Meal-related Changes in Plasma Calcitonin Levels in Patients with Medullary Thyroid Carcinoma

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Abstract

In 3 patients with medullary thyroid carcinoma, plasma calcitonin levels showed 3 distinct peaks associated with a simultaneous rise in plasma gastrin after each meal. It is suggested that endogenous gastrin secreted following food intake stimulated the calcitonin secretion from the tumor. The peak of the plasma calcitonin secretion after the evening meal was less prominent than that for breakfast or lunch, while no significant differences were observed in peak values in plasma gastrin after each meal. The reason for this discrepancy remains to be clarified.

Materials and Methods

Patients

Patient 1 was a 65-year-old married female complaining of glucosuria and hypertension. Two nodules were found in the bilateral lobes of the thyroid. Her brother had been operated on for medullary thyroid carcinoma, and 2 of her 6 children were found to have medullary thyroid carcinoma and pheochromocytoma. Laboratory tests revealed a high plasma calcitonin level (5 ng/ml), impaired glucose tolerance and increased urinary excretion of catecholamines. The preoperative diagnosis was multiple endocrine neoplasia type 2A. Bilateral adrenal pheochromocytomas were demonstrated by angiography and a total adrenalectomy was performed successfully. One month after the adrenalectomy, blood samples were taken to determine the calcitonin and gastrin levels according to the protocol described below. A total thyroidectomy was performed, and histological examination of the tumors confirmed the diagnosis of medullary thyroid carcinoma.

Patient 2 was a 32-year-old married female. No family history of medullary thyroid carcinoma was elicited. A subtotal thyroidectomy with modified radical neck dissection had been carried out for bilateral medullary thyroid carcinoma 5 years ago. A high plasma calcitonin level (1.4 ng/ml) and selective venous sampling suggested the presence of residual tumors in her neck, although no mass was
palpable. After taking the blood samples for this study, surgery was performed and revealed medullary thyroid carcinoma in the residual thyroid and cervical lymph nodes.

Patient 3 was a 13-year-old girl with multiple endocrine neoplasia type 2B. She had tumors in the bilateral thyroid lobes and cervical lymph nodes. She had bumpy lips, neuromas on the tongue and hypertrophic corneal nerves. Urinary excretion of catecholamines was within normal limits. Blood pressure did not respond to glucagon (1 mg) or histamine (50 μg), suggesting that pheochromocytoma was unlikely. After taking the blood samples for this study, a total thyroidectomy was performed. Histological examination confirmed the diagnosis of medullary thyroid carcinoma.

**Diets**

The patients were given regular hospital diets of 2,175±123 Cal/day. Protein, fat and carbohydrate contents in each meal were; 17.2±1.2g, 15.3±0.2g and 86.9±8.1g for breakfast, 25.2±4.3g, 20.0±10.9g and 128.3±12.3g for lunch, 25.6±3.5g, 17.3±9.4g and 131.4±13.2g for the evening meal, respectively.

**Sampling**

Blood samples for calcitonin, gastrin and calcium measurement were collected before meals and at 0, 30, 60, 120 and 180 min after meals. Meals were taken at 0830, 1200 and 1700 hr. Plasma was isolated immediately, and stored at -20°C for later analysis.

**Assays**

Plasma calcitonin was determined by double antibody radioimmunoassay. Synthetic human calcitonin used for both iodination and for the reference standard was kindly supplied by the Protein Institute of Osaka University. Anti-human calcitonin rabbit serum was supplied by Calbiochem. Human calcitonin was labeled with 125I (New England Nuclear Co.) by the method of glucose oxidase with lactoperoxidase (Tower et al., 1977). Dilution of human plasma and standard calcitonin resulted in parallel displacements. The minimum detectable dose was 4.0 pg/tube. The coefficient of the variations was 8% within an assay and 20% between assays. Normal subjects were found to have plasma calcitonin levels ranging from nondetectable to 100 pg/ml. Details of the assay procedure and its evaluation have been described elsewhere (Okada et al., 1978). All samples for this study were determined in duplicate in the same assay.

Plasma gastrin was determined by a radioimmunoassay (Yalow and Berson, 1970) using a commercial kit (Commissaiat, Sorin Biomedica). Normal range of plasma gastrin in fasting state was from nondetectable to 60 pg/ml.

Serum calcium was measured with a Technicon Autoanalyzer.

**Results**

Figure 1 shows diurnal patterns of plasma calcitonin and gastrin concentration in 3 patients with medullary thyroid carcinoma. Sharp rises of plasma calcitonin and gastrin concentration were observed after each meal in all cases. The increases in plasma calcitonin concentrations after the meals were 41% (case 1), 24% (case 2) and 69% (case 3) after breakfast; 37% (case 1), 28% (case 2) and 14% (case 3) after lunch. However, the increases after the evening meal were only 10% (case 1 & 2) and 15% (case 3). The peak values were usually obtained immediately after the meals or 30 min later.

Plasma gastrin concentrations increased after each meal, as shown in Fig. 1. The increases in plasma gastrin concentrations after the meals were 62% (case 1), 74% (case 2) and 218% (case 3) after breakfast; 112% (case 1), 125% (case 2) and 119% (case 3) after lunch; and 68% (case 1), 133% (case 2 & 3) after the evening meal. The peak values for plasma gastrin were usually obtained within 30 min after the meals.

Serum calcium levels were also determined in case 1 & 2, but little changes were observed as shown in Fig. 1.

**Discussion**

Recently, Hillyard et al. (1977) reported on the circadian variation in plasma calcitonin in normal subjects. They found that normal calcitonin level showed a circadian variation with a peak around midafternoon. However, there are no reports on circadian variation in plasma calcitonin in patients with medullary thyroid carcinoma.

It is well known that plasma calcitonin levels rise markedly in response to various
Fig. 1. Diurnal variation in plasma calcitonin (●—●) and gastrin (○—○) concentration in 3 patients with medullary thyroid carcinoma (patient #1-#3). Serum calcium levels (×—×) are also shown for patients #1 and #2. Meals were taken at 0830, 1200, and 1700 h. There were 3 distinct peaks of plasma calcitonin associated with a simultaneous rise in plasma gastrin after each meal.

stimuli such as calcium, gastrin, glucagon or alcohol in patients with medullary thyroid carcinoma (Tashjian et al., 1970; Hennessy et al., 1973; Dymling et al., 1976). Since plasma gastrin levels rise after meals in normal subjects (Korman et al., 1971), plasma calcitonin is also expected to rise after meals. However, Hillyard et al. (1977) did not comment on calcitonin secretion in relation to meals or endogenous gastrin secretion after meals.

The present report demonstrated that plasma calcitonin and gastrin levels rose simultaneously after each meal with no rise in serum calcium concentration. It is reported that gastrin stimulates calcitonin secretion (Hennessy et al., 1973), and that calcitonin, on the contrary, inhibits gastrin secretion (Oyama et al., 1973; Fahrenkrug et al., 1975). Therefore, it is likely that endogenous gastrin secreted following food intake stimulates the calcitonin secretion from the medullary thyroid carcinoma.

The increase in plasma calcitonin after the evening meal was less prominent than that after breakfast or lunch. Endogenous gastrin after meals does not account for this phenomenon, because there was no significant difference in secreted plasma gastrin levels between meals. Some other factors responsible for this phenomenon remain to be clarified.

It is important to take these meal-related changes into consideration when studying the stimuli of calcitonin secretion or when following up medullary thyroid carcinoma patients by monitoring plasma calcitonin levels.

Acknowledgements

This study was supported in part by research grants from the Ministry of Education, Science and Culture and the Ministry of Health and Welfare, Japan.
References
