Kidney International, Vol. 43 (1993), pp. 1104–1109

Parathyroid sensing of the direction of change of calcium in uremia

JONATHAN T.C. KWAN, JEANETTE C. BEER, KATE NOONAN, and JOHN CUNNINGHAM

Departments of Nephrology and Clinical Biochemistry, The Royal London Hospital and Medical College, London, England, United Kingdom

Parathyroid sensing of the direction of change of calcium in uremia. It could be advantageous for the parathyroids to be able to sense not only the absolute concentration of extracellular Ca^{2+}, but also the rate and direction of change of Ca^{2+}, thereby allowing the parathyroids to respond earlier to threats to Ca^{2+} homeostasis. By using high and low Ca^{2+} dialysis in a single session, we examined the parathyroid response to direction of change of Ca^{2+} during acute Ca^{2+} perturbation in nine hemodialysis patients. Separate PTH/ionized calcium (PTH/iCa) response curves were generated for rising Ca^{2+} and falling Ca^{2+}. Significant directional hysteresis (higher PTH level during falling than during rising Ca^{2+}) was found. During hypercalcemia, PTH levels were between 2.2 and 1.6 times higher at iCa concentrations of between 0 and +0.1 mM above the baseline iCa, when Ca^{2+} was falling than when it was rising. During the phase of induced hypocalcemia, parathyroid fatigue was seen in six of the nine patients. Fatigue patients tended to have higher basal PTH (1-84) levels than those not showing fatigue. The existence of fatigue provides an explanation for directional hysteresis during hypocalcemia, and therefore parathyroid sensing of the direction of change of Ca^{2+} could not be assessed during hypocalcemia. These studies demonstrate a capacity of the parathyroids to sense the direction of movement of Ca^{2+} during hypercalcemia.

The principal physiological regulators of parathyroid hormone (PTH) secretion are extracellular calcium (Ca^{2+}) concentration [1, 2] and plasma calcitriol [1,25$(OH)_2D_3$] level [3, 4]. A sigmoidal relationship between PTH secretion and Ca^{2+} has been found both *in vitro* [5–8] and *in vivo* [9–11], such that even slight perturbation of the ambient extracellular ionized calcium (iCa) concentration induces a large reciprocal change in the PTH level within seconds [12]. This sigmoidal response has also been documented in dialysis patients with hyperparathyroidism [13–15] and in uremic patients receiving calcitriol therapy [16, 17]. In a recent study of hemodialysis patients, we have also found that calcitriol modified this PTH/iCa relationship in a manner suggestive of a reduction in the operating range but not the sensitivity of the parathyroids to Ca^{2+} [18].

Studies by others and ourselves have suggested that PTH release may be determined not only by the absolute Ca^{2+} concentration but also by the direction and the rate of change of Ca^{2+} [11, 19–21]. Physiologically, such an anticipatory capacity would be advantageous by enabling the parathyroids to recognize and respond more rapidly to threats to Ca^{2+} homeostasis.

An hysteretic relationship between PTH and Ca^{2+}, in which at a given blood Ca^{2+} concentration a higher level of PTH exists during induction of hypocalcemia than during recovery from hypocalcemia, and also during the recovery from induced hypercalcemia than during the induction of hypercalcemia, was first described in normal humans by Conlin et al [22]. Using an intact molecule (PTH, 1-84) assay these authors measured PTH levels during separate calcium and citrate infusions which gave rise to a perturbation of iCa concentration to 0.15 mM above and below the baseline iCa. More recently, Felsenfeld et al when examining the PTH (1-84) response to induced hypocalcemia and hypercalcemia by separate hypocalcemic and hypercalcemic dialyses also documented similar hysteretic findings in hemodialysis patients with low turnover aluminum bone disease [15].

However, because our own preliminary findings [18] indicated that during acute hypocalcemia many uremic patients exhibited parathyroid fatigue, whereby increased PTH release is not sustained during progressive hypocalcemia, the possibility exists that the previously described hysteretic relationship between PTH and Ca^{2+} may reflect no more than exhaustion of PTH stores within the parathyroid cells. The present study was designed to examine the hysteresis resulting from fatigue, and to distinguish it from a specific capacity of the parathyroid cells to sense the direction of change of Ca^{2+}.

Methods

Patients

Nine (6 males, 3 females) adult stable hemodialysis patients with varying degrees of hyperparathyroidism were studied. Their age ranged from 24 to 70 (median 55) years and they had been on hemodialysis from two to 60 (median 24) months. The renal diagnoses included: three adult polycystic kidney disease, two chronic glomerulonephritis, two unknown, one bilateral nephrectomy for renal cell cancer and one chronic pyelonephritis. At the time of the study, no patient had received vitamin D analogues for at least three months previously and none had undergone parathyroidectomy. All the patients were dialyzed on Nephross hollow-fiber dialyzers (Organon Teknika) and used standard dialysate buffered by acetate with a dialysate flow rate of 500 ml/min and blood flow rate of 3 ml/kg body wt/min. The response of the PTH/iCa relationship to pulse oral

Received for publication August 26, 1992
and in revised form October 19, 1992
Accepted for publication October 19, 1992

Table 1. Clinical details of patients

Patient no.	Age *years*	Sex	Duration of dialysis *months*	Basal ionized calcium *mmol/liter*	Serum phosphate *mmol/liter*	PTH *pg/ml*	Serum alkaline phosphatase[a] U/liter	Serum aluminium *μg/liter*
1	38	M	6	1.15	1.56	18	49	25
2	55	M	34	1.28	2.07	62	112	30
3	70	M	60	1.20	2.43	86	165	80
4	44	M	24	1.06	0.97	129	338	25
5	51	M	5	1.15	2.02	269	71	70
6	56	F	70	1.03	1.26	269	110	30
7	57	M	109	1.12	2.29	338	181	45
8	24	F	2	1.07	1.65	820	119	9
9	55	F	16	1.12	1.23	924	124	5

[a] ALP (normal range 30 to 120 U/liter)

calcitriol in six of the patients was the subject of a previous report [18].

Protocols

PTH/iCa curves were generated by sequentially dialyzing patients against a dialysate with a Ca^{2+} concentration of 2.5 mM, followed immediately by a period of Ca^{2+}-free dialysis. This was then followed by a further period of dialysis against Ca^{2+} concentration of 2.5 mM until the baseline iCa concentration was reached again. This cycle of high, low, and high Ca^{2+} dialysis aimed during a single dialysis session to raise, and then depress, the whole blood iCa by 0.25 mM above and below baseline, followed by a return to the baseline iCa. The procedure perturbed the patients' iCa in a predictable manner that showed good reproducibility on repeated studies. Throughout the procedure, blood samples for iCa and PTH measurement were taken at five minute intervals.

Assays

Intact parathyroid hormone (1-84) was measured by an immuno-radiometric assay (Allégro, Nichols Institute, San Juan Capistrano, California, USA). The normal range for this assay in our laboratory is 10 to 65 pg/ml, with a within-run CV of <7% and a between-run CV of <5% in the range 10 to 1000 pg/ml. All samples for PTH estimation from the same patient were measured in the same assay run. Ionized calcium was measured in fresh whole blood using a Kone "Microlyte" ion selective analyzer (Kone Instruments, Warrington, UK). The mean ± SD concentration of iCa in 50 normal subjects was 1.22 ± 0.06 mM. Serum total calcium (adjusted to 46 g/liter of albumin) [23], albumin, phosphate and alkaline phosphatase were measured by standard procedures using a Technicon SMAC III Analyser (Technicon, Basingstoke, UK). Serum aluminum was measured by flameless atomic absorption spectrophotometry [24].

Data analysis

Data are expressed as mean ± SE. The paired PTH and iCa values obtained were used to plot the PTH/iCa response curves, generated separately for each direction of movement of calcium in the individual patients. The PTH data were transformed semi-logarithmically to improve the linearity of the relationships and allow comparison as previously described [18]. Regression analyses of the semi-log plots were performed by the method of least squares. Data comparison was carried out by Student's paired *t*-test, with a P value of <0.05 being regarded as significant.

Results

The clinical details of the patients are shown in Table 1. The severity of hyperparathyroidism as judged by the basal PTH concentrations in these patients varied widely (18 to 820 pg/ml) with a mean of 324 pg/ml. Mean (range) serum alkaline phosphatase (NR 30 to 100) was 142 (49 to 338) U/liter. Serum aluminium was 35 (5 to 80) μg/liter with only two patients having levels elevated above 50 μg/liter. Radiological evidence of hyperparathyroid bone disease was seen in three patients (Nos. 4, 7 and 9) in whom serum alkaline phosphatase was also elevated.

The PTH/iCa curves from three different sections of the calcium perturbation protocol: (a) rising Ca^{2+} from baseline, (b) falling Ca^{2+}, and (c) rising Ca^{2+} towards baseline of the nine patients showed considerable heterogeneity despite the use of identical study protocols (Fig. 1).

The mean (SE, range) durations required to increase iCa from basal level by 0.25 mM, to reduce from peak hypercalcemia to 0.25 mM below the basal iCa level and to increase iCa from the nadir of hypocalcemia back to basal level again were 71 (8, range 30 to 115) minutes, 98 (10, 55 to 155) minutes and 34 (5, 15 to 65) minutes, respectively.

Directional hysteresis was evident in seven out of nine patients (Patients 1 through 3, 6 through 9), and particularly so in the hypocalcemic region. However, in six patients (Patients 2, 5 through 9), an additional component of "parathyroid fatigue" was seen during the phase of induced hypocalcemia. The likelihood of showing parathyroid fatigue appeared to relate to the basal PTH level; with one exception (Patient 2), all the patients who showed parathyroid fatigue had basal PTH levels between four and 15 times the upper limit of normal (mean 447 pg/ml). The three "non-fatigue" patients had normal (patient 1, 18 pg/ml) or only moderately raised PTH levels (patients 3, 86 pg/ml and 4, 129 pg/ml, respectively).

The presence of hysteresis in this region of induced hypocalcemia cannot therefore be ascribed with certainty to directional sensing of Ca^{2+} by the parathyroid cells. Further analysis of

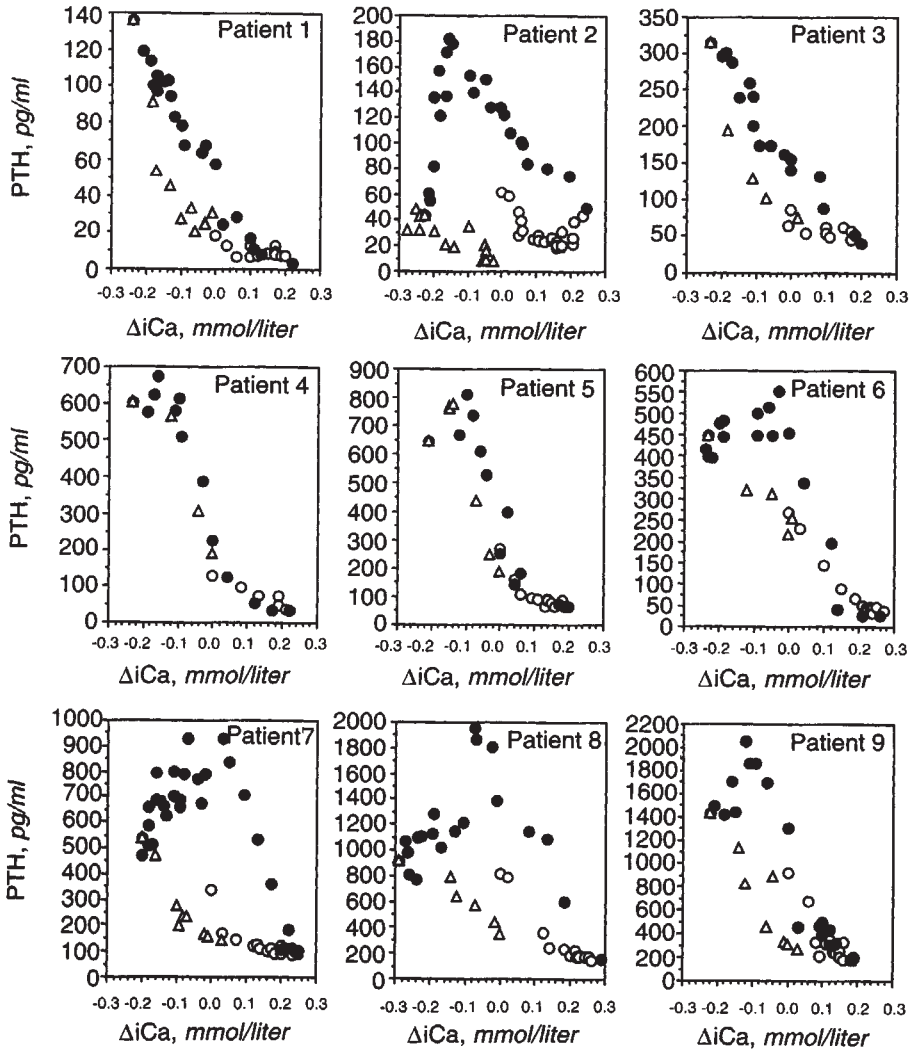

Fig. 1. *Individual PTH/iCa plots of the nine patients.* Symbols are: (○) rising calcium from baseline; (●) falling calcium from peak hypercalcemia to the nadir of hypocalcemia; (△) rising calcium from the nadir of hypocalcemia back to baseline.

parathyroid sensing of the direction of change in Ca^{2+} concentration was therefore confined to the region of induced hypercalcemia in which the period of rising Ca^{2+} preceded that of falling Ca^{2+}, thereby excluding fatigue as a possible confounding factor.

Data from the hypercalcemic region were used to generate the linear regression equations of the 18 $\log_e$PTH/iCa plots. Their corresponding coefficients of correlation, r, and P-values are shown in Table 2. This indicated that the mean slope of the regression lines during rising Ca^{2+} was significantly different from that of the falling Ca^{2+} (-5.3 ± 0.7 vs. -8.3 ± 1.0, respectively, $P < 0.03$), demonstrating that the parathyroid response to increment or decrement of Ca^{2+} was greater when the extracellular Ca^{2+} concentration was recovering from the peak of induced hypercalcemia (falling Ca^{2+}) than it was during the induction (rising Ca^{2+}). A composite plot of $\log_e$PTH against the change of iCa (ΔiCa) in the nine patients was constructed by pooling the data obtained using the regression equations to calculate $\log_e$PTH values at different values of ΔiCa (between 0 and +0.25 mM) for the individual patients (Fig. 2). This showed upward and rightward shift of the line representing the composite slope of falling Ca^{2+} in relation to that representing rising Ca^{2+}. The intercepts of the two composite lines in abscissae drawn at ΔiCa of 0, +0.05, and +0.1 mM were significantly different ($P < 0.004$, $P < 0.006$, $P < 0.02$, respectively), indicating that at these concentrations of iCa, serum PTH was significantly greater when iCa was falling than when it was rising. The respective ratios of PTH at these iCa concentrations were: 2.2 at 0 mM, 1.9 at +0.05 mM and 1.6 at +0.1 mM.

Across the hypercalcemic region (baseline iCa + 0.25 mM), the mean operating range (defined by the regression equations) of the parathyroids was significantly greater when Ca^{2+} was falling than when it was rising (521 ± 61 pg/ml vs. 215 ± 26 pg/ml, $P < 0.043$; Fig. 3).

Discussion

The regulation of PTH secretion is tightly linked to Ca^{2+} sensing by the parathyroid cells [25]. There is now an increasing body of evidence to support the concept that extracellular Ca^{2+}, as well as other di- and trivalent cations (such as Mg^{2+} and Ba^{2+}), modulates parathyroid function by a cell membrane receptor-like mechanism [26], with the cations being the primary messengers, which are coupled to intracellular effector systems by one or more guanine nucleotide regulatory proteins

Table 2. Linear regression equations of rising Ca^{2+} versus falling Ca^{2+}

Patient no.	Rising Ca^{2+}			Falling Ca^{2+}		
		r	*P*		*r*	*P*
1	y = 2.6–3.3x	0.548	0.0424	y = 3.8–11.8x	0.963	0.0005
2	y = 3.9–5.1x	0.864	0.0001	y = 4.8–3.2x	0.959	0.0002
3	y = 4.2–2.1x	0.735	0.0100	y = 5.1–6.3x	0.958	0.0026
4	y = 5.0–5.5x	0.914	0.0040	y = 5.2–8.9x	0.965	0.0077
5	y = 5.3–6.0x	0.894	0.0001	y = 5.7–7.6x	0.914	0.0161
6	y = 5.4–3.9x	0.869	0.0001	y = 7.4–11.4x	0.951	0.0001
7	y = 5.7–8.4x	0.976	0.0001	y = 6.2–12.3x	0.929	0.0073
8	y = 6.5–5.4x	0.915	0.0001	y = 7.4–5.8x	0.953	0.0123
9	y = 6.7–8.0x	0.862	0.0010	y = 6.8–7.9x	0.890	0.0013

Slopes: rising Ca^{2+} vs. falling Ca^{2+} (mean ± SE); −5.3(0.7) vs. −8.4(1.0), $P < 0.03$.
Intercepts (at x = 0): rising Ca^{2+} vs. falling Ca^{2+} (mean ± SE); 5.0 (0.4) vs. 5.8 (0.4), $P < 0.004$.
y = Log_ePTH (pg/ml); x = ΔiCa (mmol/liter).

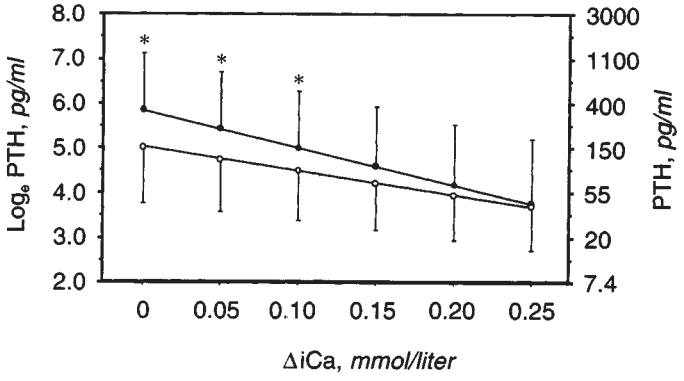

Fig. 2. *Composite plot of logePTH against ΔiCa to show directional hysteresis in the hypercalcemic region (baseline iCa to +0.25 mM).* Symbols are: (●) falling iCa; (○) rising iCa. *$P < 0.02$.

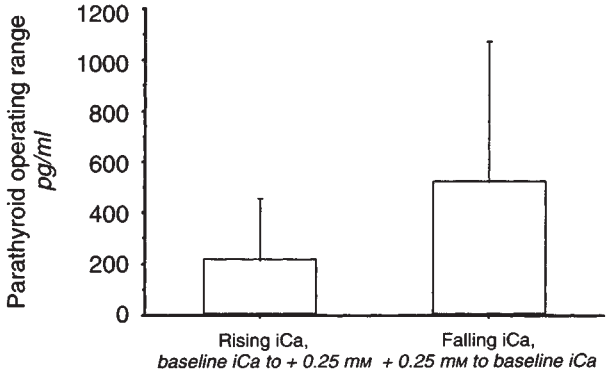

Fig. 3. *Mean ± SE PTH operating ranges of the parathyroid during rising and falling iCa in the hypercalcemic region (baseline iCa +0.25 mM).* $P < 0.043$.

(G proteins) [27, 28], which are in turn linked to intracellular second messenger signaling systems including phosphoinositides [29, 30], cAMP [31] and intracellular Ca^{2+} concentration [32, 33]. Recent studies have also suggested that this putative cation-receptor may have a molecular mass of 500,000 kD, with potentials for multiple metal binding sites [34], and exhibit properties suggestive of positive cooperativity on binding on Ca^{2+} [25].

Teleologically, it could be advantageous for the parathyroids to be able to sense the direction of change of Ca^{2+} as well as the absolute Ca^{2+} concentration when defending against threats to Ca homeostasis. In this study we demonstrated that, in the region of hypercalcemia, the sensitivity of the parathyroids to changes in Ca^{2+} (reflected by the slope of the PTH/iCa relationship) is greater and the operating range of the parathyroids (reflected by the intercepts of the PTH/iCa relationship at various abscissae in the region of hypercalcemia, Fig. 3) is set higher when Ca^{2+} is falling than when it is rising. This hysteretic phenomenon is unlikely to be an artifact caused by a lag between alterations in the glandular secretory activity and changes in the circulating levels of PTH as this would be expected to produce the opposite effect with PTH levels tending to be lower for a given level of Ca^{2+} during recovery from peak hypercalcemia. Furthermore, it is also unlikely that rate-dependent control of PTH levels during the induction and the accelerated recovery of hypercalcemia can explain this finding as in previous *in vivo* studies rate-dependence of the control of PTH secretion was not seen during hypercalcemia [20–22]. Nor is it likely that variability of changes of other cations and anions during dialysis is a confounding factor—such variability is likely to have been small, and its impact on PTH secretion slight or non-existent. The observations in this study therefore suggest that the parathyroids are able to sense the direction of change of Ca^{2+}, at least in the region of hypercalcemia.

The exact mechanism for this hysteresis is unclear. It could be explicable on the basis of the different levels of cooperativity caused by ligand-receptor binding as a result of different directional Ca^{2+} movements. Another explanation could be related to the changes in the extracellular Ca^{2+}-dependent intracellular degradation of PTH [35]. When the extracellular Ca^{2+} concentration is reduced, a greater proportion of the newly synthesized PTH escapes breakdown and is available for secretion. However, change in the rate of degradation of PTH in response to alterations in the extracellular Ca^{2+} concentration has been estimated to require at least 40 minutes [35]. This mechanism is therefore unlikely to play a significant role in the genesis of the directional hysteresis seen in the hypercalcemic region in which rapid PTH response to Ca^{2+} was seen within minutes of the change in the direction of Ca^{2+} movement (Fig. 1).

It is evident from the present study that when parathyroid

secretory capacity was assessed in this manner, marked parathyroid fatigue occurred during induced hypocalcemia in some patients. In the study by Felsenfeld et al [15], parathyroid fatigue was not described. This perhaps was because of patient selection, in that their patients were patients with low turnover aluminum bone disease who had relatively low basal and maximal PTH levels (132 ± 37 and 389 ± 91 pg/ml vs. 447 ± 140 and 1080 ± 311 pg/ml as found in our 6 "fatigue" patients). Lower PTH levels, comparable with those studied by Felsenfeld et al [15], were found in our three patients showing "no fatigue" during the study (78 ± 32 and 371 ± 159 pg/ml for basal and maximal PTH levels, respectively). That fatigue appeared to affect patients with more severe hyperparathyroidism could be explained on the basis of a more rapid depletion of intracellular PTH stores stimulated by hypocalcemia, on a background of rapid PTH release to maintain the high basal PTH level. A preliminary report of studies in normal subjects and patients with primary hyperparathyroidism using tri-sodium citrate infusion clamp technique to induce sustained and steady hypocalcemia of 0.2 mM below the baseline iCa has demonstrated a similar fatigue phenomenon, PTH (1-84) peaked within five to 10 minutes at a level four to six times the baseline concentration, but then declined to a steady state of only two to three times the baseline level [36].

Because it takes about 30 minutes for newly synthesized PTH to become available for secretion [35], the early secretory response of the parathyroid cells to hypocalcemia must involve the release of pre-formed hormone. In bovine species, such hormonal stores are thought to be sufficient to maintain maximal hypocalcemic stimulated rate of PTH secretion for about 1 to 1.5 hours [9]. It is also known that the changes in the level of pre-pro-PTH mRNA in response to alterations in extracellular calcium require ≥ three hours in rats [37] and ≥ 12 hours in cows [38]. Such responses are therefore too slow to provide increased amounts of newly synthesized hormone for release within minutes of the onset of persistent hypocalcemia. On the basis of these findings, and despite the fact that a greater proportion of the newly synthesized PTH escapes breakdown when the extracellular Ca^{2+} concentration is reduced [35], it is not surprising that parathyroid fatigue was seen in our patients who were subjected to progressive and prolonged hypocalcemia.

In our analysis of the PTH/iCa response, we have not defined "set point" in our PTH/iCa plots, partly because the physiological relevance of set point, maximal PTH, minimal PTH and slope to set point, as previously defined in *in vitro* systems [7] is less certain in *in vivo*. This is borne out in the present study in which the development of parathyroid fatigue presents both conceptual and analytical problems in that the physiological significance of the point at which fatigue develops is uncertain, and subsequent curve fitting and definition of those curve-derived indices dependent on the fatigue point may be flawed.

In conclusion, we have demonstrated directional hysteresis of the parathyroid response to Ca^{2+} in uremic patients with varying degrees of hyperparathyroidism. Only parathyroid sensing of the direction of change of Ca^{2+} can adequately explain the observed hysteresis during hypercalcemia. In contrast, during hypocalcemic perturbation parathyroid fatigue may confound the interpretation of hysteresis, especially in patients with severe or moderately severe hyperparathyroidism. These findings have demonstrated the existence of an additional teleologically plausible component to the regulation of PTH secretion by extracellular Ca^{2+}.

Reprint requests to Dr. John Cunningham, Department of Nephrology, The Royal London Hospital, Whitechapel, London E1 1BB, England, United Kingdom.

References

1. Sherwood LM, Potts JTJ, Care AD, Mayer GP, Aurbach GD: Evaluation by radioimmunoassay of factors controlling the secretion of parathyroid hormone: Intravenous infusions of calcium and wthylenediamine tetracetic acid in the cow and the goat. *Nature* 209:52–55, 1966
2. Sherwood LM, Mayer GP, Ramberg CF, Kronfeld DS, Aurbach GD, Potts JTJ: Regulation of parathyroid hormone secretion: Proportional control by calcium, lack of effect of phosphate. *Endocrinology* 83:1043–1051, 1968
3. Chertow BD, Baylink DJ, Wergedal JE, Su MH, Norman AW: Decrease in serum immunoreactive parathroid hormone in rats and in parathyroid hormone secretion in vitro by 1,25-dihydroxycholecalciferol. *J Clin Invest* 56:668–678, 1975
4. Silver J, Naveh-Many T, Mayer H, Schmeizer HJ, Povtzer MM: Regulation by vitamin D metabolites of parathyroid hormone gene transcription *in vivo* in the rat. *J Clin Invest* 78:1296–1301, 1986
5. Brown EM, Gardner DG, Aurbach GD: Calcium-regulated parathyroid hormone release in primary hyperparathyroidism. Studies *in vitro* with dispersed parathyroid cells. *Am J Med* 66:923–931, 1977
6. Rudberg C, Akerstrom G, Ljunghall S, Grimelius L, Johannson H, Pertroft H, Wide L: Regulation of parathyroid hormone release in primary and secondary hyerparathyroidism—Studies *in vivo* and *in vitro*. *Acta Endocrinol* 101:408–413, 1982
7. Brown EM: 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* 56:572–581, 1983
8. LeBoff MS, Shoback D, Brown EM, Thatcher J, Leombruno R, Beaudoin D, Henry M, Wilson R, Pallotta J, Marynick S, Stock J, Leight G: Regulation of parathyroid hormone release and cytosolic calcium by extracellular calcium in dispersed and cultured bovine and pathological human parathyroid cells. *J Clin Invest* 75:49–57, 1985
9. Mayer GP, Hurst JG: Sigmoidal relationship between parathyroid hormone secretion rate and plasma calcium concentration in calves. *J Clin Invest* 57:678–683, 1978
10. Rudberg C, Akerstrom G, Johansson H, Ljunghall S, Malmaeus J, Wide L: Effects of 1,25- and 24,25-dihydroxycholecalciferol on parathyroid hormone release from human parathyroid cells in vitro. *Acta Endocrinol Copenh* 105:354–359, 1984
11. Brent GA, LeBoff MS, Seely EW, Conlin PR, Brown EM: Relationship between the concentration and rate of change of calcium and serum intact parathyroid hormone levels in normal humans. *J Clin Endocrinol Metab* 67:944–950, 1988
12. Blum JW, Treschel U, Born W, Tobler PH, Taylor CM, Binswanger U, Fischer JA: Rapidity of plasma 1,25-dihydroxyvitamin D responses to hypo- and hypercalcemia in steers. *Endocrinology* 113:523–526, 1983
13. Felsenfeld AJ, Rodriguez M, Coleman M, Ross D, Llach F: Desferrioxamine therapy in hemodialysis patients with aluminum-associated bone disease. *Kidney Int* 35:1371–1378, 1989
14. Felsenfeld AJ, Rodriguez M, Dunlay R, Llach F: A comparison of parathyroid-gland function in haemodialysis patients with different forms of renal osteodystrophy. *Nephrol Dial Transplant* 6:244–251, 1991
15. Felsenfeld AJ, Ross D, Rodriguez M: Hysteresis of the parathyroid hormone response to hypocalcemia in hemodialysis patients with low turnover aluminum bond disease. *J Am Soc Nephrol* 21:1136–1143, 1991

16. DUNLAY R, RODRIGUEZ M, FELSENFELD A, LLACH F: Direct inhibitory effect of calcitriol on parathyroid function (sigmoidal curve) in dialysis patients. *Kidney Int* 36:1093–1098, 1989
17. DELMEZ JA, TINDIRA C, GROOMS P, DUSSO A, WINDUS DW, SLATOPOLSKY E: Parathyroid hormone suppression by intravenous 1,25-dihydroxyvitamin D. *J Clin Invest* 83:1349–1355, 1989
18. KWAN JTC, ALMOND MA, BEER JC, NOONAN K, EVAN SJW, CUNNINGHAM J: "Pulse" oral calcitriol in uraemic patients: Rapid modification of parathyroid response to calcium. *Nephrol Dial Transplant* 7:829–834, 1992
19. ADAMI S, MUIRHEAD N, MANNING RM, GLEED JH, PAPAPOULOS SE, SANDLER LM, CATTO GRD, O'RIORDAN JLH: Control of secretion of parathyroid hormone in secondary hyperparathyroidism. *Clin Endocrinol* 16:463–473, 1982
20. CUNNINGHAM J, ALTMANN P, GLEED JH, BUTTER KS, MARSH FP, O'RIORDAN JLH: Effect of direction and rate of change of calcium on parathyroid hormone secretion in uraemia. *Nephrol Dial Transplant* 4:339–344, 1989
21. GRANT FD, CONLIN PR, BROWN EM: Rate and concentration dependence of parathyroid hormone dynamics during stepwise changes in serum ionized calcium in normal humans. *J Clin Endocrinol Metab* 71:370–378, 1990
22. CONLIN PR, FAJTOVA VT, MORTENSEN RM, LEBOFF MS, BROWN EM: Hysteresis in the relationship between serum ionized calcium and intact parathyroid hormone during recovery form induced hyper- and hypocalcemia in normal humans. *J Clin Endocrinol Metab* 69:593–599, 1989
23. RAMAN A: The calcium fractions of normal serum. *Clin Biochem* 4:141–146, 1971
24. D'HAESE PC, VAN DE VYVER FL, DE WOLF FA, DE BROE ME: Measurement of aluminium in serum, blood, urine and tissue of chronic hemodialyzed patients by use of electrothermal atomic absorption spectrometry. *Clin Chem* 31:24–29, 1985
25. BROWN EM: Extracellular Ca^{2+} sensing, regulation of parathyroid cell function, and role of Ca^{2+} and other ions as extracellular (first) messengers. *Physiol Rev* 71:371–411, 1991
26. NEMETH EF: Regulation of cytosolic calcium by extracellular divalent cations in C-cells and parathyroid cells. *Cell Calcium* 11:323–327, 1990
27. FITZPATRICK LA, AURBACH GD: Calcium inhibition of parathyroid hormone secretion is mediated via a guanine nucleotide regulatory protein. *Endocrinology* 119:2700–2703, 1986
28. CHEN CJ, BARNETT JV, CONGO DA, BROWN EM: Divalent cations suppress 3′,5′-adenosine monophosphate accumulation by stimulating a pertussis toxin-sensitive guanine nucleotide-binding protein in cultured bovine parathyroid cells. *Endocrinology* 124:233–239, 1989
29. BROWN EM, ENYEDI P, LEBOFF M, ROTBERG J, PRESTON J, CHEN C: High extracellular Ca^{2+} and Mg^{2+} stimulate accumulation of inositol phosphates in bovine parathyroid cells. *FEBS Lett* 218:113–118, 1987
30. SHOBACK DM, MEMBRENO LA, MCGHEE JM: High calcium and other divalent cations increase inositol triphosphate in bovine parathyroid cells. *Endocrinology* 123:282–289, 1988
31. BROWN EM, GARDNER DG, WINDECK RA, AURBACH GD: Relationship of intracellular 3′,5′-adenosine monophosphate accumulation to parathyroid hormone release from dispersed bovine parathyroid cells. *Endocrinology* 103:2323–2333, 1978
32. SHOBACK DM, THATCHEM J, LEOMBRUNO R, BROWN EM: Effects of extracellular Ca^{++} and Mg^{++} in dispersed bovine parathyroid cells. *Endocrinology* 113:424–426, 1983
33. JUHLIN C, LUNDGREN S, JOHANSSON H, LORENTZEN J, RASK L, LARSSON E, RASTAD J, AKERSTROM G, KLARESKOG L: 500 Kilodalton calcium sensor regulating cytoplasmic Ca^{2+} in cytotrophoblast cells of human placenta. *J Biol Chem* 265:8275–8280, 1990
34. COHN DV, MACGREGOR RR: The biosynthesis, intracellular processing and secretion of parathormone. *Endocrinol Rev* 2:1–26, 1981
35. HABENER JF, POTTS JT JR: Parathyroid hormone: Biochemical aspects of biosynthesis, secretion, action, and metabolism. *Physiol Rev* 64:985–1053, 1984
36. SCHWARZ P, SØRENSEN HA, MCNAIR P, TRANSBØL I: Induced hyocalcaemia and intact PTH responsiveness in patients with primary hyperparathyroidism, primary hypoparathyroidism and normal man. (abstract) *Bone Miner* 17:129, 1992
37. YAMAMOTO M, IGARISHI T, MURAMATSU M, FUKAGAWA M, MOTOKURA T, OGATA E: Hypocalcemia increases and hypercalcemia devreases the steady state level of parathyroid hormone messenger RNA in the rat. *J Clin Invest* 83:1053–1056, 1989
38. RUSSELL J, LETTIERI D, SHERWOOD LM: Direct regulation by calcium of cytoplasmic messenger ribonucleic acid coding for preproparathyroid hormone in isolated bovine parathyroid cells. *J Clin Invest* 72:1851–1855, 1983