Med. J. Cairo Univ., Vol. 62, No. 3, September: 677 - 682, 1994

Somatostatin Gastrin and C-Peptide in Thyroid Dysfunctions

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Abstract

Three groups of subjects were chosen; 20 patients with primary hypothyroidism, 20 patients with primary hyperthyroidism and a third group of 15 euthyroid subjects as a control group. Plasma somatostatin, gastrin and C-peptide were determined in both fasting and 1h postprandial after standard oral glucose load. FT_3, FT_4, TSH, oral glucose tolerance curve, serum cholesterol and triglycerides were also determined. It was found that both basal and stimulated somatostatin plasma concentrations were elevated in hypothyroidism and diminished in hyperthyroidism. On the contrary, serum gastrin and C-peptide were decreased. Elevated somatostatin level in hypothyroidism has an inhibitory effect on gastrin and C-peptide. C-peptide was elevated in hyperthyroidism, however glucose intolerance was noticed in only 20% of these subjects. Elevated gastrin level in hyperthyroidism suggests a role for gastrointestinal disturbances observed in these patients.

Introduction

SOMATOSTATIN was first isolated from the hypothalamus and was subsequently found in large amounts in endocrine cells of the stomach, pancreas and thyroid gland [1]. It has a profound inhibitory effect on growth hormone (GH) secretion as well as many other hormones, including TSH, insulin, glucagon, gastrin, secretin and vasoactive intestinal polypeptide [2]. Somatostatin infusion is known to inhibit triiodothyronine (T_3) and thyroxine (T_4) release [3]. Gavin and Moeller in 1983 [3,4] had shown that somatostatin inhibits the hepatic T_4 deiodenase, thus promoting its conversion to rT_3 rather than T_3.

This study was done to investigate the level of somatostatin as well as gastrin and C-peptide in hypo and hyperthyroidism to clarify their role in these clinical situations.

Subjects and Methods

The study was carried out on 20 patients with hyperthyroidism (13 females and 7 males) and 20 patients with hypothyroidism (13 females and 7 males) as well

as 15 euthyroid subjects as control group (8 males and 7 females). The mean age for the studied groups was 39.15±14.22 y for the first, 39.50±16.52 y for the second and 30.13±12.96 y for the third group respectively. All participants were subjected to full history, thorough medical examination, routine laboratory investigations as well as oral glucose tolerance curves, serum cholesterol and triglycerides. None of the participants suffered form diabetes mellitus, obesity, renal or hepatic disorders.

After overnight fast blood samples were withdrawn, part of each sample was allowed to clot, the serum was separated for glucose estimation, free T_3, free T_4, TSH, C-peptide and gastrin determination. Serum C-peptide is evaluated as a monitor to islet cell function; since it has prolonged half life than insulin and the possibility of existence of insulin autoantibodies associated with thyrotoxicosis is nullified. Another part of the blood sample was collected in EDTA-containing tubes (7.2 mg/56 ml of blood). Aprotinin (Trasylol) was added at a concentration of 500 KIU/ml. Plasma was aspirated & kept frozen at -20°C till somatostatin assay. Part of 1 h samples were also estimated for somatostatin.

Radioimmunoassay was done to determine plasma somatostatin [5] and C-peptide [6] using the kits manufactured by Incstar. Corp. (Stillwater, MN). Serum gastrin was estimated using the double antibody technique of radioimmunoassay [7]. The kits are manufactured by ICN biomedical Inc. (Carson, CA).

Determination of serum thyroid stimulating hormone TSH was done using immunoradiometric assay (IRMA) [8]. The kit is supplied by Saire-Medgeni, Belgium. The kits of both free T_3 and free T_4 [8] were provided by Diagnostic Products Corporation (DPC, Los Angeles CA). Serum glucose was estimated by glucose oxidase method [9], kits were supplied by Biomerieux (Cedex, France).

Results

The results are shown in tables 1 & 2.

Somatostatin (basal and stimulated) showed a significant increase (p <0.001) in the hypothyroid group when compared to the euthyroid and hyperthyroid groups. The latter showed more decrease.

Serum gastrin level was insignificantly elevated in the hyperthyroid group versus the euthyroid group, but when compared with the hypothyroid group it showed the lowest levels. The C-peptide level followed the same pattern like gastrin; being higher in the hyperthyroid group and lowest in the hypothyroid group (p < 0.025)

Discussion

Somatostatin is distributed in several organs and has several functions as hormone, neurotransmitter, neurohormone (pituitary regulator) and paracrine (cell to cell), autocrine (on cell of origin) and intraluminal action [2]. Next to the upper gastrointestinal tract and pancreas, the thyroid gland is the largest somatostatin producing organ where its granules are located in the C-cells together with calcitonin [1].

In the present study both the mean basal and stimulated plasma somatostatin concentrations were significantly elevated in primary hypothyroidism and reduced in primary hyperthyroidism in relation to normal subjects. This was also demonstrated by Berelowitz et al. in 1980 [10] and Skare et al. in 1986 [11].

Table (1): Plasma Somatostatin, Gastrin and C-Peptide in the Ivestigated groups (Mean±SD).

		Somatostatin pg/me	Gastrin pg/ml	C-peptide mmol/L
Euthyroid group (n=15)	B.	19.95±2.92	152.08±28.16	3.32±0.96
	S.	30.27±3.77	173.75±39.20	5.28±1.62
Hyperthyroid group (n=20)	B.	13.76±5.67	166.25±59.81	3.62±1.28
	S.	23.66±7.01	194.16±65.29	5.79±1.98
	P_1B.	<0.005	>0.05	>0.05
	S.	<0.001	>0.05	>0.05
Hypothyroid group (n=20)	B.	31.25±6.59	127.30±20.06	2.63±0.79
	S.	46.65±7.29	149.61±29.61	4.01±1
	P_1 B.	<0.001	<0.02	<0.05
	S.	<0.001	>0.05	<0.025
	P_2 B. S.	<0.001	<0.05	<0.025
		<0.05	<0.05	<0.01

B= Basal, S=Stimulated SS level after 1h of glucose intake p1= comparison with the euthyroid group. p_2= Comparison between hyperthyroid and hypothyroid groups.

Table (2): FT_3, FT_3, TSH, Fasting and postprandial Serum glucose, Cholesterol and Triglycerides in the Investigated groups (Mean±SD).

	FT_3 pmol/L	FT_4 pmol/L	TSH mU/L	Plasma glucoste mg/dl					Cholesterol mg/dl	Triglycer-ides gm/dl
				Fasting	30 min	60 min	90 min	120 min		
Euthyroid group (n=15)	6.73± 1.47	14.88± 6.35	2.98± 1.35	85.93± 9.57	100.6± 9.57	127.13± 13.25	113.70± 12.46	95.27± 8.82	194.6± 95.27	95.27± 22.34
Hyperthyroid group (n=20)	28.50± 17.62	56± 17.62	0.22± 0.14	99.3± 10.94	123.95± 15.98	169.57± 22.34	141.34± 22.34	118.69± 15.69	221.25± 62.17	89.75± 27.61
P_1	<0.001	<0.001	<0.001	<0.01	<0.01	<0.01	<0.01	<0.05	<0.05	<0.05
Hypothyroid group (n=20)	1.82± 0.78	4.87± 6.46	13.65± 6.26	73.75± 9.31	83.2± 9.64	112.50± 13.44	101.55± 10.62	86.8± 12.11	2.39± 72.18	142.35± 43.25
P_1	<0.001	<0.001	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
P_2	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

P_1 = Comparison with the euthyroid group. P_2 = Comparison between hyperthyroid and hypothyroid groups.

Ingbar [12] proposed that somatontatin may be elevated as a result of the net result of inhibited both secretion and catabolism if the inhibition being exerted more on catabolism. However, in this work TSH was found to be elevated in hypothyroidism, inspite of the presence of high level of somatostatin in response to oral glucose load (as a monitor to somatostatin secretory response).

The interrelationship between somatostatin, T_3, T_4 and TSH should be elucidated to speculate another interpretation. Somatostatin is incorporated in the hypothalamic control of TSH and GH secretion and it inhibits their secretion in a feedback manner. This action of somatostatin as suggested by Dhillon et al. [13] is a local inhibitory neuroendocrine hormone by the paracrine cells related to the hypothyroid state. This was confirmed by De Rossa et al. [14] who demonstrated that somatostatin infusion does not influence TSH in normal subjects. However, long term somatostatin infusion in hyperthyroid subjects reduces total T_3 and free T_3 and produced marked rise in rT_3 suggesting stimulated extrathyroidal deiodination effect of somatostatin on T_4 converting it to the physiologically inactive form, rT_3.

Furthermore, somatostatin analogue administration is an effective treatment for patients with neoplastic inappropriate secretion of TSH [15].

The findings of the present work suggest that somatostatin elevation has not only an action on the thyroid cells to inhibit their secretory function, but also it may interfere, somehow, with T_4, 5-deiodenase that converts T_4 to T_3 in peripheral tissues. Alternatively, somatostatin might stimulate T 5-deiodenase activity, so that it promotes T_4 conversion to rT_3 rather than T_3. Combined action of somatostatin on both enzymes could not be nullified. Further work is required to clarify the exact role of somatostatin on peripheral deiodination of T_4.

The inhibited thyroid hormones cause a feedback rise in the TSH secretion which is probably not inhibited by somatostatin, TSH secretion in response to TRH is enhanced and TRH stimulates GH secretion only in hypothyroidism (not in the euthyroid state). GH secretion is actually impaired in response to many stimuli in hypothyroidism but TSH secretion is increased [16].

Somatostatin has many interactions with other hormones and other regulatory systems of the body. Also there is a differential inhibitory action of somatostatin on other hormones according to the endogenous plasma level of somatostatin. There are different types of somatostatin receptors in different tissues and post-receptor effects of other hormones on somatostatin secretion have been reported [17].

We observed impaired glucose tolerance, not diabetes mellitus in 5 out of 20 hyperthyroid cases and the mean levels of plasma glucose at 60 and 90 minutes were significantly elevated in comparison to the euthyroid cases. C-peptide level was elevated in the hyperthyroid cases, however when compared with the level in the euthyroid cases there was no significant difference. Glucose metabolism is disturbed in thyroid disorders and impaired glucose tolerance is recognised in thyrotoxicosis [18].

Many workers reported controversial results concerning plasma insulin concentrations in thyroid disease [19].

Share et al. [11] demonstrated that somatostatin as well as insulin plasma levels

are increased in hypothyroidism and reduced in hyperthyroidism. They concluded that the feedback regulation between islet cell hormones (glucagon, insulin and somatostatin) cannot explain these findings in thyroid disorders and suggested that a common metabolism (altered metabolic clearance rate) governs the level of these hormones in thyroid disorders. However, they found that glucagon was not significantly changed, if this was the sole underlying mechanism, plasma levels of glucagon would change simultaneously.

A statistically negative correlation (r = -0.<119 $p < 0.065$) was found between plasma glucose level and plasma somatostatin level in the fasting state and at 1 hour postprandial in hypothyroidism as glucose stimulates somatostatin secretion. It may be attributed to the inhibitory effect of somatostatin on glucose level either directly on absorption or via inhibition of glucagon secretion which are more affected than beta cells by about 50 times by the inhibitory effect of somatostatin [2].

Basal and 1h postprandial serum gastrin concentration were elevated in hyperthyroidism compared to hypothyroidism and an inverse correlation (r= -0.510 $p <$ 0.05 was found between gastrin and somatostatin levels. Somatostatin serves as a part of a negative feedback loop regulating gastrin secretion [1].

In thyrotoxicosis the frequency of bowel movements is increased and gastric emptying and intestinal motility are accelerated, the intestinal absorption of all nutrients is increased, this may be attributed to hypergastrinaemia and diminished basal and stimulated levels of somatostatin in hyperthyroidism.

There are certain clinical applications for these results, plasma somatostatin determination will be useful in the follow up of medullary carcinoma and somatostatinoma, considering the patient's thyroid state whether hypothyroid or hyperthyroid before suspecting recurrence. Also somatostatin may be considered in pregnant hyperthyroid patients specially when surgery and antithyroid treatment are risky. Moreover, thyroid functional state should be followed up in patients receiving somatostatin analogues for any cause, as somatostatin may impair thyroid function as a whole, thyroid replacement may be considered when necessary.

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