Calcium modulation of the renin-aldosterone axis

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ABSTRACT. Changes in the extracellular calcium concentration have important effects on hormone secretion. *In vitro*, kidney juxtaglomerular cells have been shown to secrete renin in an inverse relationship to the extracellular calcium concentration. The effect of physiologic changes in calcium on renin secretion in humans is less clear. We therefore investigated the effects of physiologic changes in extracellular calcium levels on renin and aldosterone secretion in 7 healthy men. Serum ionized calcium, ACTH, plasma renin activity (PRA), and aldosterone levels were serially measured during 90-min infusions of dextrose, disodium edetate (EDTA) and calcium gluconate, and the latter two infusions were repeated with dexamethasone pre-treatment. ACTH levels decreased during the 5% dextrose in water and the EDTA infusions but increased during the calcium infusion. Similarly, PRA and aldosterone levels fell during the D5W and EDTA infusions but this decrease was absent with increments in calcium levels. Dexamethasone administration suppressed ACTH and the aldosterone response to calcium but did not affect the PRA response to the calcium infusion. Our data indicate that increases in calcium within the physiological range blunt the diurnal decline in both PRA and aldosterone. This appears to be a direct effect of calcium on PRA but mediated through ACTH in the case of aldosterone.

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INTRODUCTION

Changes in the extracellular calcium (Ca) concentration within the physiologic range have important effects on hormone secretion. These effects are best exemplified by the inverse relationship between intact parathyroid hormone (iPTH) secretion and ionized calcium (Ca_{ion}) (1), which is mediated by a 120-kDa, G protein-coupled, Casensing receptor (CaR) expressed on parathyroid cells (2). We recently demonstrated that, in humans, an increase in the Ca_{ion} concentration within the physiologic range also increases ACTH secretion (3) possibly through the CaR which is expressed in certain areas of the brain (4). The CaR is also present in the kidney and may mediate, at least in part, the known effects of extracellular calcium on renal function, namely reducing glomerular filtration rate, exerting a natriuretic action, and inhibiting the actions of vasopressin (5, 6).

The juxtaglomerular (JG) cells of the kidney modulate the secretion of renin in response to extracellular signals that alter intracellular Ca (7-9). Like parathyroid cells, JG cells increase secretion in response to a decrease in intracellular Ca. Another feature shared by these two cell types is the inverse relationship between the extracellular Ca concentration and hormone secretion *in vitro* (7-9). However, *in vivo* studies in humans have not consistently confirmed this relationship. Ca infusion studies that produced supraphysiologic levels of Ca have shown either no change or a decrease in plasma renin activity (PRA) (10-13). Our present studies were therefore designed to test the hypothesis that changes in Ca_{ion} concentration within the physiologic range play a role in the regulation of renin and aldosterone in healthy normotensive humans.

MATERIALS AND METHODS

Subjects

Ten healthy men (mean±SD: 26±5 years) were studied. Before enrollment each volunteer underwent a physical examination and a laboratory evaluation that included a multichannel chemistry analysis and a complete blood count with differential. The study was reviewed and approved by the Human Research Committee of the Brigham and Women's Hospital. Informed written consent was obtained from each subject prior to participation.

Key-words: ACTH, calcium, aldosterone, renin.

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Study design

Infusions of Ca or disodium edetate (EDTA) were administered on separate days following a protocol that was previously described in detail [Protocol I, (14)]. We repeated Protocol I following dexamethasone suppression of ACTH (Protocol II) to exclude ACTH effects on the renin-angiotensin-aldosterone system (RAAS), particularly on aldosterone secretion. Subjects were studied while in balance on a low sodium diet in order to activate the RAAS. We felt that this would optimize the chances of demonstrating the putative suppressive effect of calcium on components of the axis.

Protocol II

Seven subjects in balance on a 10 mEq/day sodium diet (4-5 days of low sodium intake) were given infusions of EDTA or Ca on two consecutive mornings. Sodium balance was confirmed by measurements of 24-h urinary sodium. The subjects arrived at 08:00 h after having fasted for at least 8 h. Intravenous catheters were placed in each antecubital fossa and kept open with 5% dextrose in water (D5W). One intravenous line was used for blood sampling and the other for the infusions.

EDTA infusion (day 1)

Subjects were supine for 60 min before the administration of the infusions to ensure that there was no effect of posture on the parameters measured. Disodium edetate (EDTA, 150 mg/ml, Endrate, Abbott Laboratories, N. Chicago, IL) mixed in D5W was administered via an infusion pump (Travenol, Deerfield, IL). Throughout the course of the infusion, blood pressure was monitored every 15 min by an automated blood pressure recorder (Dinamap monitor, Critikon, Inc., Tampa, FL). EKG tracings were obtained from a cardiac monitor (Physio Control Lifepak 7, Rowayton, CT) every 30 min. The protocol consisted of three 30-min intervals with progressively increasing rates of EDTA infusion of 15, 18, and 22 mg/kg/h. Blood samples for Ca_{ion}, PTH, ACTH, cortisol, aldosterone, and PRA were collected at baseline and every 10 min throughout the infusion.

Ca infusion (day 2)

On the following day, Ca gluconate (Astra, Westboro, MA) was infused over three 30-min intervals at infusion rates of 1.2, 2.0, and 2.8 mg/kg/h. The phlebotomy protocol was identical to that described for day 1.

PAH infusion (day 1 and day 2)

For the first five subjects, renal blood flow (RBF) was determined by paraaminohippurate (PAH) clearance (15). PAH (Merck Sharp & Dohme, West Point, PA) was given as a loading dose of 8 mg/kg followed by a constant infusion of 12 mg/min (15 ml mixed in 90 ml normal saline and infused at 25 ml/h). The constant infusion began 60 min prior to the start of the EDTA or Ca infusion. Blood samples for PAH levels were collected at 30-min intervals during both infusions.

Protocol II

Seven subjects (including 4 subjects from Protocol I) were studied in balance on a 10 mEq/day sodium diet. We were unable to study all the subjects from Protocol I under protocol II, as the latter was developed *post-hoc* after evaluating the results of the first protocol. On day 1, subjects were given an infusion of D5W. Following dexamethasone administration, they were given infusions of EDTA (day 2) and Ca (day 3). The infusions were administered on three consecutive mornings.

D5W infusion (day 1)

D5W was infused at volumetric rates identical to those used for EDTA infusion. Infusion and phlebotomy protocols were the same asses described above. This infusion was carried to mimic the calcium and EDTA infusions in all respects: volume, stress related to IV placement, dextrose effect etc. It also allowed the evaluation of the effect of time, independent of calcium changes, on PRA and aldosterone levels.

EDTA (day 2) and Ca (day 3) infusions

Subjects took dexamethasone 1 mg at 24:00 h on the night before each infusion. The EDTA and Ca infusions were otherwise identical to those described in Protocol I.

Volumes infused

The amount of fluid infused was about 150 ml over the 90-min period. Since the calcium and EDTA solutions were largely sodium free, the amount of sodium infused was negligible.

Laboratory tests

Blood for Ca_{ion} was collected anaerobically and measured with an AVL 987-S calcium analyzer (AVL Scientific Corporation, Roswell, GA), which has an intra-assay coefficient of variation (CV%) of 0.39% and an inter-assay CV% of 1.7-2.5% for Ca_{ion} levels between 1.12 and 1.48 mmol/l. Intact PTH (iPTH) and ACTH levels were measured with immunoradiometric assays. For iPTH the normal range is 10-65 pg/ml, and the intra- and inter-assay CV%s are 1.7% and 6.5% at iPIH concentrations of 37.7 pg/ml and 44.1

pg/ml respectively. For ACTH levels, the normal range is 9-5 pg/ml; the intra- and inter-assay CV%s are 1% and 3% respectively. PRA, aldosterone, and cortisol were measured by radioimmunoassay techniques previously described (3, 16, 17). Urinary sodium was measured by flame photometry with lithium as an internal standard. Serum creatinine and PAH were measured by autoanalyzer.

Statistical methods

Data from the infusion studies included multiple measures (i.e., for Ca_{ion}, ACTH, PRA, etc.) obtained by repeated sampling over time. These data were therefore analyzed by a two-factor repeated-measures ANOVA, with use of a subject by day (infusion type) by time factorial design using SAS (SAS, Cary, NC). When significant day by time interactions were observed, additional one-factor repeated-measures ANOVA was performed followed by pairwise comparisons among time means using the Newman-Keuls test. The results were expressed as the mean±SE. Differences with $p<0.05$ were considered statistically significant.

RESULTS

Protocol I

Ca_{ion} levels decreased during the EDTA infusion ($p=0.0001$) and increased during the Ca infusion ($p=0.0001$, Fig. 1A). iPTH levels increased from 28±3 to 105±8 pg/ml ($p=0.0001$) during the EDTA infusion and decreased from 30±2 to 6±1 pg/ml ($p=0.0001$) in response to the Ca infusion.

PRA levels decreased during the EDTA infusion ($p=0.0001$) but remained unchanged during the Ca infusion (Fig. 1B). In addition, aldosterone followed a similar pattern, decreasing during the EDTA infusion ($p=0.0001$) but remaining unchanged during the Ca infusion (Fig. 1C). ACTH, PRA, and aldosterone levels were significantly different between the two infusion days. ACTH levels decreased, though not significantly, during the EDTA infusion but increased during the Ca infusion ($p=0.0007$, Fig. 1D). Cortisol levels fell significantly from 11.7 to 9.2 µg/dl during the EDTA infusion, $p=0.03$ and rose slightly but significantly with the calcium infusion from 9.3 to 10.9 µg/dl, $p=0.001$. The slopes between the two days were significantly different.

Pulse rate did not change during the calcium infusion, the mean values at the beginning and end of that infusion were 60±3 and 58±3 beats/min for Protocol I and 65±3 and 58±4 beats/min for Protocol II. RBF and blood pressure also did not change significantly from baseline during either the EDTA or the Ca infusion (Table 1).

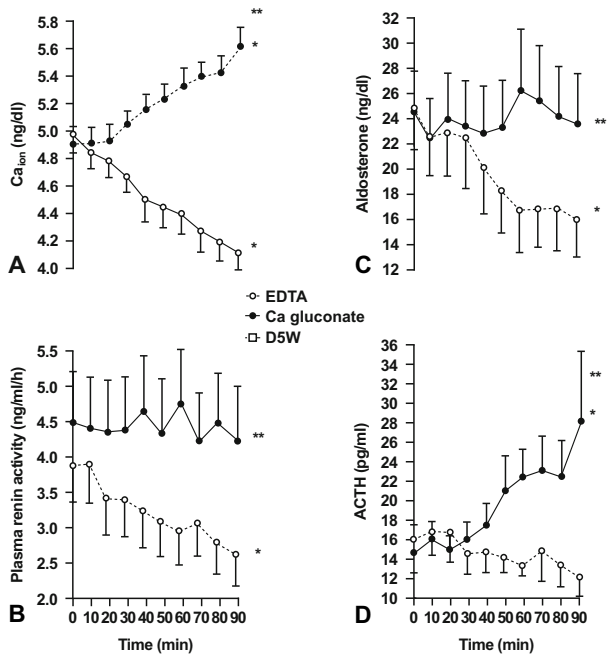

Fig. 1 - *Levels of ionized calcium (Ca_{ion}) (1A), PRA (1B), aldosterone (1C), and ACTH (1D) versus time during 90-min infusions of calcium gluconate and EDTA. *p<0.05 for a change in hormonal values during the EDTA or the calcium infusion; **p<0.05 for significantly different hormonal levels between the EDTA and the calcium infusions.*

Table 1 - *Blood pressure (BP) and renal blood flow (RBF) during EDTA and calcium infusions.*

	EDTA infusion		Calcium infusion	
	0 min	90 min	0 min	90 min
BP (mmHg)	115±4/68±2	121±7/70±3	120±4/71±3	127±7/75±3
RBF (ml/min/1.73 m^2)	556±63	551±60	528±60	543±54

Values are mean±SE.

Protocol II

Because data from Protocol I showed an increase in ACTH levels in response to an increase in Ca_{ion} levels, we conducted a second study to exclude an ACTH-mediated effect of Ca_{ion} on aldosterone and PRA. EDTA and Ca infusions were repeated following the administration of dexamethasone to suppress ACTH. A D5W infusion was also performed (before dexamethasone administration) to determine whether the demonstrated decrements in PRA and aldosterone during the EDTA infusion in Protocol I were due to decrements in Ca levels *per*

se or whether they merely reflected diurnal variation. After dexamethasone pre-treatment Ca_{ion} levels again decreased during the EDTA infusion (p=0.0001), increased during Ca infusion (p=0.0001), and remained unchanged during D5W infusion (Fig. 2A). Also similar to Protocol I, iPTH increased during the EDTA infusion (p=0.0001), fell during the Ca infusion (p=0.0001), and did not change during D5W infusion.

PRA decreased significantly during the D5W infusion (p=0.0012) and during the EDTA infusion (p=0.0001), and did not change during the Ca infusion (Fig. 2B). Aldosterone levels were identical during D5W, EDTA and Ca infusions following dexamethasone pretreatment (Fig. 2C). ACTH levels fell during D5W infusion, though not significantly (Fig. 2D). As expected, ACTH and cortisol levels were suppressed by dexamethasone and did not change during either the EDTA or the Ca infusion (Fig. 2D). Cortisol levels were <1.2 µg/dl throughout the EDTA and calcium infusions but decreased significantly during the D5W infusion from 13.9 to 10.3 µg/dl, p=0.002. The latter provides clear evidence for a circadian variation in cortisol secretion.

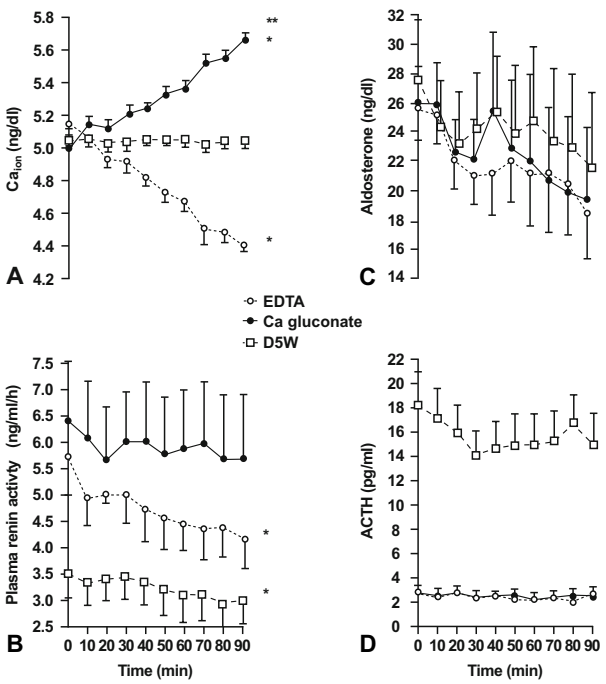

Fig. 2 - *Levels of ionized calcium (Ca_{ion}) (2A), PRA (2B), aldosterone (2C), and ACTH (2D) versus time during a 90-minute control infusion of dextrose and 90-min infusions of calcium gluconate and EDTA following administration of dexamethasone. *p<0.05 for a change in hormonal values during the EDTA or the calcium infusion.*

DISCUSSION

These studies show that PRA levels decrease with a diurnal pattern and this process is not affected by induced hypocalcemia. However, increases in Ca_{ion} within the physiologic range abolish this diurnal fall and maintain PRA levels unchanged. This effect of Ca on PRA persisted when ACTH was suppressed by dexamethasone.

Aldosterone levels followed a pattern similar to PRA. However, the absence of these changes on aldosterone after dexamethasone administration indicates that they were mediated via ACTH.

D5W infusions were performed to elucidate whether the observed decrements in PRA and aldosterone levels during the EDTA infusion were due to decreasing Ca levels or to circadian variation. It is interesting that PRA levels also decreased during the D5W infusion, which indicates a normal diurnal decline, but also decreased when ACTH was suppressed with dexamethasone, indicating that this diurnal variation was not ACTH-mediated. Increments in Ca_{ion} prevented the diurnal decrease in PRA.

Because RBF and blood pressure remained unchanged with variations in Ca_{ion}, the observed changes in PRA were not caused by changes in renal hemodynamics or perfusion pressure. The lack of change in pulse rate and blood pressure also suggests that this effect was independent of potential calcium-induced changes in catecholamine levels. Similarly, posture, stress and fluid load were kept constant across all studies in order to minimize the effect of these parameters on PRA and aldosterone secretory dynamics.

Given the available data on the effects of Ca on renin secretion, our findings were unexpected. *In vitro* studies have shown that calcium influx into JG cells inhibits renin secretion (7-9). Conversely, renin secretion is stimulated by lowering the extracellular calcium concentration (18) and by calcium channel blockers (19). The effect of calcium channel blockers may be hemodynamic rather than specific to JG cells (20). The few *in vitro* studies demonstrating a stimulatory effect of calcium on renin secretion have all involved re-introduction of calcium into preparations previously treated with calcium-free media (21-23). *In vivo* studies in animals have also demonstrated an inhibitory effect of Ca on renin secretion (24-28), while hypocalcemia was shown to raise PRA in dogs (29).

Human studies have yielded inconsistent results showing either a decrease or no change in PRA levels in response to Ca infusion (10-13). However, these studies have been limited by the small number of subjects, inclusion of individuals with hypertension and renal insufficiency, and uncontrolled sodium balance which is an important modulator of PRA. In ad-

dition, many studies lacked an adequate control infusion, which is a serious drawback given the diurnal variation of aldosterone and PRA. Previous studies using three- and four-hour infusions of calcium in 10 and 5 subjects, respectively, showed no change in PRA levels (10, 12), leading to the conclusion that Ca did not affect PRA. Since these infusions were begun in the morning, a decrease in PRA would be expected unless Ca indeed blunted this effect, as demonstrated in our studies.

While there are limitations to the type of short-term studies we conducted, all of the *in vitro* studies showing an unequivocal suppression of renin by calcium are also short-term (7-9) and a carefully designed short-term study was therefore needed in humans to corroborate (or reject) these *in vitro* observations. Also, although a low salt diet does not reflect the usual Western diet, it was selected to enhance RAAS activity in order to unequivocally resolve the stipulated inhibitory effect of calcium on that axis, as has been described *in vitro* and in animal studies.

A dose-related effect of Ca on PRA may account for some of the variability in previously reported results. Low-dose Ca infusion in dogs increased PRA, which then decreased to baseline when the Ca dose was increased (26, 27). Cyclooxygenase inhibitors abolished this increase in PRA, thus suggesting a prostaglandin-mediated mechanism for renin stimulation (25). In our study, we employed a relatively low-dose infusion of Ca gluconate in order to yield variations in Ca_{ion} within the physiologic range.

Studies evaluating the impact of chronic elevations in Ca levels on PRA have also suggested a stimulatory effect. In individuals with essential hypertension, PRA levels have been observed to vary directly with Ca_{ion} levels (30). Elevated PRA levels are also present in individuals with chronic hypercalcemia due to hyperparathyroidism (31), an effect that may be mediated through calcium or PTH (32, 33). In addition, oral Ca gluconate supplementation for 16 weeks resulted in increased PRA levels in healthy men compared with control subjects (34). Since our group has localized the Ca receptor to the macula densa (35), it is therefore possible that Ca directly stimulated renin secretion through activation of its own receptor.

iPTH levels varied inversely with Ca_{ion} levels as expected. Exogenous PTH increases renin secretion both *in vitro* (32) and *in vivo* in humans and dogs (33, 34, 36), with evidence to suggest that it acts via changes in calcium ion flux (32). In our study, despite a large increase in iPTH levels during the EDTA infusion, PRA levels actually fell. This decline was not attributable to changes in iPTH or Ca_{ion} concentration, as similar results were seen during the D5W infusion when iPTH and Ca_{ion} levels remained constant and within the normal range.

Studies evaluating Ca effects on aldosterone levels more consistently show an increase in aldosterone with a Ca infusion (10, 11, 13). In addition, one study demonstrated that this effect persisted in 2 subjects given dexamethasone (11), a finding contrary to our results in 7 subjects given dexamethasone. The lack of an effect of Ca on aldosterone levels post-dexamethasone in our studies suggests that aldosterone changes were mediated via ACTH and not through a direct effect on the zona glomerulosa.

In summary, we demonstrated a non-ACTH-mediated diurnal decrease in PRA that was negated by physiologic increments in Ca_{ion}. A similar effect of Ca on aldosterone levels was also evident although this was blocked by dexamethasone, suggesting an effect mediated by Ca-induced increments in ACTH. Possible mechanisms for this effect of Ca on the PRA include low-dose Ca-mediated stimulation of prostaglandin synthesis and/or direct or indirect effects of Ca on the JG cells, possibly through the CaR. While our observations are from short-term studies, they may be relevant to the understanding of calcium-induced mechanism(s) in the regulation of PRA in hypertensive individuals.

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REFERENCES

1. Brown E.M.
   Four-parameter model of the sigmoidal relationship between parathyroid hormone release and extracellular calcium concentration in normal and abnormal parathyroid tissue.
   J. Clin. Endocrinol. Metab. *56:* 572, 1983.
2. Brown E.M., Gamba G., Ricardi D., Lombardi M., Butters R., Kifar O., Sun A., Hediger M.A., Lytton J., Hebert S.C.
   Cloning and characterization of an extracellular Ca^{2+}-sensing receptor from bovine parathyroid.
   Nature *366:* 575, 1993.
3. El-Hajj Fuleihan G., Brown E.M., Gleason R., Scott J., Adler G.K.

Calcium modulation of adrenocorticotropin levels in women. A clinical research center study.
J. Clin. Endocrinol. Metab. *81:* 932, 1996.

4. Rogers K.V., Dunn C.K., Hebert S.C., Brown E.M.
Localization of CaR mRNA in adult rat CNS by *in situ* hybridization.
Brain Res. *744:* 47, 1997.
5. Brown E.M., Hebert S.C.
A cloned extracellular Ca^{2+}-sensing receptor: Molecular mediator of the actions of extracellular Ca^{2+} on parathyroid and kidney cells?
Kidney Int. *49:* 1042, 1996.
6. Suki W.N., Eknoyan G., Rector F.C. Jr., Seldin D.W.
The renal diluting and concentrating mechanism in hypercalcemia.
Nephron. *61:* 50, 1969.
7. Park C.S., Malvin R.L.
Calcium in the control of renin release.
Am. J. Physiol. *235:* F22, 1978.
8. Baumbach L., Skott O.
Renin release from isolated rat glomeruli: Seasonal variations and effects of D600 on the response to calcium deprivation.
J. Physiol. *310:* 285, 1981.
9. Park C.S., Han D.S., Fray J.C.S.
Calcium in the control of renin secretion: Ca^{2+} influx as an inhibitory signal.
Am. J. Physiol. *240:* F70, 1981.
10. Marone C., Beretta-Piccoli C., Weidmann P.
Acute hypercalcemic hypertension in man: Role of hemodynamics, catecholamines, and renin.
Kidney Int. *20:* 92, 1980.
11. Isaac R., Raymond J.P., Rainfray M., Ardaillou R.
Effects of an acute calcium load on plasma ACTH, cortisol, aldosterone and renin activity in man.
Acta Endocrinol. (Copenh.) *105:* 251, 1984.
12. Epstein S., Sagel J., Brodovcky H., Tuff S., Eales L.
Absence of an acute effect of calcium or parathyroid hormone administration on plasma renin activity in man.
Clin. Sci. Molec. Med. *50:* 79, 1975.
13. Aoki K., Miyagawa K.
Correlation of increased serum calcium with elevated blood pressure and vascular resistance during calcium infusion in normotensive man.
J. Hyperten. *8:* 579, 1990.
14. Brent G.A., LeBoff M.S., Seely E.W., Conlin P.R., Brown E.M.
Relationship between the concentration and rate of change of calcium and serum intact parathyroid hormone levels in normal humans.
J. Clin. Endocrinol. Metab. *67:* 944, 1988.
15. Shoback D.M., Williams G.H., Moore T.J., Dluhy R.G., Podolsky S., Hollenberg N.K.
Defect in the sodium-modulated tissue responsiveness to angiotensin II in essential hypertension.
J. Clin. Invest. *72:* 2115, 1983.
16. Emanuel R.L., Caionn J.P., Williams G.H.
Double antibody radioimmunoassay of renin activity and angiotensin II in human peripheral plasma.
J. Lab. Clin. Med. *81:* 632, 1973.
17. Underwood R.H., Williams G.H.
The simultaneous measurement of aldosterone, cortisol, and corticosterone in human peripheral plasma by displacement analysis.
J. Lab. Clin. Med. *79:* 848, 1972.
18. Hackenthal E., Paul M., Ganten D., Taugner R.
Morphology, physiology, and molecular biology of renin secretion.
Physiol. Rev. *70:* 1067, 1990.
19. Matsumura Y., Uriu T., Shinyama H., Sasaki Y., Morimoto S.
Inhibitory effects of calcium channel agonists on renin release from rat kidney cortical slices.
Pharm. Exp. Ther. *241:* 1000, 1987.
20. Dietz J.R., Davis J.O., Freeman R.H., Villarreal D., Echtenkamp F.
Effects of intrarenal infusion of calcium entry blockers in anesthetized dogs.
Hypertension *5:* 482, 1983.
21. Cher D.S., Poisner A.M.
Direct stimulation of renin release by calcium.
Proc. Soc. Exp. Biol. Med. *152:* 565, 1976.
22. Hinko A., Franco-Saenz R., Mulrow P.J.
Biphasic alteration of renin release by calcium.
Proc. Soc. Exp. Biol. Med. *175:* 454, 1984.
23. Schwertslag U., Hackenthal E., Hackenthal R., Rohs G.H.
The effects of calcium and calcium-ionophores (X 537 A and A 23187) on renin release in the isolated perfused rat kidney.
Clin. Sci. Molec. Med. *55:* 163, 1978.
24. Kotchen T.A., Guthrie G.P.
Effects of calcium on renin and aldosterone.
Am. J. Cardiol. *62:* 41G, 1988.
25. Kotchen T.A., Mauli K.I., Luke R., Rees D., Flamenbaum W.
Effects of acute and chronic calcium administration on plasma renin.
J. Clin. Invest. *54:* 1279, 1974.
26. Lahera V., Fiksen-Olsen M.J., Romero J.C.
Role of prostaglandins in the renal response to calcium infusion.
Am. J. Physiol. *258:* F1096, 1990.
27. Lahera V., Fiksen-Olsen M.J., Romero J.C.
Stimulation of renin release by intrarenal calcium infusion.
Hypertension *15* (Suppl. 1): I-149, 1990.
28. Watkins B.E., Davis J.O., Lohmeier T.E., Freeman R.H.
Intrarenal site of action of calcium on renin secretion in dogs.
Circ. Res. *39:* 847, 1976.
29. Zawada E.T. Jr., Johnson M.
Effects of changes in serum calcium and parathyroid hormone on plasma renin in intact mongrel dogs.
Nephron. *40:* 368, 1985.

30. Resnick L.M., Muller F.B., Larag J.H.
Calcium-regulating hormones in essential hypertension: Relation to plasma renin activity and sodium metabolism.
Ann. Intern. Med. *105:* 649, 1986.

31. Gennaris C., Nami R., Gonnelli S.
Hypertension and primary hyperparathyroidism: The role of adrenergic and renin-angiotensin-aldosterone systems.
Miner. Electrolyte Metab. *21:* 77, 1995.

32. Saussine C., Judes C., Massfelder T., Musso M.J., Sincori U., Harredouche T., Helwig J.J.
Stimulatory action of parathyroid hormone on renin secretion *in vitro*: A study using isolated rat kidney, isolated rabbit glomeruli and superfused dispersed rat juxtaglomerular cells.
Clin. Sci. *84:* 11, 1993.

33. Grant F.D., Mandel S.J., Brown E.M., Williams G.H., Seely E.W.
Interrelationships between the renin-angiotensin-aldosterone and calcium homeostatic systems.
J. Clin. Endocrinol. Metab. *75:* 988, 1992.

34. Lijnen P., Petrov V.
Effect of oral calcium supplementation on intracellular calcium and plasma renin in man.
J. Endocrinol. *146:* 421, 1995.

35. Riccardi D., Hall A.E., Chattopadhyay N., Xu J., Brown E.M., Hebert S.C.
Localization of the extracellular Ca^{2+} (polyvalent cation) sensing protein in rat kidney.
Am. J. Physiol. *274* (Renal Physiol): F611, 1998.

36. Powell C.R., McCredie D.A., Rotenberg E.
Renin release by parathyroid hormone in the dog.
Endocrinology *103:* 985, 1978.