>
<td>Renal venous plasma</td>
<td>5.4 ± 0.3</td>
<td>8.3 ± 0.9</td>
<td>11.0 ± 1.4</td>
<td>11.7 ± 1.3</td>
<td>6.3 ± 0.3</td>
</tr>
<tr>
<td>IV. Calcium gluconate (administered first; n = 3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral plasma</td>
<td>4.5 ± 0.3</td>
<td>6.0 ± 1.1</td>
<td>7.2 ± 0.3</td>
<td>7.0 ± 1.4</td>
<td>5.7 ± 0.2</td>
</tr>
<tr>
<td>Renal venous plasma</td>
<td>4.6 ± 0.4</td>
<td>7.5 ± 0.3</td>
<td>8.5 ± 0.8</td>
<td>11.5 ± 2.8</td>
<td>5.6 ± 0.4</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM.
Calcium gluconate infusion did not alter the concentrations of sodium, potassium, or chloride in peripheral plasma or in renal venous plasma. However, the calcium concentration in peripheral plasma increased by 1.7–2.9 mEq/liter compared to the preinfusion control level (group III, Table 1). Similarly, calcium gluconate infusion increased renal venous calcium concentration by 2.9–6.3 mEq/liter above the control level. Also, plasma calcium concentration was still elevated slightly during the two recovery measurements made at 60 and 75 minutes after the end of calcium gluconate infusion (Table 1). The slightly elevated control levels of calcium of 5.3 and 5.4 mEq/liter for peripheral and renal venous calcium concentration in group III (Table 1) are due to the prior infusion of calcium chloride in five dogs. This slight elevation is evident by comparison of the control values in groups III and IV; in group IV the control values of 4.5 and 4.6 mEq/liter \( (n = 3) \) were obtained before infusion of calcium gluconate as the first calcium infusion.

Although intrarenal calcium gluconate infusion did not alter significantly creatinine clearance \( (n = 4) \), data in Figure 4 show that it did produce a slight increase in urine output and in renal calcium excretion; also, renal potassium excretion increased from 25 to 43 μEq/min. However, calcium infusion did not influence significantly urinary sodium or chloride excretion. In addition, calcium gluconate infusion did not alter mean arterial blood pressure. Venous hematocrit (control = 53.8 ± 1.3%) tended to decrease throughout the length of the experiment and the change was significant at the end of the third experimental period at 52.4 ± 1.2%.
EFFECTS OF INTRARENAL CALCIUM CHLORIDE INFUSION IN DOGS WITH A NONFILTERING KIDNEY

In the series of seven dogs with nonfiltering kidneys, mean control renal blood flow was 127 ± 17 ml/min (Fig. 5) or 56% of the 225 ± 25 ml/min observed in dogs with an intact kidney prior to calcium chloride infusion. These dogs with nonfiltering kidneys were therefore given an intrarenal calcium chloride infusion at 0.14 ± 0.018 mg Ca++/kg per min to produce a renal venous plasma level of calcium equivalent to that in experiments I and II. Data in Figure 5 show that calcium chloride infusion decreased renal blood flow in dogs with a nonfiltering kidney by 30 minutes and renal blood flow returned toward the control level by 60 and 75 minutes after the cessation of calcium infusion. The dogs with a nonfiltering kidney showed 50% reduction in renin secretion during the last 30 minutes of calcium infusion, and renin secretion remained suppressed during the subsequent recovery periods (Fig. 5).

This series of dogs exhibited progressive hyperkalemia in both peripheral and renal venous plasma, with an increase from a control level of 4.3 ± 0.2 to 5.0 ± 0.2 mEq/liter by the time final recovery samples were obtained (Table 2). Calcium chloride did not affect sodium concentrations in peripheral or in renal venous plasma (Table 2). Calcium chloride infusion increased calcium concentration in both peripheral and renal venous plasma (Table 2). The plasma concentration of both peripheral and renal venous calcium was still greater than the control level during recovery observations at 60 and 75 minutes after the end of calcium chloride infusion. Calcium chloride infusion did not significantly elevate peripheral or renal venous plasma chloride concentrations, or alter mean arterial pressure or hematocrit.

Discussion

The present experiments with sodium-depleted dogs have demonstrated that intrarenal infusion of calcium salts suppressed renin secretion. These findings extend the results from prior reports that intrarenal calcium chloride (0.3 mg/kg per min) decreased renal venous PRA in normal dogs during mannitol diuresis. Similarly, results from the current study corroborate those of Maull et al. which showed that intrarenal calcium gluconate infusion (0.3 mg/kg per min) decreased renal venous PRA. However, the present data are in disagreement with the report of Iwao et al. to the effect that intrarenal calcium chloride infusion (14 mg Ca++/min) increased renin secretion. The explanation for this discrepancy might be due to the dose of calcium employed or to the fact that four of the five dogs studied by Iwao's group had low control renal venous PRA levels which made it difficult to detect calcium-induced inhibition of renin secretion. The observation of decreased renin secretion regardless of the anionic species infused supports the concept that calcium is the agent primarily responsible for inhibiting renin secretion.

The main objective of the present study was to determine the intrarenal site of action of calcium to decrease renin release during hypercalcemia. The work of others on intact dogs and rats has failed to elucidate the mechanisms involved. In the intact dog, the effects of calcium might be mediated through the renal vascular receptor, the macula densa, or both, and, of course, a direct action on the renal vasculature and juxtaglomerular cells is possible.

In the present experiments calcium failed to influence renal perfusion pressure, therefore an alteration in stretch of the renal afferent arteriole and activation of the renal vascular receptor seems unlikely. The present finding that calcium reduced renal blood flow confirms the earlier report that an intrarenal calcium infusion increased renal vascular resistance. It seems unlikely, therefore, that this change in renal blood flow decreased renin release, since renal ischemia usually is associated with increased renin secretion. It is noteworthy that calcium reduced renal blood flow without influencing creatinine clearance so that filtration fraction was increased; under these circumstances the increase in renal resistance might result primarily from increased efferent arteriolar constriction. However, it should be pointed out also that a decrease in efferent arteriolar constriction conceivably could have occurred and decreased renin release through the vascular receptor mechanism if an overriding constriction in the efferent arteriole occurred to produce a net increase in renal vascular resistance.

Studies of the dogs with an intact kidney provided data on a possible macula densa mechanism for the decrease in renin release. Calcium loading has been reported to increase renal sodium excretion, and an increase in the load of sodium at the macula densa must be considered as a possible action of calcium to decrease renin secretion. This idea is consistent with the report of Kotchen et al. that intrarenal calcium infusion in dogs increased renal sodium excretion and increased renin secretion. However, in the present study calcium infusion failed to alter sodium excretion during either calcium chloride or calcium gluconate infusion. It is noteworthy that the peripheral plasma levels of calcium achieved in the present study were
slightly higher than those observed by Kotchen et al.,10 no renal venous levels of calcium were reported by the Kotchen group. Also, neither plasma sodium concentration nor creatinine clearance was altered, therefore an increase in the filtered load of sodium failed to occur. Consequently, the present data provide no support for the idea that increased sodium load activated the macula densa to inhibit renin release during hypercalcemia.

However, another possibility must be considered whereby calcium might influence the macula densa. Suki et al.4 suggested that calcium inhibits sodium reabsorption from the thick ascending limb of Henle. Such impairment of the renal tubular reabsorptive mechanism for sodium might increase the sodium load at the macula densa. The lack of an observed natriuresis in the current study might then be explained by enhanced distal tubular sodium reabsorption mediated by a high plasma level of aldosterone which is known to occur in sodium-depleted dogs.13 Under these conditions, a local increase in renal tubular load of sodium at the macula densa could decrease renin release.

It has been suggested recently that both sodium and chloride ions or chloride ions alone within the early distal renal tubule are capable of affecting the macula densa receptor.7, 13 Also, recent evidence has revealed that chloride rather than sodium is actively transported in the thick ascending limb of the loop of Henle. Therefore, the influence of calcium on the chloride load and its effect at the macula densa must be considered. In the present study, however, renin secretion was reduced during the calcium gluconate infusion while filtered load of chloride was unaffected; plasma chloride concentration and creatinine clearance was unchanged. This finding and the lack of chloriuresis during calcium gluconate infusion in the current study makes this explanation unlikely.

It was shown by Shade et al.8 that intrarenal potassium infusion increased potassium excretion and decreased renin secretion in dogs. Their findings revealed that the action of potassium was dependent on an intact renal tubular system, since the inhibitory effect was not present in dogs with a nonfiltering kidney. Calcium infusion invariably produced a slight increase in potassium excretion in the present experiments in dogs with an intact kidney, but since the calcium response occurred in dogs with a nonfiltering kidney this possible mechanism can also be excluded.

Recently it has been suggested that the calcium ion is essential for the feedback signal from the macula densa to regulate single-nephron glomerular filtration rate.14, 15 By use of micropuncture techniques, these investigators concluded that distal tubular perfusates require the calcium ion to reduce glomerular capillary hydrostatic pressure and single-nephron glomerular filtration rate. In our current study, calcium infusion failed to alter creatinine clearance; the nature of the present data is such that it does not allow for evaluation of the necessity of the presence of calcium for activation of the macula densa.

The series of experiments involving calcium chloride infusion into dogs with a nonfiltering kidney was designed to provide another approach for elucidation of the mechanism of calcium action. Production of the nonfiltering kidney model has been shown to eliminate the macula densa mechanism for renin release.9, 16, 17 Absence of glomerular filtration in this series of dogs was verified by the lack of appearance of Lissamine dye in the superficial renal tubules. Further evidence that the procedure used produced a nonfiltering kidney was reported by Johnson et al.,18 who showed that creatinine clearance after reopening the ureter was only 2.2 ml/min compared to a normal value of 46 ± 4 ml/min. Thus, destruction of macula densa function in dogs with a nonfiltering kidney allows assessment of the effect of intrarenal calcium chloride on renin secretion as mediated solely by nontubular mechanisms. It also might be noted that the progressive hyperkalemia occurring in the dogs with nonfiltering kidneys did not affect renin secretion, since Shade et al.8 demonstrated that intrarenal potassium infusion did not reduce renin secretion in such dogs. In our current study the similarity of the responses to calcium in dogs with filtering kidneys and dogs with nonfiltering kidneys suggests that a direct action of calcium at the macula densa is not important in the control of renin secretion.

Another possibility which might be considered is that calcium in some way depressed the adrenergic nervous system so that decreased renin release occurred. A re-
spontaneously could be mediated through the adrenal catecholamines or the renal nerves although there is no direct evidence supportive of either idea. It seems unlikely that prostaglandins are involved, since Hedqvist\(^\text{19}\) has reported that an increased calcium concentration reversed the inhibitory effect of prostaglandin E\(_2\) on norepinephrine release in an in vitro system. It should be emphasized that the increments in the peripheral plasma level of calcium in the present study were considerably less than for the increases in renal venous plasma calcium. Also, from our knowledge of the role of calcium in catecholamine release from the adrenal medulla, hypercalcemia would be expected to increase rather than decrease adrenal medullary secretion.\(^\text{20}\) Indeed, organ perfusion studies have revealed that a high calcium concentration increased the rate of catecholamine release from cat adrenal glands.\(^\text{22}\) Thus, it seems unlikely that a decrease in function of the adrennergic nervous system produced the decrease in renin secretion during hypercalcemia.

Our current findings of reduced renin secretion during calcium infusion into dogs with a nonfiltering kidney probably reflect an effect of calcium at the vascular component of the juxtaglomerular apparatus. Specifically, it appears that the inhibition occurred either in the vascular smooth muscle receptor itself or directly in the juxtaglomerular cells. As was previously discussed, it is unlikely that calcium acted on the renal vascular receptor, since the cation reduced renal blood flow which reflects an increase in vascular smooth muscle tone. By exclusion, therefore, calcium probably produced its effect on renin secretion primarily by a direct action on the juxtaglomerular cells.

The precise intracellular mechanism of renin secretion by juxtaglomerular cells is unknown. However, it has been suggested that granules containing renin undergo exocytosis on fusion with the plasma membrane.\(^\text{23}\) Thus, it is possible that renin secretion depends on the prevailing membrane characteristics of juxtaglomerular cells. It has been demonstrated that increased extracellular calcium concentration stabilizes nerve and muscle fibers by decreasing sodium and potassium permeability and by raising the depolarization threshold for action potential initiation.\(^\text{24}\) These observations open the possibility that hypercalcemia might inhibit renin secretion by stabilizing the juxtaglomerular cell membrane. Data from the current experiments are compatible with this concept because they show that intrarenal calcium infusion consistently inhibited renin secretion.

## References

Intrarenal site of action of calcium on renin secretion in dogs.
B E Watkins, J O Davis, T E Lohmeier and R H Freeman

Circ Res. 1976;39:847-853
doi: 10.1161/01.RES.39.6.847
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1976 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/39/6/847