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Research Article

The secretion of parathyroid hormone (PTH) and calcitonin (CT) was studied in 30 patients with medullary thyroid carcinoma. Most patients with elevated levels of CT were normocalcemic and also had normal basal levels of PTH. Five of six patients with associated hyperparathyroidism were hypercalcemic and had elevated basal PTH levels. Hormone secretion was also studied during infusions with standard and low doses of calcium. PTH unexpectedly increased during 12 of 18 calcium infusions. Such a paradoxical increase in PTH was seen in those patients with the greatest increase in CT and the least increase in calcium during the calcium infusion. Accordingly, increases in PTH concentration during the calcium infusions could be correlated directly with increases in CT and correlated inversely with increases in calcium. These observations suggest that, in some patients with medullary thyroid carcinoma, a further increase in the abnormally elevated CT levels may stimulate PTH secretion. Therefore, at least in acute studies, there may be a functional, as well as a genetic, relationship between the secretion of these two hormones in patients with this thyroid tumor.

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Secretion of Parathyroid Hormone in Patients with Medullary Thyroid Carcinoma

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ABSTRACT The secretion of parathyroid hormone (PTH) and calcitonin (CT) was studied in 30 patients with medullary thyroid carcinoma. Most patients with elevated levels of CT were normocalcemic and also had normal basal levels of PTH. Five of six patients with associated hyperparathyroidism were hypercalcemic and had elevated basal PTH levels. Hormone secretion was also studied during infusions with standard and low doses of calcium. PTH unexpectedly increased during 12 of 18 calcium infusions. Such a paradoxical increase in PTH was seen in those patients with the greatest increase in CT and the least increase in calcium during the calcium infusion. Accordingly, increases in PTH concentration during the calcium infusions could be correlated directly with increases in CT and correlated inversely with increases in calcium. These observations suggest that, in some patients with medullary thyroid carcinoma, a further increase in the abnormally elevated CT levels may stimulate PTH secretion. Therefore, at least in acute studies, there may be a functional, as well as a genetic, relationship between the secretion of these two hormones in patients with this thyroid tumor.

INTRODUCTION

It is well established that there is a high incidence of primary hyperparathyroidism in patients with medullary thyroid carcinoma (1-3). The cause for this association is not well established, but it may have either a genetic or functional basis (3-5). To pursue earlier preliminary observations (6), we have studied the secretion of parathyroid hormone (PTH)¹ and calcitonin (CT) in 30

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¹Abbreviations used in this paper: CP, calcitonin; PTH, parathyroid hormone.

patients with medullary thyroid carcinoma. Hormone measurements were made in the basal state and during tests of hormone secretion. Our results suggest that there may be a functional relationship between the secretion of PTH and CT in patients with medullary thyroid carcinoma.

METHODS

30 patients with histologically proven medullary thyroid carcinoma were studied; most patients had a family history of this tumor. Basal measurements of PTH, CT, and calcium were made in each patient. All studies were performed before any neck surgery. 18 calcium infusions were performed in 10 patients. For 13 of the infusion studies, calcium as the chloride salt was infused at a rate of 5 mg/kg/h for 3-4 h. In one infusion (Table I, no. 3), calcium was given at a rate of 0.5 mg/kg/h for 3 h. In five infusions (Table I, nos. 6, 7, 15, 16, 18), 150 mg of calcium was given in 50 ml of normal saline over 5-10 min.

Blood samples were collected for calcium and hormone measurements at hourly intervals during the 3-4 h infusions and at 10-15-min intervals for up to 3 h after the short calcium infusions. CT and PTH were measured by previously described radioimmunoassays (7-10). The antiserum used for PTH measurement reacts with both the amino terminus and carboxy terminus of the PTH molecule (9, 10). All samples were measured in replicate assays at multiple dilutions. Phase separation was accomplished by charcoal-coated dextran (10). Intra- and inter-assay variation were 10 and 20%, respectively. The normal range for PTH in this assay system is 200-800 pg/ml of human PTH; however, there is some overlap among subjects with normal and abnormal parathyroid function (9, 11). In our CT assay, most normal subjects have hormone concentrations of less than 100 pg/ml (12). Calcium was measured by atomic absorption spectrophotometry.

RESULTS

Fig. 1 summarizes the basal measurement of PTH and CT in the patients studied. There is no apparent correlation between the two hormones. Most subjects had elevated levels of CT and were normocalcemic. At surgery, six subjects (O) had primary hyperparathy-

TABLE I
PTH, CT, and Calcium Levels before and after Calcium Infusion in Medullary Thyroid Carcinoma

	PTH			CT			Calcium		
	Basal	Infusion	Percent change	Basal	Infusion	Percent change	Basal	Infusion	Percent change
	pg/ml			pg/ml			mg/100 ml		
1. (D. C.)	520	730	+40	433	1,620	+274	9.2	9.9	+8
2. (C. D.)	830	1,124	+35	420	8,066	+1,820	8.8	11.6	+32
3. (B. H.)	517	980	+89	15,733	25,666	+63	9.5	9.9	+4
4. (B. H.)	765	450	-41	23,000	27,000	+17	9.5	13.8	+45
5. (W. N.)	100	290	+190	560	3,126	+458	10.1	11.8	+17
6. (L. D.)	200	1,350	+575	66	1,007	+1,546	10.0	10.2	+2
7. (L. D.)	330	1,420	+330	250	1,075	+330	8.9	9.8	+10
8. (L. D.)	270	1,230	+355	280	2,700	+864	10.2	12.4	+22
9. (L. D.)	470	1,900	+304	95	3,575	+3,663	9.4	12.4	+32
10. (F. U.)	488	260	-46	69,333	80,133	+15	8.5	13.0	+53
11. (K. Y.)	710	270	-61	2,425	2,300	-5	9.0	12.1	+34
12. (O. U.)	310	372	+20	1,000	1,500	+50	9.5	13.6	+43
13. (D. F.)	2,267	1,533	-32	4,267	5,637	+32	11.7	13.4	+15
14. (D. F.)	2,217	1,306	-41	3,933	4,867	+23	11.5	13.6	+16
15. (D. F.)	1,750	2,275	+30	3,833	5,400	+40	11.9	12.4	+4
16. (D. F.)	1,217	2,567	+110	3,500	4,707	+34	11.6	12.6	+9
17. (M. C.)	64	25	-60	4,085	10,000	+144	9.6	12.0	+25
18. (M. C.)	20	770	+3,750	1,517	6,200	+308	8.4	9.1	+8

The maximum change for each of the parameters is indicated. For the high dose calcium infusions (1, 2, 4, 5, 8-14, 17), this usually took place at the end of the study. Fig. 4, left panel, is exemplary of the changes during the low dose calcium infusions (3, 6, 7, 15, 16, 18). Each of the infusion values for PTH and CT is significantly ($P < 0.05-0.001$) different from its control by Student's *t* test. All patients in this study had familial medullary thyroid carcinoma. Identification of the patients is indicated by their initials in parentheses.

roidism, five had hyperplasia, and one had an adenoma; the parathyroid gland was either normal or not examined in the rest. Each of the patients with hyperplasia had a family history of medullary thyroid carcinoma; the patient with adenoma had no family history of the thyroid tumor. Of the six patients with surgically proven hyperparathyroidism, all were hypercalcemic (10.8-14.0 mg/100 ml), five had elevated basal levels of PTH, and one had a concentration of 630 pg/ml, which was inappropriately high for the calcium of 11.6 mg/100 ml. The remaining calcium abnormality, found in one patient (not infused), was hypocalcemia (7.9 mg/100 ml), presumably on the basis of diarrhea and malabsorption.

Table I summarizes all of the data in the 18 calcium infusions. Fig. 2 shows the changes in PTH that occurred during the infusions. In 12 of the studies, there was an unanticipated increase in PTH after the infusion of calcium. In these 12 subjects, calcium infusion led to a mean increase in PTH of 485%. Although PTH was suppressed in 6 calcium infusions, for all 18 of the calcium infusions, there was still a mean increase in PTH of 308%. When the increases in PTH during the calcium infusions were rank ordered, they correlated

directly with the increases in CT during the infusion ($r = 0.76, P < 0.001$) and correlated inversely with the increase in calcium during the infusion ($r = -0.62, P < 0.01$) (13). In five normal subjects, the short (150 mg) calcium infusion either suppressed or had no effect on plasma PTH.

In three patients, it was possible to compare the effects of two types of calcium infusion on PTH (Figs. 3 and 4). In one of these patients (Fig. 3) a standard (15 mg/kg/3 h) calcium infusion (Table I, no. 4) produced a 45% increase in calcium and only a 17% increase in CT. During this study, PTH was suppressed by 41%. In the same patient, a low dose (1.5 mg/kg/3 h) calcium infusion (Table I, no. 3) increased calcium by only 4% but stimulated CT by 63%. During this study, PTH was increased by 89%. In another patient (Fig. 4), two standard (15 mg/kg/3 h) calcium infusions (Fig. 4, right) each increased plasma calcium by approximately 2 mg and stimulated CT by 32 and 23%, respectively; PTH was suppressed by 32 and 41%, respectively (Table I, nos. 13 and 14). In the same patient, two 10-minute infusions of only 150 mg of calcium (Fig. 4 left) had a minimal influence on plasma calcium but did increase plasma CT

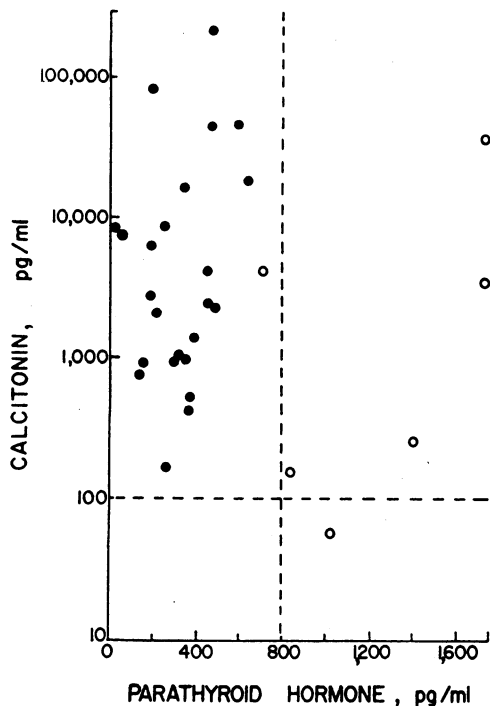


FIGURE 1 Basal concentrations of PTH and CT in 30 patients with medullary thyroid carcinoma. Dashed lines indicate upper limits of normal for each of the hormone concentrations. Most of the patients had elevated basal levels of CT. Only six patients (○) had hypercalcemia and hyperparathyroidism. Five of these six patients had elevated basal levels of PTH; in the other, PTH was near the upper limits of normal and inappropriately high (630 pg/ml) for the elevated calcium of 11.6 mg/100 ml. There was no correlation among plasma CT, PTH, or calcium.

comparably to the standard calcium infusion; PTH was stimulated by both of these short calcium infusions (Table I, nos. 15 and 16). Similarly, in the third patient, a standard calcium infusion (Table I, no. 17) led to a suppression of PTH, while a low dose calcium infusion (Table I, no. 18) stimulated PTH.

DISCUSSION

Two explanations have been offered for the high incidence of hyperparathyroidism in patients with medullary thyroid carcinoma. The most widely supported view is that the two diseases are genetically related (2, 3). An alternative explanation is that there is a functional relationship between them: since the majority of patients with medullary thyroid carcinoma are normocalcemic, it has been speculated that the hyperparathyroidism is due to a response of the parathyroid glands to the high levels of the hypocalcemic peptide, CT that are found in patients with this tumor (4, 5).

Our measurements of basal levels of PTH and CT (Fig. 1) tend to support the view that the hyper-

parathyroidism and hypercalcitoninism are genetically, rather than functionally, related. There is no correlation between basal levels of PTH and CT. In addition, of the 20% of patients with thyroid tumor who did have associated hypercalcemia and hyperparathyroidism, all but one had a family history of medullary thyroid carcinoma. However, studies during calcium infusion in patients with medullary thyroid carcinoma indicate that the relationships between PTH and CT may be more complicated than revealed by only basal determinations. Calcium infusion did result in the expected increase in CT concentration in these patients (Table I). However, two-thirds of the calcium infusions led to an unexpected increase in PTH (Fig. 2), rather than the anticipated decrease of PTH that is usually caused by induced hypercalcemia. PTH was stimulated rather than suppressed by those calcium infusions that produced the greatest increase in calcitonin and the smallest increase in calcium. In fact, the increases in PTH during calcium infusion could be correlated directly with the increases in CT and correlated inversely with increases in calcium.

One possible explanation for this paradoxical in-

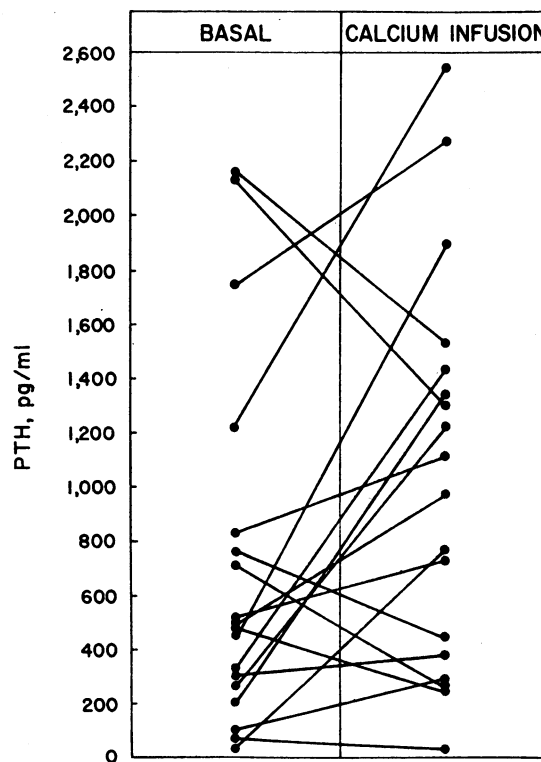


FIGURE 2 The effect of 18 calcium infusions on PTH secretion in 10 patients with medullary thyroid carcinoma. Both standard and low dose calcium infusions are represented (see Table I and Figs. 3 and 4). Plotted is the maximal increase in hormone concentration. Each of the infusion values is significantly ($P < 0.05-0.001$) different from its control by Student's *t* test.

crease in PTH during calcium infusion is that the abnormal increase in CT that occurs in these patients during the infusion is a stimulus to PTH secretion: in those infusions in which there is also a marked increase in calcium, the rise in calcium may counteract this proposed stimulatory effect of CT on PTH; in those infusions in which there is only a small increase in calcium, the stimulatory effect of CT on PTH becomes manifest.

We were able to test this hypothesis directly in three of our patients with medullary thyroid carcinoma. In one (Fig. 3), a low dose calcium infusion (Table I, no. 3), which produced a 63% increase in CT but only an 0.4-mg increase in calcium, resulted in almost a doubling of PTH; in the same patient, a standard dose calcium infusion (Table I, no. 4), which increased calcium by 4.3 mg but only increased CT by 17%, resulted in a suppression of PTH secretion. In another patient, two standard dose (Table I, nos. 13 and 14) and two low dose (Table I, nos. 15 and 16) calcium infusions were performed (Fig. 4). The increases in CT during all four calcium infusions were comparable. However,

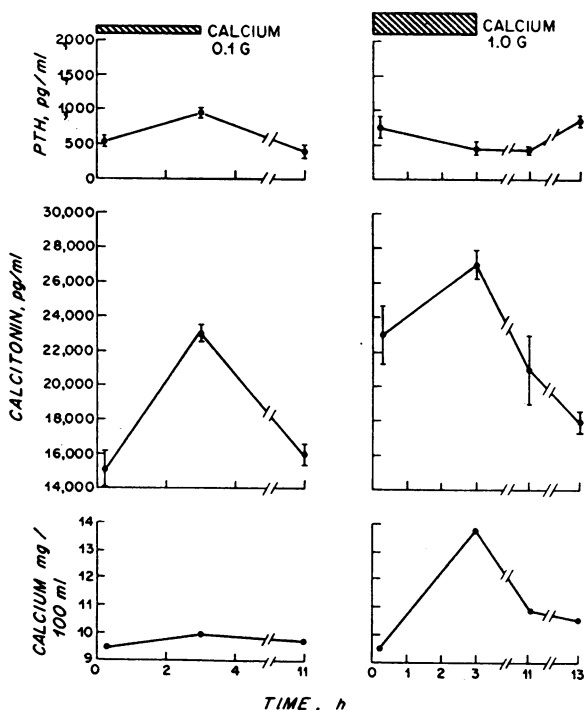


FIGURE 3 A standard (15 mg/kg/3 h; Table I, No. 4) and low dose (1.5 mg/kg/3 h; Table I, no. 3) calcium infusion in a patient with medullary thyroid carcinoma. Both infusions stimulated CT secretion. During the standard infusion (right), calcium increased by 45%, and PTH was suppressed. During the low dose infusion (left) calcium increased only 4%, and PTH was unexpectedly increased. The high dose infusion followed the low dose infusion by 5 days. The total dose of calcium is indicated (brackets represent standard error).

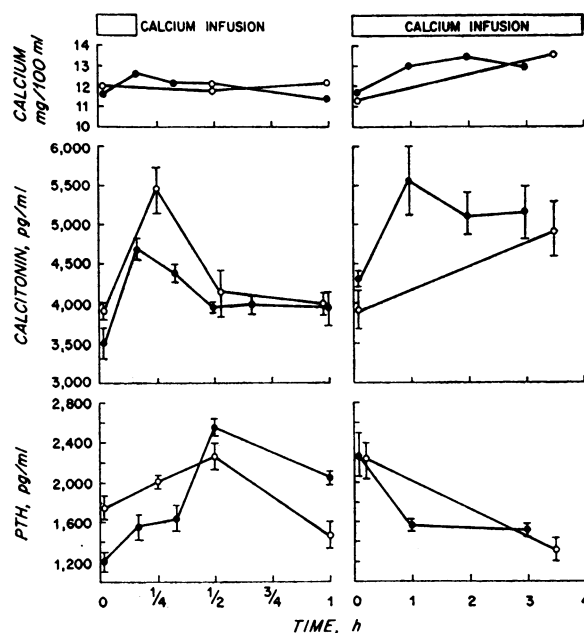


FIGURE 4 Two standard (5 mg/kg/h) calcium infusions (right) and two short (150 mg in 10 min) calcium infusions (left) in a patient with medullary thyroid carcinoma. The standard infusions (Table I, nos. 13 and 14) produced approximately a 2-mg increase in calcium, an increase in CT, and a decrease in PTH. However, the short infusions (Table I, nos. 15 and 16), which elevated CT but had minimal effects on blood calcium, produced an unexpected increase in PTH. The four infusions were done approximately 5 days apart and in random order (brackets represent standard error).

during the standard calcium infusions, calcium increased by several milligrams; but during the low dose calcium infusions, calcium increased by less than 1 mg. The secretion of PTH was stimulated during the low dose calcium infusion and suppressed by the standard dose calcium infusion. In the third patient, a standard calcium infusion (Table I, no. 17) decreased PTH, while a low dose infusion (Table I, no. 18) increased PTH. Therefore, in each of these three patients, a low dose calcium infusion stimulated, while a standard calcium infusion suppressed, plasma PTH. Any normal fluctuations of calcium in these patients are more likely to approximate those induced by the low dose calcium infusions that stimulated the secretion of PTH.

Further investigations are necessary to establish the relationship between PTH and CT in patients with medullary thyroid carcinoma. Such investigations should also utilize provocative agents for CT secretion that do not influence blood calcium. Glucagon and gastrin may be suitable CT secretagogues (2, 12, 14), and studies of their effects are in progress. However, the variable effect of both glucagon and gastrin on CT secretion may make such studies difficult to interpret (15-18).

Although our results do suggest a functional relationship between hyperparathyroidism and medullary thyroid carcinoma, these observations cannot be interpreted to indicate that CT has a direct effect on PTH secretion in normal subjects. The peripheral concentration of CT in our patients is much higher than ever seen in normal subjects, and the concentration in the vicinity of the parathyroid glands may be even much higher. Therefore, this apparent direct stimulation of PTH by CT should be considered a pharmacological effect at this time.

However, our observations do suggest that, under certain circumstances, CT may stimulate the secretion of PTH; this effect may play some role in the high incidence of hyperparathyroidism in patients with medullary thyroid carcinoma. This view is supported by in vitro studies which demonstrate that large doses of CT increase the secretion of PTH by porcine parathyroid gland slices (19). Although Melvin Tashjian, and Miller (3) did not observe any increase in PTH during calcium infusion in six patients with medullary thyroid carcinoma, a standard calcium infusion was used that increased plasma calcium up to 13–14 mg/100 ml; this marked increase in calcium may have countered any stimulatory effect of CT on PTH. In addition, one of their patients did not exhibit the expected decrease in PTH during the calcium infusion. A difference in specificity of the immunoassay procedures for PTH used in our study and in the study of Melvin et al. may also explain some of the discrepancies. The PTH antisera used in this study has reactivity that spans the linear sequence of the molecule (9–11). Melvin et al. do not give any data regarding the specificity of their PTH antisera. In any case, additional studies should be designed to investigate further the relationship between CT and PTH in patients with medullary thyroid carcinoma.

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