Plasma Human Calcitonin (hCT) Levels in Normal and Pathologic Conditions, and their Responses to Short Calcium or Tetragastrin Infusion

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Synopsis

Plasma hCT levels were less than 50 pg/ml in 50 normal subjects. In 16 patients with medullary carcinoma of the thyroid (MCT), plasma hCT levels were distinctively elevated and they fell significantly after total thyroidectomy, but in 11 of them plasma levels were still high, indicating the presence of metastases. In 74 patients with the other types of malignancy, plasma hCT levels were found to be high in 9 cases (3 oat cell carcinoma of the lung, 4 malignant carcinoids, one malignant pheochromocytoma and one acute myelocytic leukemia). Except for the leukemic case, all these tumors were derived from neural crest. In 12 patients with primary hyperparathyroidism, plasma hCT levels were less than 20 pg/ml. In 13 hypoparathyroid patients, two with pseudohyopoparathyroidism and one with pseudoidiopathic hypoparathyroidism, plasma hCT levels were slightly elevated. Some patients with uremia had elevated plasma hCT levels, but there was no relation between plasma levels of hCT and those of PTH, urea nitrogen or creatinine. In response to Ca (4.5 mg/kg/10 min) or tetragastrin (4 μg/kg/5 min) infusion, a marked increase in plasma hCT was observed in all patients with MCT, but not in normal subjects. In 5 hypoparathyroid patients, a significant increase to both stimuli was also observed in all cases. Two patients with pseudopseudohypoparathyroidism responded to the Ca load.

These results indicate that the determination of plasma hCT levels especially after the short Ca or tetragastrin infusion is important to study various pathological conditions.

Recently it has become possible to determine plasma levels of human calcitonin (hCT) using radioimmunoassay (Clark et al., 1969; Tashjian et al., 1970; Dietrich et al., 1970; Deftos, 1971; Heynen et al., 1974), but this radioimmunoassay is not so popular when compared with that of the other polypeptide hormones because of shortness of immunizing antigen. We have reported previously a radioimmunoassay for porcine calcitonin (Adachi et al., 1974), but in that attempt there was no cross reaction with hCT. In the present study, we used the antiserum obtained from rabbits immunized with synthetic hCT, which was suitable to measure plasma levels of hCT.

Using this assay system, we have determined plasma hCT levels in normal subjects and in patients with various types of malignant tumor including medullary car-
cinoma of the thyroid (MCT), uremia and parathyroid disorders. In addition, we have evaluated the effect of 10-min calcium infusion (Ca 4.5 mg/kg) and of 5-min tetragastrin (4 μg/kg) infusion on plasma hCT levels in normal subjects and in patients with MCT and parathyroid disorders.

Materials and Methods

Synthetic human calcitonin (hCT), 400 MRC units per mg, a gift from Dr. J. L. Hughes of the Organic Chemistry Department of Armour Pharmaceutical Company, Kankei, Ill., U.S.A. (Lot 692-081-2), was used for iodination and the assay standard. Human CT used for immunization was the synthetic product made by Teikoku Hormone Manufacturing Co., Tokyo, Japan (Gondo et al., 1973). Another batch of synthetic hCT was obtained from E. Merck, Darmstadt, Germany. Porcine CT, 73.4 MRC units per mg, and salmon CT, 4290 MRC units per mg, were obtained from Armour Pharmaceutical Company. Highly purified bovine parathyroid hormone (bPTH) was purchased from Wilson Laboratories, Park Forest South, Ill., U.S.A. Synthetic human gastrin I was obtained from Imperial Industries Ltd., Alderly Park, Macclesfield, Cheshire, England and highly purified glucagon from Eli Lilly Co., Indianapolis, Indiana, U.S.A. Tetragastrin used for the stimulation test was the synthetic product of Teikoku Hormone Manufacturing Co., Tokyo, Japan. Synthetic secretin was kindly provided by Prof. Noboru Yanaihara, Department of Bioorganic Chemistry, Shizuoka College of Pharmacy, Shizuoka, Japan. Plasma parathyroid hormone (PTH) levels were determined by the use of radioimmunoassay as reported previously (Tanaka et al., 1974).

Antisera were obtained from rabbits immunized with hCT conjugated with bovine serum albumin. The conjugated material which contained about 1 mg hCT was emulsified with an equal volume of complete Freund’s adjuvant and was injected subcutaneously to rabbits in multiple sites at least one month apart for 6 months.

Iodination and purification of hCT:

Synthetic hCT was labeled with ¹²³I according to the method reported by Hunter and Greenwood (Hunter and Greenwood, 1962). One and a half ml 5% egg albumin solution in 0.4 M phosphate buffer, pH 7.5, was added to the iodination tube and mixed well. The iodinated mixture was transferred to a tube containing 5 mg QUSO, which was washed twice with 0.05 M Mercaptoethanol and extracted with 1.5 ml solution of 20% acetic acid in 10% acetic acid (Tashjian, 1969). The iodinated hCT was further purified by passing through Sephadex LH-20 column (0.9×20 cm) with 0.1 M acetic acid as eluent. Two peaks were usually observed following column chromatography and the first peak was used for the assay. This repurification was carried out immediately before adding to the incubation mixture. The specific activity was around 60 μCi/μg when determined by adding the iodinated hCT to the radioimmunoassay system.

Preparation of incubation mixture:

The final incubation volume was 0.5 ml, which consisted of 0.1 ml standard hCT diluted with CT free plasma or 0.1 ml assay sample, 0.1 ml ¹²³I-hCT, 0.1 ml diluted antiserum and 0.2 ml diluted buffer containing 0.1% normal rabbit serum and 0.025 M EDTA. The diluted buffer was 0.1 M phosphate buffer, pH 7.5, containing 0.5% porcine serum albumin and 500 KIU/ml Trasylol. This diluted buffer was used to dilute ¹²³I-hCT and antiserum. Sheep or porcine plasma was used as hCT free plasma, because it behaved identically as plasma obtained from the patient who had received total thyroparathyroidectomy.

The stock solution of standard hCT (100 ng/ml 0.1 M acetic acid) was diluted with 0.1 M acetic acid containing 0.1% porcine serum albumin to a concentration of 5 ng/ml, which was kept frozen at −70°C until incubation mixture was set up. To make further dilutions for composing the standard curve, hCT free plasma was employed.

After incubating at 4°C for 24 hr, about 1,000 cpm labeled hCT was added to each tube and 7 tubes containing only the labeled hCT were prepared to obtain the total counts. Further incubation was carried out for 72 hr at 4°C and 0.1 ml of sheep antirabbit gamma globulin serum diluted properly was added. After another 48 hr incubation at 4°C, the tubes were centrifuged in 1,500×g for 25 min by a cold centrifuge. After decanting the supernatants the precipitates were counted in a well-type gamma-counter.

Patients studied:

Blood samples were collected after an overnight fast in 50 normal subjects, 90 patients with various types of malignant tumor, 10 with pituitary diseases, 38 with chronic renal failure and 27 with parathyroid diseases. Malignant tumors of 90 patients were as follows: 16 medullary carcinomas of the thyroid (MCT), 15 non-medullary carcinomas of the thyroid, 19 carcinomas of the lung (9 oat cell carcinomas and 10 squamous cell carcinomas), 12 malignant carcinoids, 9 malignant melanomas, 7 carcinomas of the esophagus, 5 thymomas and 2 myelocytic leukemia (acute and chronic). The other 5 patients were an individual case of multiple myeloma, lymphosarcoma,
pheochromocytoma, ectopic pinealoma and carcinoma of the stomach. None had hypercalcemia.

Parathyroid diseases of 27 patients were as follows: 12 primary hyperparathyroidism, 5 pseudohyperparathyroidism, 4 pseudoidiopathic hypoparathyroidism (Nusynowitz, 1973), 4 idiopathic hypoparathyroidism and 2 pseudopseudohypoparathyroidism. Plasma hCT levels were determined before therapy.

Pituitary diseases of 10 patients were as follows: 6 active acromegaly, 2 untreated pituitary Cushing’s syndrome and 2 postadrenalectomy Cushing’s syndrome with pituitary tumor.

Calcium and tetragastrin infusion test:

In 6 normal subjects and 16 patients, the effect of 10-min calcium infusion (Ca 4.5 mg/kg) on plasma hCT levels was examined. Two per cent CaCl₂ and 50 ml saline as a vehicle were used. Of the 16 patients tested, 7 had MCT, 2 had primary hyperparathyroidism, 2 had pseudohypoparathyroidism, 2 had idiopathic hypoparathyroidism, 2 had pseudopseudohypoparathyroidism, and one had pseudoidiopathic hypoparathyroidism. Blood samples were collected before and 10, 25, 40 and 70 min after starting the infusion to determine hCT and Ca levels.

In 7 normal subjects and 13 patients, the effect of tetragastrin (4 µg/kg) administered intravenously on plasma hCT levels was also examined. Tetragastrin solution (150 µg/ml) was injected slowly for 5 min. Of the 13 patients examined, 5 had MCT, 2 had primary hyperparathyroidism, 2 had pseudohypoparathyroidism, 2 had idiopathic hypoparathyroidism, one had pseudopseudohypoparathyroidism, and one had pseudoidiopathic hypoparathyroidism. Blood was obtained before and 10, 20 and 35 min after starting the infusion to determine hCT and Ca levels.

Results

Iodination, purification and standard curve

After iodinated and purified with QUSO, the iodinated hCT was chromatographed by passing through a Sephadex LH-20 column using 0.1 M acetic acid for elution just prior to adding the tracer to the incubation. As shown in Fig. 1, two peaks were usually observed and the front peak was used for the assay. The standard curve obtained using the chromatographed ¹²⁵I-hCT was considerably more sensitive than that obtained using the non-chromatographed material, as shown in Fig. 2. A 10% fall of the tracer B/T was usually observed by adding 4 pg/tube of hCT. The

![Fig. 1. The repurification of ¹²⁵I hCT. The iodinated hCT was purified by passing Sephadex LH-20 column (0.9×20 cm) with 0.1 M acetic acid as eluent. The ordinate indicates cpm per 0.1 ml of the eluted solution and the abscissa elution volume.](image)

![Fig. 2. The solid line indicates the standard curve using the repurified ¹²⁵I-hCT and the dotted line indicates it using ¹²⁵I-hCT without repurification.](image)
coefficient of variation of intra- and inter-assay was 11 and 20%, respectively.

**Dose response and cross reaction**

As shown in Fig. 3, plasma from patients with MCT showed a dose-response curve parallel to that obtained using hCT. Synthetic hCTs obtained from the other sources, such as Merck or Teikoku Hormone, showed a dose response curve indistinguishable from that of standard hCT (Armour). Porcine and salmon CT, bovine PTH, secretin, gastrin or glucagon showed no cross reaction a dose up to 500 ng/ml.

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Fig. 3. The solid line indicates the dilutional curve of synthetic hCT (Armour) and the dotted lines indicate that of plasma obtained from patients with MCT. The semidotted line indicates the dilutional curve of porcine and salmon CT, bovine PTH, gastrin, secretin and glucagon.

Fig. 4. Plasma hCT levels in normal subjects and patients with various diseases. Log scale on the abscissa.
Plasma hCT levels in normal subjects and patients with various diseases (Fig. 4)

Plasma hCT levels were less than 50 pg/ml in 50 normal subjects and less than 20 pg/ml (undetectable range) in 42 of them.

a) Carcinoma of the thyroid: Of the 31 patients with thyroid carcinoma, 16 had MCT and showed high plasma hCT levels ranging from 175 to 352,000 pg/ml. Eight of them had been treated by total thyroidectomy, but their plasma hCT levels were still elevated. In 15 patients with the other types of thyroid carcinoma (12 papillary and 3 follicular), plasma hCT levels were less than 20 pg/ml.

b) Carcinoma of the lung: Of the 9 patients with oat cell carcinoma, three were found to have elevated plasma levels of 300, 310 and 370 pg/ml, but in the others plasma hCT levels were less than 40 pg/ml.

c) Malignant carcinoid: Of the 12 patients with malignant carcinoid, four had high plasma hCT levels ranging from 60 to 160,000 pg/ml. A patient with plasma level of 160,000 pg/ml was a case of the ectopic ACTH-MSH syndrome. In the other 8 patients, plasma hCT levels were less than 50 pg/ml.

d) Melanoma: In 9 patients with malignant melanoma, plasma hCT levels were less than 20 pg/ml in all cases.

e) Other malignancies: In 19 of them one patient with acute myelocytic leukemia had the level of 150 pg/ml and one with malignant pheochromocytoma the level of 170 pg/ml, but in the remainders with various types of malignancy plasma hCT levels were less than 50 pg/ml.

f) Pituitary tumor: In 10 of them one patient with Nelson’s syndrome had the level of 96 pg/ml, but in the rest plasma levels were less than 20 pg/ml.

g) Renal insufficiency: In 38 patients with chronic renal failure, twenty-four were found to have plasma hCT levels of less than 50 pg/ml, but in other 14 patients plasma hCT levels were in the range of 55 to 900 pg/ml. However, there was no correlation between plasma levels of hCT and those of PTH, urea nitrogen or creatinine.

h) Parathyroid disease: In 12 patients with primary hyperparathyroidism, plasma hCT levels were less than 20 pg/ml in all cases. In 5 patients with pseudohypoparathyroidism, three had the levels between 28 and 70 pg/ml and the others those of less than 20 pg/ml. In 4 patients with idiopathic hypoparathyroidism, one had the level of 26 pg/ml and in the remainders the plasma levels of hCT were less than 20 pg/ml. In 4 patients with pseudoidiopathic hypoparathyroidism, one had the level of 53 pg/ml and the others that of

![Fig. 5. Plasma hCT levels before and after total thyroidectomy for patients with MCT. Double circles indicate patients with Sipple's syndrome. Log scale on the ordinate.](image-url)
53 pg/ml and the others that of less than 20 pg/ml. Two patients with pseudopseudohypoparathyroidism had the level of 35 and less than 20 pg/ml.

i) Plasma hCT levels before and after thyroidectomy in patients with MCT: As shown in Fig. 5, plasma hCT levels fell significantly after the total thyroidectomy with radical neck dissection in 7 cases whose plasma hCT levels were determined before and after the operation. However, in 5 cases their plasma hCT levels were still high even after the operation except for 2 cases in whom plasma levels were down less than 50 pg/ml. In 9 cases plasma hCT levels were determined only after the operation and their values were high in 6 cases. In those cases whose plasma hCT levels were high even after the operation, metastases were always found.

Calcium and tetra gastrin infusion test
One to 2 mg/dl increase in serum Ca level was usually observed in normal subjects, patients with MCT and hypoparathyroid patients 10 min following the Ca infusion. In 6 normal subjects plasma hCT levels did not respond to the Ca infusion in any cases. In contrast, a marked increase in plasma hCT was observed in all 7 cases with MCT as shown in Fig. 6. The maximum increase was observed at the end of infusion in 5 cases and 25 and 70 min in the rest 2 cases. The degree was 2 to 106 times to the initial level.

Plasma Ca levels did not show any significant changes following the tetra gastrin infusion. Although plasma hCT levels did not respond to the tetra gastrin infusion in 7 normal subjects, a significant increase in plasma hCT level was observed in 5 cases.
with MCT, as shown in Fig. 7. The maximum increase was at 10 min after starting the infusion in 3 cases and 20 min in 2 cases. The degree of increase was 2 to 23 times to the initial level.

Fig. 8. The short Ca infusion test. Blood samples were collected before and 10, 25, 40 and 70 min as described before, and the maximum values were plotted as “after”. Primary hyperparathyroidism of a patient (Y. I.) was due to carcinoma. Log scale on the ordinate.

Fig. 9. The tetragastrin infusion test. Blood samples were collected before and 10, 20 and 35 min as described before, and the maximum values were plotted as “after”. Primary hyperparathyroidism of a patient (Y. I.) was due to carcinoma. Log scale on the ordinate.
Calcium and tetragastrin infusion test in patients with hyper- and hypoparathyroidism

As shown in Figs. 8 and 9, plasma hCT responses to the Ca or tetragastrin infusion were observed in a patient with primary hyperparathyroidism due to parathyroid adenoma. However, no response was observed to both stimuli in a case of parathyroid carcinoma. Also shown in Fig. 8 and 9, in various types of 5 hypoparathyroid patients a significant increase in plasma hCT was observed to both stimuli in all cases. In 2 patients with pseudopseudohypoparathyroidism, plasma hCT responded to the Ca infusion, but in one patient tested there was no response to the tetragastrin infusion. The degree of increase in plasma hCT in response to the tetragastrin infusion was less when compared with those to the Ca infusion.

Discussion

Because of the marked differences between the several forms of CT, it has been necessary to develop a specific radioimmunoassay of each of these CTs in order to determine plasma levels. We have previously reported a radioimmunoassay for porcine CT, but using this assay we could not measure hCT (Adachi et al., 1974). Here, in this study we report a radioimmunoassay for hCT using anti-hCT serum which was produced in rabbits. The iodinated hCT was repurified using Sephadex LH-20 column eluted with 0.1 M acetic acid. Acetic acid was used because hCT is stable in acid pH. This procedure gave the most reactive $^{125}$I-hCT.

This radioimmunoassay was sensitive enough in detecting plasma hCT levels down to 20 pg/ml. Plasma from patients with MCT showed a dilutional curve parallel to that of the standard hCT and there was no difference in the dilutional curves when synthetic hCTs obtained from 3 different sources, namely Armour, Merck and Teikoku were used. There was no cross reaction with porcine and salmon CT, bovine PTH, secretin, gastrin or glucagon a does up to 500 ng/ml. These data indicate that the radioimmunoassay system is specific for hCT.

Plasma hCT levels were less than 50 pg/ml in 50 normal subjects and less than 20 pg/ml (undetectable range) in 42 of them (84%). This is different from the level of 9-393 pg/ml previously reported from other laboratories (Deftos et al., 1971; Samaan et al., 1973; Sizemore et al., 1973; Bieler et al., 1973; Hesch et al., 1973; Moukhtar et al., 1973). Our lower values could be due to the different hCT used as a standard or to the different specificity of antiserum.

In patients with MCT plasma hCT levels were distinctly elevated. This is an extremely sensitive indicator for the diagnosis of the disease as reported previously (Tubiana et al., 1968; Melvin et al., 1971; Deftos et al., 1972; Goltzman et al., 1974; Queener and Bell, 1975). Even after the total thyroidectomy, plasma hCT levels were high in 11 out of 16 operated cases, indicating the presence of metastases.

Plasma hCT levels in 59 patients with malignant tumor are worth of discussion. Three patients with oat cell carcinoma of the lung, 4 patients with malignant carcinoid, one with malignant pheochromocytoma and one with acute leukemia were found to have moderately elevated plasma hCT level. There are several reports about the elevated plasma hCT levels in patients with malignant tumor (Milhaud et al., 1970; Silva et al., 1974; Coombes et al., 1974 and 1975), especially in those with oat cell carcinoma of the lung or carcinoid tumor. Whether this is derived from the tumor production of hCT or some other mechanisms involved will need further studies, including the measurement of tumor
hCT content. Calcitonin was proved to be the most constant biologically active substances that has been identified in tumor of APUD (amine precursor uptake and decarboxylation) series (Milhaud et al., 1974). Except for one case with leukemia, all patients who were proved to have high plasma hCT levels had the tumor derived from neural crest origin.

In 38 patients with chronic renal failure plasma hCT levels were elevated in 14 cases (37%). There was no correlation between plasma levels of hCT and those of PTH or Ca. Ardaillou et al. reported that the metabolic clearance rate of hCT was considerably reduced in patients with chronic renal failure (Ardaillou et al., 1970). These high plasma hCT levels could be the result of decreased degradation in vivo or excretion from the kidney.

In 12 patients with primary hyperparathyroidism, plasma hCT levels were less than 20 pg/ml in all cases, even though they had elevated plasma levels of Ca or PTH. The explanation for this observation will need further studies. However, a possible explanation is that a small undetectable increase in plasma hCT which is impossible to detect in this radioimmunoassay system may be enough to counteract the elevated levels of plasma Ca in such cases. Another possibility is that the prolonged elevation of plasma Ca or PTH may suppress the hCT secretion from the thyroid. Tashjian's group reported concomitant hyperplasia of calcitonin containing parafollicular cells in the thyroid obtained from patients with primary hyperparathyroidism, but they did not observe an appreciable increase in plasma hCT levels (LiVolsi et al., 1973). As reported here, one case with parathyroid adenoma responded to Ca and tetragastrin load. These results might indicate that hCT which is synthesized in parafollicular cells in primary hyperparathyroidism is not secreted, but stored there.

The value of stimulation test for hCT using Ca or gastrin in patients with MCT is well established (Cooper et al., 1971; Melvin et al., 1972; Hennessy et al., 1974; Sizemore and Go, 1975). The 4-hour Ca infusion test is cumbersome as a screening test for MCT. Recently Parthemore et al. reported a short Ca infusion test for screening MCT (Parthemore et al., 1974). We used 10-min Ca infusion test (Ca 4.5 mg/kg) and it was found that the infusion was enough to stimulate hCT secretion in patients with MCT, but that no normal subjects so far studied responded to this stimulus.

It has been reported that pentagastrin to stimulate hCT secretion in patients with MCT (Hennessy et al., 1974; Sizemore and Go, 1975). We used tetragastrin a dose of 4 μg/kg/5 min, which was found to stimulate the hCT secretion in patients with MCT, but not in normal subjects. However, the degree of responses was weak when compared with that observed in case of Ca infusion.

The mechanism that patients with various types of hypoparathyroidism responded to the Ca or tetragastrin infusion is not clear. Tashjian et al. (1966) reported an increase in hCT content of the thyroid obtained from patients who had been in a hypocalcemic state for appreciable time. Deftos et al. (1973) found an increase in plasma hCT levels in hypocalcemic subjects following the administration of Ca or pentagastrin. The stored hCT may be released in response to Ca or tetragastrin load. However, the reason why 2 patients with pseudopseudohypoparathyroidism responded to the Ca infusion is hard to explain. Further studies will be required for clarifying detailed mechanisms.
References


