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Research Article

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ABSTRACT To evaluate the effect of Ca^{++} on renin release, plasma renin activity (PRA) was measured after acute and chronic Ca^{++} administration. 1% $CaCl_2$ was infused into one renal artery of 10 anesthetized dogs (0.3 mg/kg/min). The excreted fraction of filtered calcium ($EF_{Ca^{++}}$) and EF_{Na^+} from the infused kidney were elevated ($P < 0.04$) during three successive 15-min infusion periods. Serum calcium concentration was significantly elevated ($P < 0.001$). Creatinine clearance, systemic arterial pressure, and renal blood flow did not change ($P > 0.10$). Compared to control (45 ng/ml/h±5.2 SE), renal venous PRA was suppressed ($P < 0.0001$) after infusion of Ca^{++} for 15, 30, and 45 min (20 ng/ml/h±4.6, 16 ng/ml/h±4.0, and 13 ng/ml/h ±2.7, respectively). 15 and 30-min after infusion, PRA did not differ from control ($P > 0.20$). Chronic Ca^{++} loading was achieved in Sprague-Dawley rats by replacing drinking water with 1% $CaCl_2$ for 17 days. At sacrifice, serum Ca^{++}, Na^+, and K^+ of controls ($n = 12$) did not differ ($P > 0.60$) from Ca^{++}-loaded rats ($n = 12$). Ca^{++} excretion (467 μeq/24 h±51) was elevated ($P < 0.001$) compared to controls (85 μeq/24 h±12). PRA (8.6 ng/ml/h±1.4) and renal renin content of Ca^{++}-loaded rats did not differ from controls ($P > 0.80$). However, after 8 days of sodium deprivation, both PRA and renal renin content of calcium-loaded animals were significantly lower than the respective values in pair-fed controls ($P < 0.005$). During the period of sodium deprivation, calcium-drinking animals were in greater negative sodium balance than controls ($P < 0.005$). The data are consistent with the hypothesis that acute and chronic calcium administration inhibit renin secretion.

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INTRODUCTION

Sodium load within the macula densa and pressure or stretch in the renal afferent arteriole are two well-studied factors involved in the regulation of renin secretion (1). Recently, it has been demonstrated that potassium balance also affects renin release (2–6), possibly by altering the load of filtered sodium presented to the distal segment of the nephron (7–9). Acute calcium infusion in the dog decreases the fraction of filtered sodium reabsorbed and results in a natruresis (10). Furthermore, during acute hypercalcemia in the dog, Suki, Eknoyan, Rector, and Seldin demonstrated decreased sodium reabsorption in the ascending limb of the loop of Henle (11). Consequently, the acute infusion of calcium not only results in increased sodium excretion, but also increases the amount of filtered sodium presented to the distal segment of the nephron. If potassium-induced renin inhibition were mediated by an effect on proximal sodium reabsorption, calcium infusion might likewise be expected to inhibit renin secretion. To evaluate this hypothesis, a series of experiments was undertaken to measure the in vivo effects of acute and chronic calcium administration on renin activity. In the acute studies, calcium chloride was infused directly into the renal artery of anesthetized dogs. Chronic calcium loading in the rat was achieved by the administration of a high calcium intake. Additionally, in the rat, the effect of chronic dietary calcium loading on the renin response to sodium deprivation was evaluated.

METHODS

For the acute calcium infusion studies, 10 male mongrel dogs, weighing between 11.6 and 21.4 kg (mean, 17.8 kg ±3.8 SD), were anesthetized with sodium pentathol (30 mg/kg). When necessary, animals were titrated with additional smaller doses of pentathol to maintain adequate anesthesia. A 26-gauge butterfly needle was inserted directly

into a single renal artery. To obtain renal venous blood, the ipsilateral renal vein was also cannulated with a 26-gauge butterfly needle. A femoral artery was cannulated with PE 8F polyethylene tubing, connected to a Statham transducer (Statham Instruments, Inc., Oxnard, Calif.) and a Sanborn model #296 recorder (Hewlett-Packard Co., Waltham Div., Waltham, Mass.) for the measurement of systemic arterial pressure. Both ureters were cannulated separately for the collection of urine from each kidney. In five studies, an electromagnetic flow probe was clamped around the cannulated renal artery, distal to the infusion site, for the measurement of renal blood flow.

After completion of these surgical procedures, a 45-min equilibration period was allowed before beginning the actual experiment. During this period, a 5% mannitol infusion was begun and continued throughout the duration of the experiment to maintain a total urine output of 0.5 ml/min. Normal saline was infused into the cannulated renal artery with a Harvard pump (Harvard Apparatus Co., Inc., Millis, Mass.) at the rate of 0.5 ml/min. For the measurement of creatinine clearance in six dogs, a priming solution of 700 mg creatinine was administered through a peripheral vein during this equilibration period, and a maintenance infusion of 36 mg creatinine/ml saline was begun and continued at the rate of 0.6 ml/min with a Harvard pump for the duration of the experiment.

The actual experiment consisted of three successive 15-min control periods, followed immediately by three 15-min calcium infusion periods, followed by two 15-min recovery periods. During the control and recovery periods, normal saline was infused into the renal artery at the rate of 0.5 ml/min. A solution of calcium chloride in normal saline was also administered at the rate of 0.5 ml/min during the calcium infusion periods. This solution was constituted to deliver calcium at the rate of 0.3 mg calcium (7.5 μeq)/kg body wt/min. Although the infusion of calcium into the peripheral vein of a dog at the rate of 0.6–1.0 mg calcium/kg body wt/min results in hypercalcemia and increased urinary sodium excretion (11), in a preliminary experiment with two dogs, we found that infusion of calcium at this rate directly into the renal artery significantly decreased glomerular filtration rate (GFR).[1] Renal arterial infusion at the rate of 0.3 mg calcium/kg body wt/min produced hypercalcuria without affecting GFR.

At the conclusion of each 15-min period, renal venous blood was drawn and anticoagulated with EDTA for the measurement of plasma renin activity (PRA). Peripheral blood was obtained for the measurement of serum calcium, sodium, potassium, and creatinine concentrations. The urine output was collected separately from each kidney during each of the 15-min periods for measurement of calcium, sodium, potassium, and creatinine excretion. From both kidneys and for each time period, the fraction of filtered sodium that was excreted (EF_{Na^+}) was calculated by dividing the sodium excretion rate by the product of the serum sodium concentration and single kidney creatinine clearance. $EF_{Ca^{++}}$ was calculated in a similar fashion. Renal blood flow was measured with a calibrated Carolina Medical Electronics electromagnetic flowmeter (Carolina Medical Electronics, Inc., King, N. C.). An occlusive zero setting was determined for each experiment.

Chronic calcium loading was achieved in male Sprague-Dawley rats by replacing drinking water with a 1% calcium chloride solution for 17 days. More concentrated solutions of calcium were not used because in a preliminary experiment, animals consuming 2% calcium chloride for 7–14 days lost weight, became azotemic, and had histologic evidence of nephrocalcinosis. Control rats drinking tap water ($n = 11$) and calcium-loaded rats ($n = 11$) were given a regular Purina diet (Ralston Purina Co., St. Louis, Mo.). During the 16th and 17th days of calcium loading, control and calcium-loaded animal were placed in individual metabolic cages for measurement of food and fluid intake; 24-h urine collections were obtained on each of the 2 days for measurement of calcium, sodium, and potassium excretion. At the completion of the 2-day balance study, the animals were sacrificed by blunt trauma, and blood was drawn by direct aortic puncture for the measurement of PRA, blood urea nitrogen (BUN), and serum calcium, sodium, and potassium concentrations. A single kidney was harvested from each of seven control and seven calcium-loaded rats for the measurement of total renal renin content.

To evaluate the effect of calcium on the renin response to sodium deprivation, 24 male Sprague-Dawley rats were given a low-sodium chloride diet prepared by Nutritional Biochemicals Div., (International Chemical & Nuclear Corp., Cleveland, Ohio) for 8 days. This diet contained 8 μeq sodium/g of diet (measured by nitric acid extraction), 13 μeq calcium/g of diet as calcium gluconate, and 33 μeq calcium/g of diet as calcium lactate (per manufacturer). 12 of the animals simultaneously received a 1% calcium chloride solution in place of drinking water, whereas the 12 control animals consumed deionized water. All animals were kept in individual metabolic cages to monitor food and fluid intake. Before the start of the low-sodium diet, several days were allotted for the animals to adjust to the cages and the synthetic diet with added sodium, 1.5 meq/10.0 g of diet. To maintain a similar dietary intake in both control and calcium-loaded rats, a paired feeding schedule was used. In six animals from each group, daily sodium balances were calculated on the basis of dietary intake and urinary excretion. On the final day of sodium deprivation, 24-h urine calcium excretion rates were measured. The animals were then sacrificed by blunt trauma, and peripheral blood was collected, as previously described, for measurement of PRA, BUN, and serum calcium, sodium, and potassium concentrations. Total renal renin content was measured in a single kidney from each of six control and six calcium-loaded animals.

In all experiments, PRA was measured in quadruplicate by the radioimmunoassay procedure of Haber, Koerner, Page, Kliman, and Purnode (12), previously validated by bioassay in our laboratory (13). Renal renin content was measured by a previously described procedure of Haas (6). Briefly, renin was extracted from individual rat kidneys by an ammonium sulfate precipitation method. An aliquot of each extract was incubated at 37°C with excess sheep renine substrate for 15 min, and the concentration of angiotensin I generated was measured by radioimmunoassay. One unit of renin is arbitrarily defined as that concentration of renin that will generate angiotensin I at the rate of 100 ng/h.

Total serum calcium was determined by titration with EDTA with calcein as an indicator. Urine was acidified, boiled, and quantitatively diluted with lanthanum chloride solution so that the calcium concentration was in the 0.2–1 meq/liter range and lanthanum was 10 mg/ml; this preparation was then analyzed for calcium by atomic absorption spectrophotometry in an acetylene-air flame at 422.7 nm. Serum and urine sodium and potassium concentra-

[1] *Abbreviations used in this paper:* BUN, blood urea nitrogen; EF_{Na}, fraction of filtered sodium excreted; GFR, glomerular filtration rate; PRA, plasma renin activity.

tions were measured with an IL flame photometer with an internal lithium standard (Instrumentation Laboratory, Inc., Lexington, Mass.). BUN was measured by the method of Crocker (14). Serum and urine creatinine concentrations were measured by the method of Kennedy, Hilton, and Berliner (15).

For the calcium infusion studies in the dog, analysis of variance was used to compare measurements during control, infusion, and recovery periods. Comparisons were made for the following selected orthogonal contrasts: infusion periods vs. control plus recovery periods; control periods vs. recovery periods; first recovery period vs. second recovery period; linear effect during infusion periods; and quadratic effect during infusion periods. Additional unplanned comparisons were made with a t test; we recognize the slightly increased possibility of an alpha error in these instances. A paired t test was used to compare excretion rates between infused and uninfused kidneys. In the chronic calcium administration experiments in the rat, comparisons between control and calcium-loaded rats were made with an unpaired t test.

RESULTS

Dog studies. In the dog experiments, during the renal arterial infusion of calcium chloride, peripheral serum calcium concentration rose progressively in a linear fashion ($P < 0.001$) during each of the three calcium infusion periods, and serum calcium concentrations during the infusion periods were significantly greater ($p < 0.001$) than during the control and recovery periods (Fig. 1). At the completion of the two recovery periods, mean serum calcium concentrations of 5.3 meq/liter±0.6 SE and 5.4 meq/liter±0.3 SE were also greater than preinfusion control values ($P < 0.001$), although lower than the mean value of 6.0 meq/liter±0.3 SE at the end of the third calcium infusion period ($P < 0.05$).

Compared to preinfusion and recovery clearances, mean creatinine clearances from both the infused and uninfused kidneys were not significantly ($P > 0.73$) different during the administration of calcium (Fig. 2). During the three periods of calcium infusion, in all animals there was a progressive linear elevation of calcium excretion ($P < 0.01$) and $EF_{Ca^{++}}$ ($P < 0.04$) from both the infused and the contralateral kidney.

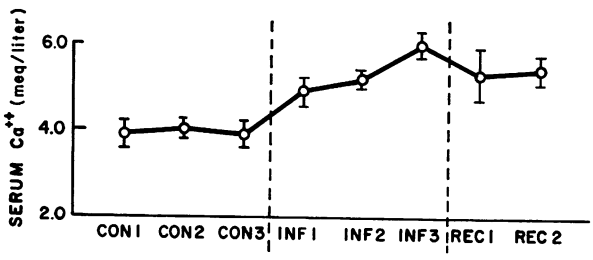

FIGURE 1 Mean (±SE) peripheral serum calcium concentrations at the completion of each control, infusion, and recovery period.

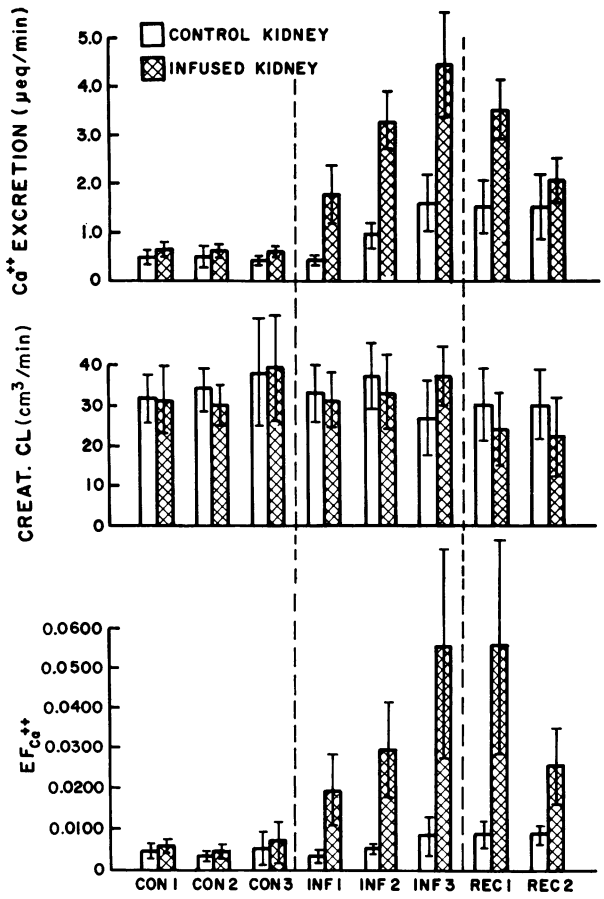

FIGURE 2 Mean (±SE) calcium excretion, creatinine clearance, and $EF_{Ca^{++}}$ from control and infused kidneys during each control, infusion, and recovery period.

The excretion of calcium and $EF_{Ca^{++}}$ from the infused kidney were greater than the respective values from the contralateral kidney during each infusion period ($P < 0.05$). Although calcium excretion decreased during the recovery periods, the excretion rate and $EF_{Ca^{++}}$ from each kidney were elevated compared to preinfusion control values ($P < 0.01$). However, calcium excretion and $EF_{Ca^{++}}$ from the infused kidney during the second recovery period were each significantly lower than during the first recovery period ($P < 0.05$).

The overall mean renal venous PRA for all three preinfusion control periods was 45 ng/ml/h±5.2 SE (Table I). At the completion of each of the three calcium infusion periods, mean PRA was 20 ng/ml/h ±4.6 SE, 16 ng/ml/h±4.0 SE, and 13 ng/ml/h±2.7 SE, respectively. During calcium infusion, PRA was significantly lower than during both the preinfusion control periods and the subsequent recovery periods ($P < 0.0001$). Renal venous PRA during the recovery periods was not significantly different from that during the preinfusion control periods ($P > 0.11$).

TABLE I

PRA in Dog Renal Venous Plasma at the Completion of Each Control (C), Infusion (I), and Recovery (R) Period

Dog	C_1	C_2	C_3	*C	I_1	I_2	I_3	R_1	R_2
					ng/ml/h				
1	67	64	—	66	38	37	7	25	—
2	26	44	—	35	29	27	27	67	64
3	32	35	33	33	22	28	25	33	34
4	28	36	26	30	—	0	14	28	71
5	90	103	—	97	11	19	11	139	131
6	17	18	15	17	13	3	3	6	6
7	56	25	30	37	14	9	9	77	53
8	41	45	41	42	1	2	2	43	—
9	81	110	48	80	42	25	20	43	47
10	18	16	18	17	11	10	10	52	48
Means±SE				45±5.2	20±4.6	16±4.0	13±2.7	51±11.6	57±12.9

* Overall mean control PRA for each dog.

To determine if the lower PRA during calcium infusion might be related to greater angiotensinase activity, the recoveries of exogenous angiotensin I were measured in renal venous plasma drawn before and during a renal arterial infusion of calcium. After 1- and 3-h incubations at 37°C, the recoveries of angiotensin in renal venous plasma during the control period were 90% and 110%, respectively. Comparable recoveries in renal venous plasma during calcium infusion were 100% and 110%, respectively, indicating the absence of angiotensinase activity in plasma collected during the administration of calcium.

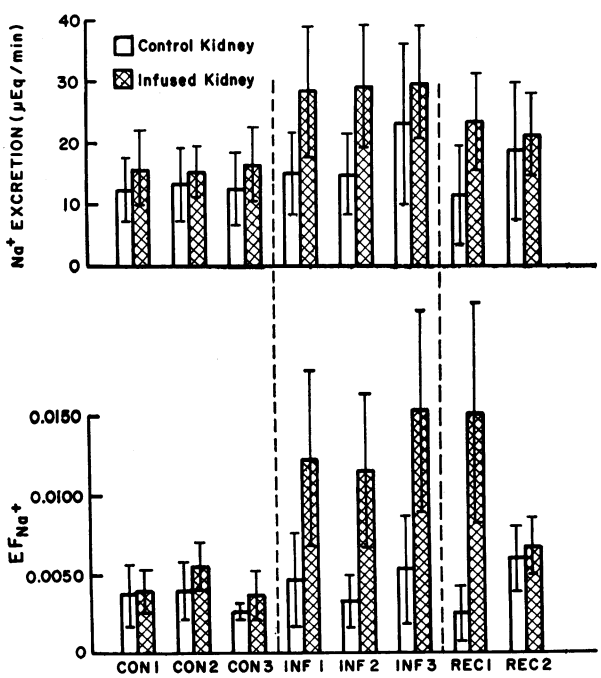

FIGURE 3 Mean (±SE) sodium excretion and EF_{Na^+} from control and infused kidneys during each control, infusion, and recovery period.

In an in vitro renin-renin substrate system, the effect of calcium on the rate of angiotensin I generation was evaluated. Human renin (7.3×10^{-5} Goldblatt U), prepared by a method of Haas, Goldblatt, Gipson, and Lewis (16) was added to incubation mixtures containing 1.0 ml sheep renin substrate (1,800 ng/ml), prepared by the Skinner method (17), and either 0.5 ml normal saline or 0.5 ml 1% calcium chloride. In each instance, after a 15-min incubation at 37°C, the rate of immunoassayable angiotensin I production was 43 ng/ml/15 min, indicating that this calcium concentration does not affect the velocity of the in vitro renin reaction.

Calcium infusion had no affect on ipsilateral renal blood flow; mean blood flow during the infusion of calcium (143 ml/min±5 SE) did not significantly differ ($P > 0.4$) from that during the control period (140 ml/min±7 SE). Similarly, mean systemic systolic (156 mm Hg±8 SE) and diastolic (104 mm Hg±10 SE) arterial pressure in the preinfusion control period did not differ significantly from that during the administration of calcium ($P > 0.10$).

The overall mean peripheral arterial serum Na^+ and K^+ concentrations during the control periods were 133 meq/liter±3.7 SE and 3.0 meq/liter±0.1 SE, respectively, and these concentrations did not change significantly during the calcium infusion or recovery periods ($P > 0.17$). During the administration of calcium, sodium excretion and EF_{Na^+} from the infused kidney increased in all animals, and both the mean sodium excretion rate and mean EF_{Na^+} during the calcium infusion were significantly greater ($P < 0.02$) than the respective values in the control and recovery periods (Fig. 3). Mean sodium excretion from the

TABLE II

Urine Excretion Rates on the 2 days before Sacrifice in Control and Calcium-Loaded Rats Consuming a Normal Sodium Intake

	Urine vol	$U_{Ca^{++}}V$	$U_{Na^+}V$	$U_{K^+}V$
	ml/24 h	*μeq/24 h*	*μeq/24 h*	*μeq/24 h*
Day 16				
Control, (n = 11)	12.9±1.6	77±14	1,722±278	2,764±233
High Ca^{++}, (n = 11)	11.5±1.1	375±84*	1,904±140	2,371±172
Day 17				
Control, (n = 11)	15.0±1.3	85±11	2,187±122	3,031±158
High Ca^{++}, (n = 11)	14.1±0.7	467±51*	1,967±185	2,896±159

* $P < 0.001$ compared to controls.

uninfused kidney was not significantly elevated above control and recovery values during the periods of calcium infusion ($P > 0.50$), and overall, during calcium infusion, sodium excretion and EF_{Na^+} from the infused kidney were greater than from the contralateral kidney ($P < 0.05$). Sodium excretion from the infused kidney during the recovery periods did not significantly differ from that during the preinfusion control periods ($P > 0.51$).

Rat studies. In the dietary calcium loading study in the rat, mean starting weights in calcium loaded (268 g±2 SE) and control (273 g±4 SE) animals did not differ ($P > 0.30$). All animals in both groups gained weight during the 17-day study period. Mean sacrifice weights of calcium-loaded (316 g±9 SE) and control (324 g±9 SE) rats did not differ from each other ($P > 0.50$), although each was significantly greater than the respective mean starting weight ($P < 0.0001$). On both the 16th and 17th days of a 1% calcium chloride solution, mean 24-h urinary calcium excretion rates were significantly greater ($P < 0.001$) than the respective values of control animals not receiving calcium (Table II). Mean daily urine volume and sodium and potassium excretion did not differ between the two groups on either of the two balance days ($P > 0.20$). At the time of sacrifice, after 17 days of calcium loading, the mean serum concentrations of calcium, sodium, and potassium did not differ ($P > 0.60$) between calcium-loaded and control animals (Table III). Mean BUN of 24 mg/100 ml±1.1 SE in the calcium-loaded rats was slightly but significantly greater than that of 20 mg/100 ml±0.2 SE in controls ($P < 0.05$). Mean PRA in calcium-loaded and control animals was 8.6 ng/ml/h±1.4 SE and 8.2 ng/ml/h±1.2 SE, respectively, and the two values are not significantly different ($P > 0.80$). Similarly, mean total renal renin content of both groups did not differ significantly ($P > 0.90$). In addition, renal renin content of the two groups did not differ after dividing the total renal renin content by the weight of the kidney to adjust for differences due to kidney weight.

Of the animals given a low-sodium diet, the mean starting (321 g±3 SE) and sacrifice (324 g±6 SE) weights of the water-drinking controls did not differ ($P > 0.10$) from those of calcium-loaded animals (324 g±5 SE and 314 g±3 SE, respectively). In each group, starting weights did not differ significantly from sacrifice weights ($P > 0.05$). On the 8th and final day of sodium deprivation, urinary calcium excretion was significantly greater ($P < 0.001$) in calcium-loaded rats (691 μeq/24 h±73 SE) than in controls (39 μeq/24 h±11 SE). Both PRA and renal renin content in controls and calcium-loaded animals were significantly greater ($P < 0.001$) than the respective values in control and calcium-loaded animals consuming a regular diet (Table III). However, mean PRA and renal renin content of sodium-deprived calcium-loaded rats were significantly lower ($P < 0.005$) than the respective values of sodium-deprived controls. Mean BUN and serum calcium, sodium, and

TABLE III

PRA, RRC (Renal Renin Content), and Serum Chemistries in Control and Calcium-Loaded Rats at the Time of Sacrifice

	PRA	RRC	BUN	Serum Ca^{++}	Serum Na^+	Serum K^+
	ng/ml/h	*U/kidney*	*mg/100 ml*	*meq/liter*	*meq/liter*	*meq/liter*
Normal sodium diet						
Control	8.2±1.2	42.9±8.6	20±0.2	5.1±0.1	145±1.9	4.8±0.2
High Ca^{++}	8.6±1.4	43.8±9.8	24±1.1*	5.1±0.2	146±1.8	4.9±0.3
Low sodium diet						
Control	56.3±4.4	993.3±116.8	24±1.1	4.8±0.2	151±1.3	5.3±0.2
High Ca^{++}	35.8±3.3‡	432.4±105.0‡	26±0.9	51.±0.2	153±0.9	5.6±0.2

* $P < 0.05$
‡ $P < 0.005$
} compared to controls consuming same sodium diet.

potassium concentrations did not differ significantly ($P > 0.20$) between controls and calcium-drinking rats after sodium deprivation. Based on comparing dietary intake and daily urinary excretion, the overall mean negative sodium balance for the control animals during the period of sodium deprivation was -167 μeq/8 days±79 SE. By comparison, pair-fed calcium-loaded rats were in significantly greater ($P < 0.005$) negative sodium balance (-597 μeq/8 days±36 SE), reflecting greater urinary sodium excretion.

DISCUSSION

In the dog, the infusion of calcium chloride into the renal artery acutely lowered renal venous renin activity. Renal blood flow was not altered by calcium infusion, indicating that the suppression of PRA reflects an inhibition of actual renin secretion. Systemic arterial pressure, GFR, and serum sodium concentration were also not affected by the administration of calcium, and the absence of these systemic changes suggests that an intrarenal mechanism may account for the inhibition of renin secretion by calcium. The lower renin activities measured during calcium infusion in the present experiment cannot be attributed to increased angiotensinase activity or to an effect of calcium on the in vitro reaction rate between renin and its substrate. Although both anesthesia and mannitol may affect renin release (18, 19), the inhibition of renin activity is clearly not related to alterations of these two variables. Both were constant throughout the entire experiment, and each dog served as his own control.

In rats consuming a regular diet, no inhibition of PRA or renal renin content was observed after substituting 1% calcium chloride for drinking water for 17 days, suggesting that this regimen had no effect on either renin synthesis or release. However, the PRA response to sodium deprivation was suppressed by the administration of calcium. Although the BUN of calcium-loaded animals was slightly greater than that of controls consuming a normal sodium intake, no such difference was observed in sodium-deprived animals, possibly because of the shorter duration of calcium loading. Consequently, it is unlikely that calcium-induced renin suppression in response to sodium deprivation is a manifestation of renal insufficiency. Furthermore, even in the diseased kidney, it has been reported that the renin responses to both volume expansion and volume contraction are intact (20). In a report of Sealy, Clark, Bull, and Laragh describing the effects of dietary potassium loading on renin activity in the rat, although plasma renin suppression did not occur in potassium-loaded animals consuming a high-sodium diet, as in the present results with calcium, a high potassium intake did inhibit the renin response to sodium deprivation (5). In the present experiment, renal renin content was elevated in both water-drinking and calcium-loaded animals after sodium deprivation, suggesting that the increased rate of renin synthesis exceeds the increased rate of renin secretion in response to dietary sodium depletion. As with the PRA responses, renal renin content of calcium-loaded animals after sodium deprivation was lower than that of water-drinking controls. These observations suggest that a high calcium intake suppresses both the increased secretion and synthesis of renin associated with sodium deprivation.

It has previously been reported that acute hypercalcemia in the dog directly and immediately inhibits sodium transport across the thick ascending limb of Henle's loop, resulting in both an increased distal sodium load and increased urinary sodium excretion (11). Alterations in both sodium delivery to the macula densa and also the transport of sodium across the macula densa have been suggested as important elements in the control of renin-angiotensin system activity (21, 22). In the present calcium infusion experiments, in the absence of alterations of renal blood flow and arterial pressure, the acute inhibition of renin release associated with an equally abrupt elevation of EF_{Na^+} during calcium administration suggests that the renin inhibition may be related to an effect of calcium on sodium transport within the nephron. Despite significant hypercalcuria in calcium chloride-drinking rats consuming a normal sodium diet, neither serum calcium concentration nor urine sodium excretion was elevated above controls not given calcium. Sodium-deprived calcium-loaded rats, however, were in greater negative sodium balance than sodium-deprived controls. Because aldosterone inhibits renin secretion by causing sodium retention, the increased sodium excretion during calcium infusion in the dog and in response to sodium deprivation in the calcium-loaded rat indicates that the inhibition of renin was not mediated by increased mineralocorticoid activity. While these results do not permit a conclusion concerning the exact mechanism of decreased renin release after the administration of calcium, the data are consistent with a sodium-related alteration in renin release, which may be modified as a stimulus by calcium.

Alternatively, calcium may have a direct effect on renin release, unrelated to alterations of sodium handling within the nephron. Although the demonstration by Michelakis that calcium actually increases renin release from renal cortical slices is not consistent with such a mechanism (23), conceivably, in vivo inhibition of renin may be related to a calcium-enhanced sensitivity of the renal vasculature or receptors to angiotensin II. Two recent abstracts of micropuncture studies

have concluded that intraluminal calcium concentration at the macula densa affects feedback regulation of single-nephron GFR (24, 25), raising the possibility of a direct interaction between calcium and the renin-angiotensin system.

In six patients with chronic renal failure, Weidmann, et al. reported that the induction of acute hypercalcemia by the intravenous infusion of calcium chloride or calcium gluconate had no effect on plasma renin activity measured by the bioassay method of Boucher (26). One possible explanation for this apparent discrepancy may be related to an altered responsivity to calcium in the diseased kidney. Additionally, before infusion, four of the six patients had renin activities in the low-normal range, and for this reason renin suppression would be difficult to detect. In the present dog experiments, renin inhibition by acute calcium infusion was demonstrated in the presence of elevated base-line values stimulated by anesthesia and surgery. In the rat studies, calcium-induced renin inhibition became apparent only after stimulation of the renin-angiotensin system by sodium deprivation. These results suggest that calcium may not have a primary role in regulating renin secretion, but rather may modify renin responses to other stimuli. In a recent report, Llach, et al. found that acute hypocalcemia, produced by EDTA in normal subjects and in patients with renal failure, had no measureable effect on plasma renin activity (27).

The present demonstration that calcium inhibits renin secretion raises the possibility that other cations may also affect renin release. Indeed, it has previously been demonstrated that the renin response to sodium deprivation is suppressed in patients with lead intoxication (28), and this suppression is apparently reversed after appropriate chelation therapy. Conversely, in anesthetized rats, Perry and Erlanger reported that intraperitoneal injections of cadmium and mercury, as well as dietary cadmium loading, evoked significant increases in peripheral renin activity, whereas intraperitoneal injections of zinc and lead did not (29).

In summary, the results of the present study demonstrate that the acute renal arterial infusion of calcium in the dog suppresses renin release. In rats consuming a normal sodium diet, the substitution of 1% calcium chloride solution for drinking water had no measureable effect on either PRA or renal renin content. Dietary calcium loading suppressed but did not abolish the renin response to sodium deprivation. The data are consistent with the hypothesis that the inhibition of renin release is related to an increased delivery of sodium to the macula densa; however, a direct effect of calcium on the juxtaglomerular apparatus cannot be excluded.

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