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ORIGINAL ARTICLE

Activation of the calcium sensing receptor stimulates gastrin and gastric acid secretion in healthy participants

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Abstract
Summary In 17 adults on a fixed metabolic diet, an 11-day course of cinacalcet increased serum gastrin and basal gastric acid output, but not maximal gastric acid output, compared with a placebo. These findings indicate that the calcium sensor receptor plays a role in the regulation of gastric acid.
Introduction Gastric acid secretion is a complex process regulated by neuronal and hormonal pathways. Ex vivo studies in human gastric tissues indicate that the calcium sensing receptor (CaR), expressed on the surface of G and parietal cells, may be involved in this regulation. We sought to determine whether cinacalcet, a CaR allosteric agonist, increases serum gastrin and gastric acid secretion.
Methods Seventeen healthy adults with normal gastric acid output were placed on an 18-day metabolic diet. On day 8 (baseline), participants were given cinacalcet (15 then 30 mg/day) or placebo for 11 days. Changes in gastric acid output, serum gastrin, and other measures were compared in the two groups.
Results Changes in serum gastrin and basal acid output (adjusted for baseline body weight) were significantly more positive in the cinacalcet group compared with placebo (P=0.004 and P=0.039 respectively). Change in maximal acid output was similar in the two groups (P=0.995). As expected, cinacalcet produced significant decreases in serum PTH (P<0.001) and ionized calcium levels (P=0.032), and increases in serum phosphorus levels (P=0.001) and urinary calcium (P=0.023).
Conclusions This study provides in vivo evidence that activation of the CaR increases serum gastrin levels and basal gastric acid secretion in healthy adults.

Keywords Calcimimetic · Calcium sensing receptor · Gastric acid · Gastrin

Clinical Trial: NCT00336739

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Introduction

It has long been observed that extracellular calcium stimulates gastrin and gastric acid secretion in humans. In 1971 Reeder et al. reported that calcium carbonate ingestion caused an increase in serum gastrin levels [1]. Two years later, experiments by Levant et al. showed that serum gastrin significantly increased 30 and 60 min after a single oral administration of calcium to fasting men [2]. In 1967 Barreras and Donaldson demonstrated that hypercalcemia, induced by an intravenous infusion of calcium, resulted in a significant increase in acid secretion [3]. Serum gastrin levels were not measured in the study. In 1968, Fortran found that oral calcium carbonate stimulated gastric acid secretion in non-fasting patients with duodenal ulcers, but other antacids such as aluminum-magnesium hydroxide and sodium bicarbonate did not [4]. Other experiments in the 1970s confirmed the increase in gastric acid secretion that followed administration of oral calcium carbonate in duodenal ulcer patients [5, 6].

The extracellular calcium-sensing receptor (CaR) offers a potential mechanism for calcium's effects on gastrin and gastric acid secretion. A member of the superfamily of G-protein-coupled receptors, the CaR was originally cloned in 1993 [7] and has recently been identified on the basal and apical surfaces of human gastrin-secreting G cells located in the antrum of the stomach [8]. Ex vivo experiments on human G cells have demonstrated that activating the CaR with increasing extracellular calcium levels stimulated gastrin release [8, 9]. CaRs are also expressed on the basolateral surface of human parietal cells located in gastric glands [10]. Recent experiments by Dufner et al. on isolated human gastric glands have shown that stimulating the CaR using known divalent and trivalent cations led to the activation of the parietal cell H^+-K^+ ATPase and gastric acid release [10].

Calcimimetic agents were developed to modulate CaRs allosterically in a manner that increases the sensitivity of the receptor to extracellular calcium [11]. There are very limited data on the impact of calcimimetics on gastrin or gastric acid secretion. In a subset of a phase 1 trial of the calcimimetic KRN568, a single oral dose of 400 mg resulted in a nonsignificant increase in serum gastrin levels in 5 out of 6 healthy participants [12]. Gastric acid secretion was not measured in this study.

The CaR is also expressed in parathyroid and renal tissues, and its role in regulating extracellular calcium homeostasis has been well-described. Activation of parathyroid gland CaRs suppresses PTH secretion [13]. In the kidney, activation of CaRs decreases renal tubular calcium reabsorption [13]. These combined effects result in reduced serum calcium and increased serum phosphorus levels.

We performed a randomized placebo-controlled intervention study to determine whether cinacalcet, a calcimimetic, will increase gastric acid secretion in healthy adult participants. We explored the possibility that this effect may be mediated by gastrin. We also report the effect of treatment with cinacalcet on serum PTH, serum ionized calcium, serum phosphorus, 24-h urinary calcium-to-creatinine ratio (UCa/Cr), and 24-h urinary magnesium-to-creatinine ratio (UMg/Cr).

Materials and methods

Study design and participants

This was a double-blind, randomized placebo-controlled study that was conducted at the Metabolic Research Unit at the Jean Mayer United States Department of Agriculture (USDA) Human Nutrition Research Center on Aging (HNRCA) at Tufts University. In order to limit the impact of dietary variation on gastric acid secretion, all participants were provided with a fixed metabolic diet and daily multivitamin and mineral supplements throughout the study. After a 7-day run-in period on the metabolic diet, baseline basal and pentagastrin-stimulated gastric acid output, serum gastrin, serum PTH, serum ionized calcium, serum phosphorus, 24-h UCa/Cr, and 24-h UMg/Cr were evaluated. Participants were then randomized to take cinacalcet (15 and then 30 mg daily) or placebo for 11 days. On the last study day (day 18), basal and pentagastrin-stimulated gastric acid output and all serum and urine measurements done at baseline (day 8) were repeated.

Healthy men and postmenopausal women between the ages of 45 and 70 were recruited from direct mailings and advertisements. Participants diagnosed with active gastrointestinal, parathyroid, kidney, liver, or heart disease were excluded from the study. Other exclusion criteria included smoking, recent alcohol abuse, antiulcer medications, hormone replacement therapy in last 6 months, glucocorticoids, anticholinergic medications, adrenergic blockers, thiazide diuretics, and drugs to treat osteoporosis. Medications not known to affect gastric acid secretion or calcium balance were allowed. Screening evaluation included a basal gastric acid analysis and blood and urine tests. Participants were excluded if gastric acid output was abnormal (normal 1–5 mEq/h in men, 0.2–3.8 mEq/h in women [14]), 24-h urinary calcium was >350 mg, serum ionized calcium was >5.28 mg/dl or ≤4.67 mg/dl, or other chemscreen was >10% above the reference range. Fifty participants were screened and 33 were excluded (reasons: 10 had abnormal gastric acid output, 7 used exclusion medications, 5 were unable to tolerate a gastric tube, 5 had excluded medical conditions, 4 had scheduling conflicts, 1 had elevated urinary calcium, and 1 was a smoker). Eligible participants were randomized to receive cinacalcet (9) or placebo (8); all participants completed the study. The human investigation review board at Tufts University approved the study, and written informed consent was obtained from each participant.

Diet and supplements

Food and beverages were provided by the Metabolic Research Unit on days 1 to 18. The contents of the daily diet, calculated with the use of version 4.05 of the University of Minnesota Food and Nutrient Database 34, released in May 2003, are shown in Table 1. Caffeine-containing beverages during the study period were limited to 12 ounces daily. Alcohol intake was not permitted during the study. Participants received the metabolic diet, as a 3-day cycle menu. They came in at least three times per week to be weighed, pick up food, and return food containers, and they completed daily food intake diaries that were reviewed by the research dietitian at each visit.

Table 1 Daily average dietary intake data

	Cinacalcet (mean ± SD)	Placebo (mean ± SD)
Energy (kcal)	2,620.1±638.1	2,611.1±584.0
Total fat (g)	104.1±31.0	106.7±29.0
Total carbohydrate (g)	372.2±82.8	360.7±68.3
Total protein (g)	61.8±19.0	63.7±14.3
Total dietary fiber (g)	24.6±3.9	25.0±3.4
Calcium (mg)[a]	420.4±30.9	411.5±15.1
Phosphorus (mg) [a]	942.2±187.5	942.9±166.9
Magnesium (mg) [a]	283.1±50.8	284.1±46.6
Sodium (mg)	2,260.8±528.1	2,303.9±438.6
Potassium (mg)	2,913.3±511.1	2,915.9±488.1
Vitamin D_3 (mcg) [a]	2.32±0.51	2.38±0.492

[a] Each participant also received a supplement of 600 mg of calcium, 266 mg of phosphorus, 50 mg of magnesium, and 125 IU (3.125 mcg) of vitamin D_3 twice daily and a multivitamin with 400 IU (10 mcg) of vitamin D_3 daily

Adherence to the metabolic diet was assessed qualitatively with daily food intake diaries and return of food containers and quantitatively with serial weight checks.

Participants were asked to stop taking their own calcium and vitamin D supplements throughout the study. They were given a supplement—Posture-D®—containing calcium 600 mg, phosphorus 266 mg, vitamin D_3 125 IU, and magnesium 50 mg—to be taken twice daily with meals, and a daily multivitamin containing 400 IU of vitamin D_3. The calcium and vitamin D_3 supplements were provided to bring intake up to approximately recommended levels. All supplements were obtained from CVS Pharmacy. Adherence to supplements was recorded on a compliance calendar.

Study capsules and dosing schedule

Cinacalcet tablets (Amgen, Thousand Oaks, CA, USA) were purchased from Tufts Medical Center Pharmacy in Boston, MA, USA. The 15-mg starting dose of cinacalcet was prepared by splitting 30-mg tablets. These tablets were then packaged in an opaque capsule along with microcrystalline cellulose. In order to keep the randomization concealed, the placebo was an identical opaque capsule packed with microcrystalline cellulose. The study capsules were prepared by Medical Pharmacy and Supply in Stoughton, MA, USA. Adherence to study capsules was assessed via a daily compliance calendar and routine pill counts by the Metabolic Research Unit nursing staff.

Participants were randomly assigned to take cinacalcet or placebo for an 11-day period. On day 8, all participants started with 15 mg cinacalcet (or placebo) orally once daily in the morning immediately after breakfast. On day 11, a fasting serum ionized calcium level was drawn as a safety check. If the ionized calcium level was ≥4.67 mg/dl (reference range 4.52–5.28 mg/dl), the cinacalcet dose was increased to 30 mg once daily. If the ionized calcium level was <4.67 mg/dl, the cinacalcet dose was unchanged (for safety reasons). On day 15, participants underwent repeated measurement of their serum ionized calcium level. If the ionized calcium level was ≥4.52 mg/dl, the cinacalcet dose was unchanged. On day 18 the participants took their last dose of cinacalcet (or placebo) on an empty stomach approximately 1.75 h prior to the blood tests and 2 h prior to the gastric acid procedure. All 9 participants in the cinacalcet group were advanced to the maximal dose (30 mg) of cinacalcet once daily until the end of the study. Seven of the 8 participants in the placebo group were also advanced to the maximal dose; 1 participant on placebo remained on 1 capsule daily based on the day 11 serum ionized calcium level.

Basal and pentagastrin-stimulated gastric acid procedure

Participants reported to the Nutrition Center on the day of the test after a 12-h overnight fast. An orogastric tube (Entriflex tube®; Kendall, Mansfield, MA, USA) was passed through the participant's mouth and into the stomach. Prior to insertion of the tube, a benzocaine solution (Hurricaine spray®; Beutlich LP Pharmaceuticals, Waukegan, IL, USA) was sprayed into the posterior oropharynx in order to minimize discomfort. The tube was situated in the stomach, with proper positioning confirmed by obtaining gastric contents. Measurements of the position of the orogastric tube were documented at the first visit, so as to achieve similar positioning on repeat testing later in the study. All gastric acid analyses were performed by one study co-investigator and one research nurse who were both blinded to treatment assignment. After allowing the participant to adjust to the presence of the tube for 15 min, gastric contents were aspirated every 15 min for a period of 30 min for basal gastric acid output analysis. After the basal samples were collected, 6 mcg/kg of pentagastrin was injected subcutaneously. A gastric specimen was collected every 15 min for 60 min. Pentagastrin was provided by Cambridge Laboratories (Newcastle-upon-Tyne, UK).

Biochemical measurements

Bloods were drawn after a 12-h fast and samples from individual participants were batched for analyses. Serum gastrin level was measured with the GammaDab Gastrin ^{125}I RIA Kit (DiaSorin, Stillwater, MN, USA) with coefficients of variation (CV) of 3.0 to 4.1%. Serum intact PTH was measured by chemiluminescent immunoradiometric assays on an automated immunoassay system (IMMULITE® 1000; Diagnostic Product Corporation (DPC), Los Angeles, CA, USA) with CVs ranging from 3.0 to 6.0%. Serum ionized calcium was measured by MEDICA EasyLyte Ca/pH Analyzer (Medica Corporation, Bedford, MA, USA) with CVs ranging from 5.0 to 7.0%. Serum phosphorus and urinary creatinine were measured on an automated clinical chemistry analyzer (Olympus AU400; Olympus America, Melville, NY, USA). CVs for the urinary creatinine assay were <4%. CVs for the serum phosphorus assay ranged from 3.0 to 6.0%. Urinary calcium and magnesium were measured by direct-current plasma emission spectroscopy (Beckman Spectrascan VI Direct Current Plasma Emission Spectrophotometer; Beckman Instruments, Fullerton, CA, USA) with CVs from 3.0 to 5.0%.

Gastric acid analysis

Two 15-min basal and four 15-min pentagastrin-stimulated gastric acid specimens were analyzed with a digital pH meter (Radiometer Analytical, Loveland, CO, USA) standardized at 2 points (7.0 and 4.0) to the nearest one hundredth. Acidity was measured by calculating the inverse log of –pH in millimoles of hydrogen ions in each sample. Millimoles were converted to milliequivalents. The volume of the contents was measured in milliliters. Gastric acid output was calculated as milliequivalents per hour. Basal acid output (BAO) was the sum of the acid in the two 15-min basal acid specimens divided by 0.5 h. Maximal acid output (MAO) was calculated as the sum of the acid in the four 15-min pentagastrin-stimulated specimens. One participant in the cinacalcet group experienced nausea and retching during the 30 min of the basal gastric acid analysis resulting in an uncertain BAO; therefore, the screening BAO was substituted as the baseline value for the final analysis.

Statistical analysis

Mean values of gastric acid output, gastrin, PTH, ionized calcium, phosphorus, 24-h UCa/Cr, and 24-h UMg/Cr at days 8 and 18, and the mean changes in these values from day 8 to day 18 were compared across groups with *t* tests for two independent samples. Pearson correlation coefficients were used to describe linear associations. Analysis of covariance was used to compute and compare means adjusted for baseline body weight across groups. Two-sided *P* values less than 0.05 were considered to indicate statistical significance. Statistical analyses were conducted with SPSS v. 14 (SPSS, Chicago, IL, USA).

Results

Nine participants were randomized to the cinacalcet group and 8 to the placebo group. Baseline clinical characteristics were similar in the two groups. The baseline demographics (mean ± SD or percentage) for the cinacalcet and placebo groups respectively were for age 56.7±7.0 years and 56.1±6.4 years, for percentage of female participants 55.6 and 50.0, for percentage of Caucasian 88.9 and 87.5, for weight 76.5±17.4 kg and 79.7±19.5 kg, and for BMI 25.8±3.5 kg/m^2 and 28.3±6.4 kg/m^2.

Daily average dietary intake (Table 1) did not differ significantly in the two groups. Adherence to the study capsules was 100% based on pill counts and a compliance calendar. There was 100% adherence reported for the dietary supplements during the intervention period. Compliance with the metabolic diet was high as indicated by body weight monitoring and self-reports through daily quality assurance food check lists. There was a <1-kg difference in weight change (day 18 to day 8 weight) in the two groups (0.47±0.52 kg in the cinacalcet group versus −0.35±0.86 kg in the placebo group, P=0.028).

Baseline body weight was positively correlated to baseline BAO (r=0.551, P=0.022) and to change in BAO (r=0.498, P=0.042) and mean baseline weight in the two groups differed (though not significantly) by about 3 kg. Therefore, all measures of gastric acid output were adjusted for baseline weight. Baseline gastric acid output measures did not differ by treatment group before or after adjustment. The unadjusted baseline and change in gastric acid measurements are shown in Table 2.

Table 2 demonstrates the weight-adjusted gastric acid measurements. During the intervention, the weight-adjusted change in BAO was significantly more positive in the cinacalcet group compared with the placebo group (P for difference in change=0.039, Table 2). Similarly, the change in BAO/MAO ratio was more positive in the cinacalcet group than in the placebo group (P for difference in change= 0.045, Table 2). The change in MAO remained similar in the two groups (Table 2).

Baseline serum and urine biochemical variables did not differ significantly in the two groups (Table 3). Changes in gastrin levels in the cinacalcet group were significantly more positive (7.0±2.4 pg/ml) than those in the placebo group (−4.6±2.4 pg/ml, P=0.004, Table 3). In the entire

Table 2 Baseline and change from baseline in gastric acid output

	Baseline (mean ± SE)	Change from baseline	
		Mean ± SE	*P* value for differences between groups
Unadjusted			
BAO (mEq/h)			
Cinacalcet	2.15±0.59	1.32±0.79	0.109
Placebo	2.43±0.55	–0.24±0.38	
MAO (mEq/h)			
Cinacalcet	11.34±2.46	–1.95±1.75	0.996
Placebo	12.85±1.56	–1.96±1.34	
BAO/MAO			
Cinacalcet	0.20±0.05	0.17±0.07	0.076
Placebo	0.18±0.02	0.01±0.03	
Adjusted for baseline body weight			
BAO (mEq/h)			
Cinacalcet	2.14±0.58	1.41±0.53	0.039
Placebo	2.44±0.61	–0.34±0.56	
MAO (mEq/h)			
Cinacalcet	11.51±2.02	–1.95±1.60	0.995
Placebo	12.66±2.14	–1.97±1.69	
BAO/MAO			
Cinacalcet	0.19±0.04	0.18±0.05	0.045
Placebo	0.18±0.05	0.01±0.06	

Table 3 Baseline and change from baseline in serum and urine biochemistry

	Baseline (mean ± SE)	Change from baseline	
		Mean ± SE	*P* value for differences between groups
Gastrin (pg/ml)			
Cinacalcet	33.1±2.6	7.0±2.4	0.004
Placebo	38.5±4.9	−4.6±2.4	
PTH (pg/ml)			
Cinacalcet	47.8±6.0	−26.9±3.9	<0.001
Placebo	43.9±5.7	14.3±6.0	
Ionized calcium (mg/dl)			
Cinacalcet	4.8±0.0	−0.3±0.1	0.032
Placebo	4.8±0.1	−0.1±0.1	
Phosphorus (mg/dl)			
Cinacalcet	3.5±0.2	0.2±0.1	0.001
Placebo	3.5±0.1	−0.4±0.1	
24-hr UCa/Cr (mg/g)			
Cinacalcet	84.9±20.0	17.9±8.2	0.023
Placebo	114.3±28.3	−12.2±8.6	
24-hr UMg/Cr (mg/g)			
Cinacalcet	96.1±11.2	−10.1±5.9	0.983
Placebo	86.6±13.0	−10.4±11.5	

To convert values for serum gastrin to pmol/L, multiply by 0.47; serum PTH to pmol/L, multiply by 0.11; serum ionized calcium to mmol/L, multiply by 0.25; serum phosphorus to mmol/L, multiply by 0.323; 24-h UCa/Cr ratio to mmol/mol, multiply by 2.82; 24-h UMg/Cr ratio to mmol/mol, multiply by 46.70

study group, the mean change in gastrin during the intervention was positively correlated with change in BAO (r=0.530, P=0.029, Fig. 1). Changes in gastrin and MAO were not correlated.

As expected, in the cinacalcet group there were significantly more negative changes in serum PTH ($P<$ 0.001) and ionized calcium (P=0.032) and significantly more positive changes in serum phosphorus (P=0.001) and 24-h UCa/Cr (P=0.023) compared with placebo (Table 3). No differences were seen in the change in 24-h UMg/Cr in the two groups (Table 3).

Following randomization, 1 participant in the cinacalcet group reported more prolonged gum bleeding following a routine dental cleaning. No other adverse events occurred during the study.

Discussion

Gastric acid secretion is a complex process regulated by neuronal and hormonal pathways that converge at the level of the gastric parietal cell, which is responsible for releasing hydrochloric acid [10, 15, 16]. The classic pathways for acid secretion mediated by acetylcholine, gastrin and histamine have been well-described; however, the mechanism of acid-regulatory factors such as extracellular calcium has only been partly characterized. Recent ex vivo studies in animal and human gastric tissues have identified the CaR as a possible mediator for the gastric effects of calcium [8–10, 17]. Our data provide the first in vivo evidence that activation of the CaR increases serum gastrin levels and basal gastric acid secretion in healthy older men and women. We used the calcimimetic, cinacalcet, an agent known to be a potent and selective allosteric activator of the CaR [11]. Cinacalcet over an 11-day period did not have an added effect on pentagastrin-stimulated maximal gastric acid secretion; however, it does not discount the possibility that a higher dose of cinacalcet would have increased maximal acid secretion. We also cannot rule out the possibility that longer-term use would have increased maximal acid secretion, particularly via chronic stimulation of gastrin release. Longstanding hypergastrinemia is an important trophic factor for both parietal cells and enterochromaffin (ECL) cells, which secrete histamine, a major stimulator of gastric acid secretion [18]. These long-term effects of elevated gastrin have been well-described in patients on proton pump inhibitor therapy. Waldum et al. reported that a 3-month course of a proton pump inhibitor, omeprazole, in patients with reflux esophagitis, increased maximal acid secretion by over 50% and also elevated gastrin and histamine levels [19]. The mechanism of rebound acid hypersecretion may be related to the activation of the gastrin–ECL cell axis caused by drug-induced hypoacidity [19].

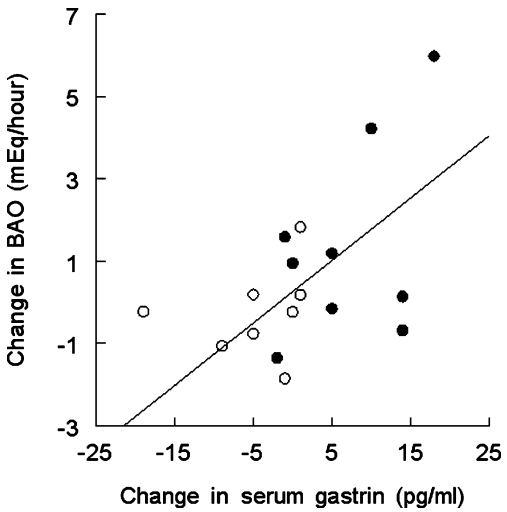

Fig. 1 Relationship between the change in serum gastrin level and the change in BAO in the cinacalcet group (*black circles*) and in the placebo group (*white circles*; r=0.530, P=0.029)

Augmenting gastric acid secretion may enhance calcium absorption. Oral calcium, particularly calcium carbonate, is better dissolved at a low pH [20]. In addition, in atrophic gastritis, calcium absorption is significantly reduced [21]. In a randomized controlled study by O'Connell et al., a 1-week course of a proton pump inhibitor significantly decreased calcium absorption in fasting elderly women [22]. We would expect that activation of the CaR may enhance intestinal calcium absorption; however, this remains to be determined.

Cinacalcet produced an anticipated decrease in serum PTH and serum ionized calcium and an increase in serum phosphorus. The 56% decrease in PTH over 11 days in our participants taking cinacalcet (30 mg daily) was modestly greater than that seen in patients with secondary hyperparathyroidism on hemodialysis who achieved approximately a 42% decrease after 8 days on 25 mg [23], and was comparable to the 50.4% reduction achieved in patients with primary hyperparathyroidism on 30 mg of cinacalcet twice daily [24].

Our results also demonstrate a rise in 24-h UCa/Cr with 11 days of cinacalcet. It is well-established in ex vivo studies that activation of the CaR decreases renal tubular calcium reabsorption in the cortical thick ascending limb of the loop of Henle and the distal convoluted tubule [25]. In vivo, the decrease in renal calcium reabsorption would be expected to result from both the direct effects of extracellular calcium on the renal CaR and the indirect effects of CaR-mediated inhibition of PTH secretion [25]. An increase in urinary calcium would also be expected if calcium absorption increased. Yet, to date, we are unaware of other in vivo data describing the effects of CaR allosteric activators on urine calcium excretion in healthy partic-

ipants. In rats, administration of a calcimimetic showed as much as a fourfold increase in urinary calcium excretion [26]. In disease states such as primary hyperparathyroidism, where filtered calcium in the kidney is high and exceeds the tubular calcium reabsorption capacity, cinacalcet normalized urinary calcium excretion in the setting of persistent mild PTH elevations, suggesting a change in the relationship between serum PTH levels and renal calcium reabsorption [24, 27]. Another study in primary hyperparathyroid patients by Silverberg et al., however, showed a transient rise in calcium excretion 2 h following a high dose (160 mg) of a calcimimetic, R-568 [28].

In ex vivo studies activation of the CaR decreases renal tubular reabsorption of magnesium as well as calcium (13). In our study, cinacalcet over an 11-day period did not increase magnesium excretion. Our null results, however, do not provide compelling evidence against the role of the CaR in regulating magnesium homeostasis since within-participant variation in urinary magnesium is high (36%), our sample size was small, and the tissue magnesium status (not reflected by urine or serum magnesium levels) was not defined in our study participants [29–31].

The strengths of this study include the fact that cinacalcet is specific to the CaR and that the dose used in the trial caused expected effects on serum PTH and ionized calcium levels. Furthermore, our participants' compliance and persistence in the study were very high. The present study also had some limitations. Our sample size was small. We measured gastric acidity as the inverse log of –pH [32], whereas other methods such as titratable acidity and 24-h intragastric pH monitoring are sometimes used. Despite this, and the inherently high variability in gastric acid measurements and urinary calcium measurements, we identified a significant effect of cinacalcet on basal gastric acid secretion and on urinary calcium excretion.

Cinacalcet in the relatively low doses of 15 then 30 mg per day for 11 days caused no gastrointestinal symptoms in our healthy participants. In contrast, dialysis patients with secondary hyperparathyroidism randomized to cinacalcet in doses of 30 to 180 mg daily had a 13% higher incidence of nausea and 14% higher incidence of vomiting than those on placebo [33]. In fact, gastrointestinal complaints are the most common reason for discontinuation of cinacalcet [34]. Increased gastric acid production may be a contributing cause of gastrointestinal complaints (or intolerance) in patients with renal failure. Studies in patients with primary hyperparathyroidism have reported no statistically significant increases in nausea and vomiting with cinacalcet 30 to 50 mg twice daily [24, 27]. Nonetheless, physicians prescribing a calcimimetic for long-term use should be aware of its impact on gastric acid production.

In summary, this study provides in vivo evidence that CaRs located in the stomach function as regulators of gastric acid secretion. Activation of the CaR with a specific CaR allosteric modulator, cinacalcet, increases serum gastrin levels and basal gastric acid output in healthy adults. It also caused the expected decreases in serum PTH and ionized calcium levels, and increases in serum phosphorus levels and urinary calcium excretion.

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Conflicts of interest None.

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