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Serotonin (5-Hydroxytryptamine) in Medullary Thyroid Carcinoma With or Without Pheochromocytoma*

FRODE ENGBAEK

Research Laboratory for Metabolic Disorders, University Department of Clinical Chemistry, and Department of Nuclear Medicine, Aarhus Kommunehospital, DK 8000 Aarhus C, Denmark

Abstract—*An increased synthesis of serotonin by medullary thyroid carcinoma (MTC) has been postulated because an increased concentration of serotonin in the MTC cells and an increased urinary excretion of 5-hydroxyindoleacetic acid have been observed in some patients with MTC. Ten patients with sporadic MTC and 18 patients with familial MTC of either the MEN-IIa or MEN-IIb types were investigated. Three of the patients with MEN-IIa and the patient with MEN-IIb had concomitant pheochromocytomas. The concentrations of serotonin in serum were measured in order to investigate the contributions of the MTC and pheochromocytoma to the overall synthesis of serotonin. The concentrations of serotonin in sera from patients with MTC or MEN-IIa without pheochromocytomas were not different from the concentrations measured in healthy subjects ($P > 0.10$). The four patients with MEN-II syndromes with pheochromocytomas had increased concentrations of serotonin in sera ($P < 0.01$), and decreases in the concentrations occurred following adrenalectomy in all four patients. The results show that (1) the MTC made only little if any contribution to the overall synthesis of serotonin in the 28 patients studied; and (2) serotonin was produced in pheochromocytoma tissue from four patients with MEN-II syndromes with pheochromocytoma.*

INTRODUCTION

MEDULLARY thyroid carcinoma (MTC) is an endocrine tumor derived from the calcitonin-secreting thyroid C cell [1]. This neoplasma occurs in sporadic and familial forms, which share certain clinical, biochemical and histological characteristics. The familial forms may be associated with pheochromocytomas and either with hyperparathyroidism [in multiple endocrine neoplasia, type IIa (MEN-IIa)] or with multiple mucosal neuromas (in MEN-IIb).

Both the thyroid C cells and the adrenal medullary cells have some neural properties such as synthesis and/or uptake of amines [2]. The presence of serotonin (5-hydroxytryptamine) in MTC [3, 4] and increased urinary excretion of 5-hydroxyindoleacetic acid from patients with MTC [5] have previously been described.

An increase in the extracerebral synthesis of serotonin causes an increase in the amount of serotonin in blood platelets [6, 7]. During blood coagulation *in vitro* the serotonin is released from the platelets into the serum. Therefore an increased synthesis of serotonin will cause an increase in the concentration of serotonin in serum.

The concentrations of calcitonin and serotonin in sera from patients with sporadic MTC, from patients with MEN-IIa without pheochromocytoma and from patients with MEN-IIa or MEN-IIb with pheochromocytomas were measured in order to investigate the contributions of the MTC and pheochromocytoma to the overall synthesis of calcitonin and serotonin. Furthermore, the effects of surgery for MTC and pheochromocytoma on the concentrations of calcitonin and serotonin in serum were studied.

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MATERIALS AND METHODS

Patients

Twenty-eight patients with MTC were studied. The tumors were identified by palpation, and the diagnoses were histologically confirmed. The data of patients are summarized in Table 1. The family C has been described previously [8], and one patient from this family underwent unilateral adrenalectomy for a pheochromocytoma prior to this study. Four patients had concomitant pheochromocytomas. These four patients were studied before adrenalectomy, after adrenalectomy (bilateral in two patients and unilateral in two patients) and after thyroidectomy (in three patients). Computerized axial tomography and slightly elevated urinary catecholamine excretion suggested the presence of a small pheochromocytoma in the remaining adrenal gland after unilateral adrenalectomy in the female patient from family H (Fig. 2A). The remaining 24 patients had urinary catecholamine excretion within the reference interval. Eleven of these patients were studied both before and within 17 months after thyroidectomy for MTC of the MEN-IIa variety. Only one sample from each of the remaining 13 patients was analyzed. Three patients had associated watery diarrhea. The concentrations of serotonin in serum from these patients were 500, 730 and 1500 nmol/l. Hormonal replacement therapies were given after bilateral adrenalectomy (0.1 mg fludrocortisone and 20–37 mg hydrocortisone per day) and after thyroidectomy (0.1–0.2 mg thyroxine per day).

Serum calcitonin and serotonin analysis

Blood was drawn from an antecubital vein and allowed to clot at room temperature for 30–120 min before centrifugation. Serum was stored at -20°C until analysis.

The concentrations of calcitonin and serotonin in sera were measured by previously described radioimmunoassays [9, 10]. The reference populations were 30 healthy volunteers for each assay. The reference intervals for calcitonin and serotonin in sera are 0–135 ng/l and 250–1800 nmol/l respectively. The day-to-day coefficients of variation are 10 and 8% respectively.

Samples with normal and increased concentrations of serotonin have linear dilution curves. Thus the compound measured is identical with authentic serotonin. The catecholamines, dopamine, epinephrine and norepinephrine at 1 mmol/l concentrations did not interfere with the assay for serotonin.

Statistical analysis

Comparisons were made with the Mann-Whitney U test (two-tailed) for two samples.

RESULTS

Calcitonin

The concentrations of calcitonin in serum were above the reference interval in all patients with sporadic MTC, and in all patients except one with familiar MTC (Figs 1 and 2). In one patient the concentration increased to above the reference interval upon stimulation with pentagastrin. Thyroidectomy for familial MTC in 14 patients caused a decrease in the concentration of calcitonin (Figs 1, 2A, B, C and E). Adrenalectomy for pheochromocytoma did not cause a systematic change in the concentration of calcitonin (Figs 2A, B, D and E).

Serotonin

The concentrations of serotonin in serum from patients with sporadic MTC and from patients with MEN-IIa without pheochromocytoma (Figs 1 and 2C) were not different from the concentrations observed in the reference population ($P > 0.10$).

The concentrations of serotonin were measured both before and after thyroidectomy in 11 of the patients with MEN-IIa. The concentrations increased more than 10% in four patients, decreased more than 10% in three patients and changed less than 10% in four patients. Thus thyroidectomy did not cause a systematic change in the concentration of serotonin in serum.

Table 1. Summary of data for the categories of patients with MTC

Diagnosis	Family	Range of ages (yr)	Sex	Patients with pheochromocytoma
Sporadic	—	32–74	6F + 4M	—
MEN-IIa	C	16–79	6F + 7M	1F
MEN-IIa	H	17–41	1F + 2M	1F + 1M
MEN-IIa	J	59	1F	1F
MEN-IIb	M	34	1F	1F

Abbreviations: F, female; M, male.

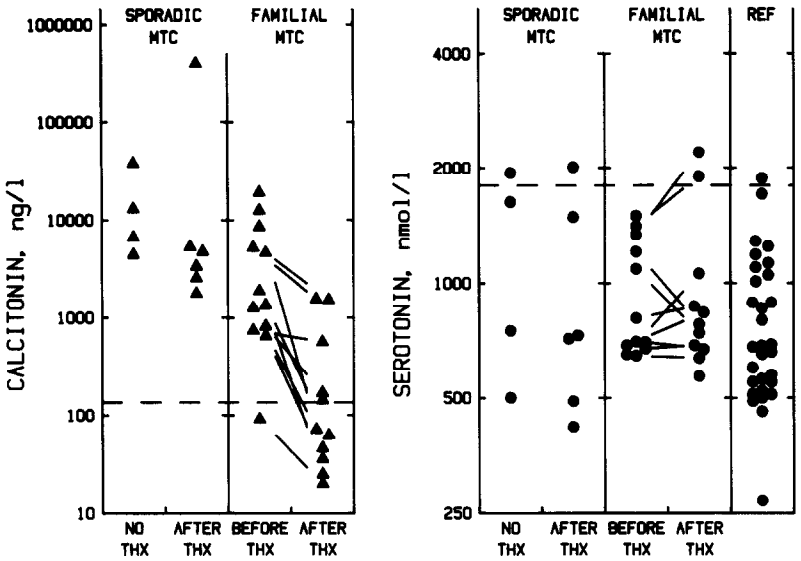

Fig. 1. Individual concentrations of calcitonin and serotonin from ten patients with sporadic MTC and from 13 patients with MEN-IIa without pheochromocytoma, family C. Seven of the patients had undergone partial or complete thyroidectomy 2–10 yr previously. The dashed lines indicate the upper limits for the reference intervals.

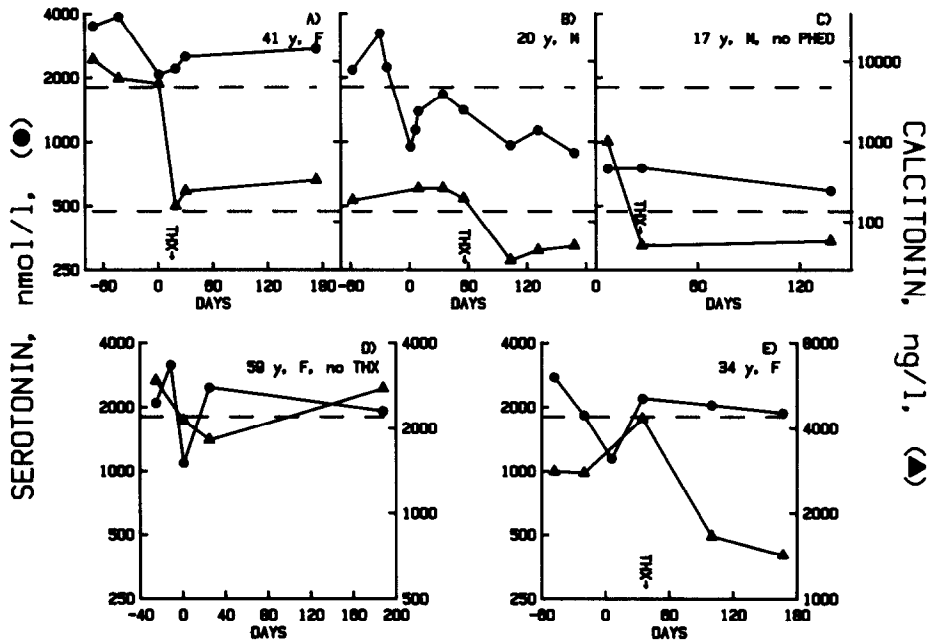

Fig. 2. The time course of the calcitonin and serotonin concentrations in five patients with MEN-II syndromes. The patients were adrenalectomized on day 0, if operated, and thyroidectomized on the day indicated by THX, if operated. (A–C) Family H with MEN-IIa. (A) A female with bilateral pheochromocytomas. (B) A male with unilateral pheochromocytoma. (C) A male without pheochromocytoma. (D) A female with MEN-IIa with bilateral pheochromocytoma, in whom thyroidectomy was omitted. (E) A female with MEN-IIb with bilateral pheochromocytoma. The dashed lines indicate the upper limits for the reference intervals.

The concentrations of serotonin were above the reference interval initially for the four patients with MEN-IIa or MEN-IIb with pheochromocytomas. These concentrations are significantly increased when compared with the concentrations from the reference population ($P < 0.01$), or with the concentrations from the patients with MTC without pheochromocytoma ($P < 0.01$).

Transient decreases in the concentrations of serotonin were observed in all four patients following adrenalectomy. These decreases are attributed to the surgical trauma. About 1 month after the adrenalectomy the concentrations of serotonin stabilized at concentrations below the pre-operative concentrations. In the patient who underwent unilateral adrenalectomy, the con-

centration decreased to within the reference interval (Fig. 2B). The concentrations stabilized at about the upper reference limit in the two patients who underwent bilateral adrenalectomy (Figs 2D and 2E), and above the upper reference limit in the patient with a small pheochromocytoma in the remaining adrenal gland (Fig. 2A).

DISCUSSION

Amines and peptides, which are produced by neuroendocrine tumors, are secreted into the blood. Therefore the increased production of amines and peptides by tumors can be detected by measuring the concentrations of the amines and peptides in the blood. Serotonin is taken up by the platelets, and during blood coagulation *in vitro*, serotonin is released into the serum, where it can be measured.

In this study the concentrations of serotonin in serum from patients with sporadic MTC or with MEN-IIa without pheochromocytoma were not different from the concentrations measured in healthy subjects. Furthermore, thyroidectomy did not cause a systematic change in the concentration of serotonin in serum. Therefore the MTC-tumors that were investigated made only an insignificant contribution, if any, to the overall synthesis of serotonin.

Increased concentrations of serotonin in MTC-tumors have been reported previously, when the tumors were compared with glands from patients with benign goitre [3]. However, when the concentrations of serotonin in MTC-tumors were compared with the concentrations measured in normal thyroid tissue, no difference was observed [4, 11].

The synthesis of serotonin from tryptophan requires two enzymes, tryptophan hydroxylase and L-aromatic amino acid decarboxylase (L-dopa decarboxylase). Although the activity of L-aromatic amino acid decarboxylase is higher in MTC-tumors than in the surrounding normal thyroid tissue [4, 12], the activity of the rate-limiting enzyme, tryptophan hydroxylase, is not greatly elevated in the single case studied [4].

In this study all four patients with MEN-II syndromes with pheochromocytomas had increased concentrations of serotonin in serum, and decreases in the concentrations of serotonin were observed in all four patients following adrenalectomy. Therefore it is proposed that serotonin is produced by pheochromocytomas, when they are a part of MEN-II syndromes. Patients with sporadic pheochromocytomas were not available for this study.

The activity of L-aromatic amino acid decarboxylase is markedly enhanced in pheochromocytomas compared with adrenal medullas [13], but the enzyme tryptophan hydroxylase has not yet been demonstrated either in the adrenal gland or in pheochromocytomas [14].

The concentrations of serotonin in pheochromocytomas from five patients with MEN-II syndromes were significantly greater than the serotonin concentrations in pheochromocytomas from three patients with sporadic pheochromocytomas [14]. Platelet serotonin concentrations have been measured in five patients with pheochromocytomas in the pre- and post-operative periods [15]. One of these patients had a MEN-II syndrome, and the platelet serotonin concentration was increased in the pre-operative period and decreased after removal of the pheochromocytoma. In the remaining four patients the platelet serotonin concentrations were within the reference interval both in the pre- and post-operative periods, and there was no change in the concentration following surgery. Combining these results and the data in the present study, it is proposed that serotonin may be produced by the pheochromocytoma only when it is a part of a MEN-II syndrome.

The presence of calcitonin in low but detectable concentrations in pheochromocytoma tissue from some patients with sporadic pheochromocytoma [16, 17] or with MEN-II syndromes [17] has been reported. In all but one of these patients [16] the contributions from the pheochromocytomas were not sufficient to markedly increase the concentration of calcitonin in the blood. In other patients the absence of calcitonin in pheochromocytoma tissue has been demonstrated using sensitive methods [17, 18]. In this study the concentration of calcitonin in serum did not change following adrenalectomy for pheochromocytomas in four patients. Therefore, in these patients the pheochromocytomas did not make any significant contribution to the concentration of calcitonin in the blood.

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