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Is association between thyroid hormones and gut peptides, ghrelin and obestatin, able to suggest new regulatory relation between the HPT axis and gut?

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ABSTRACT

Background: Ghrelin and obestatin are important appetite- and energy-regulating peptides, secreted by the stomach. These gut peptides and thyroid hormones are involved in metabolism regulation. Although subclinical thyroidism is common, to date, very few studies have been reported about gut hormones in thyroid dysfunction, and their results are controversial. The purpose of this study was to investigate ghrelin and obestatin in patients with subclinical hypo- and hyperthyroidism. Moreover, is association between thyroid hormones and gut peptides able to suggest new regulatory relation between the HPT axis and gut?
Materials and methods: The study group included 70 subclinical hypo- and hyperthyroid subjects (in equal groups) and 35 healthy euthyroid controls. Serum values of ghrelin, obestatin, free T3, free T4, thyroid-stimulating hormone and the ratio of ghrelin to obestatin were measured in all participants.
Results: Ghrelin and obestatin both decreased in subclinical hypothyroid subjects (320 ± 81 ng/l and 44.3 ± 11.7 ng/l, respectively) compared to the control group (487 ± 110 ng/l and 58.5 ± 10.3 ng/l, respectively). On the other hand, ghrelin and obestatin both increased in subclinical hyperthyroid subjects (750 ± 289 ng/l and 71.1 ± 27.3 ng/l, respectively) compared to the control group. In addition, ghrelin and obestatin showed strong correlations with TSH, FT3 and FT4.
Conclusion: This study shows that gut hormones are significantly associated with thyroid hormones. Thus, there may be a cross talk between the HPT axis and gut. We would like to consider new regulatory relation for description of the found data.

1. Introduction

Three peptides are produced by ghrelin gene: acyl ghrelin, des-acyl ghrelin and obestatin; all may be part of a complex system with multiple elements that comprise the center of an integrated gut–brain axis that modulates appetite, digestion, gut motility, adiposity and energy partition [1,2]. Ghrelin is a gastrointestinal peptide produced by the stomach, and the endogenous ligand for the growth hormone secretagouge receptor (GHSR) [3,4]. In the energy balance and regulation of body weight, ghrelin plays an important role with orexigenic properties. It increases food intake, weight gain and adipogenesis [5–7]. Obestatin is an anorexigenic gut-peptide hormone that is generated by way of post-translational modification of preproghrelin, and secreted by the stomach [8]. This ghrelin-associated peptide functions by inhibiting appetite, slowing down gastric emptying, decreasing body weight gain and controlling energy expenditure [9–11]. Obestatin is capable of binding to GPR39 (G protein-coupled receptor 39) to regulate the functions of gastrointestinal tissue [12]. Furthermore, the two gut peptides have been investigated in several pathologies, including obesity, anorexia nervosa (AN) and diabetes [10,13–15].

Hypothalamus–pituitary–thyroid (HPT) axis is also associated with metabolic changes that affect body mass, appetite, basal metabolic rate and energy balance. Thyroid diseases are among the most common endocrinological disorders [16]. Hypothyroidism is related to weight gain, decreased appetite and basal metabolic rate, whereas hyperthyroidism is related with weight loss, increased appetite and metabolic rate [17,18].

The peripheral hormones ghrelin, obestatin and thyroid play integrated regulatory roles in and provide feedback information on the nutritional and energetic status of the body. These hormones modulate central pathways in the brain, including the hypothalamus, to influence food intake, energy expenditure and to maintain energy homeostasis [9,19,20]. Moreover, the association between changes in thyroid state and variations in circulating gut hormones is unsettled, due to the paucity of available studies and the conflicting results

Abbreviations: FT3, Free tri-iodothyronine; FT4, Free thyroxine; TSH, Thyroid-stimulating hormone; BMI, Body mass index; HPT, Hypothalamus–pituitary–thyroid.

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Table 1
Anthropometric, clinical and biochemical characteristics of the participants.

Parameters	Hypothyroid group	Control group	Hyperthyroid group	P value		
				a	b	c
Age (year)	52.4 ± 13.7	50.5 ± 9.0	54.5 ± 12.0	NS	NS	NS
BMI (kg/m^2)	24.1 ± 1.7	23.8 ± 1.5	23.3 ± 1.1	NS	NS	NS
TSH (mIU/l)	18.24 ± 9.76	2.81 ± 0.74	0.03 ± 0.03	<0.001	<0.001	<0.001
FT3 (pmol/l)	5.78 ± 0.34	7.82 ± 0.52	10.42 ± 0.66	<0.001	<0.001	<0.001
FT4 (pmol/l)	12.16 ± 3.76	14.74 ± 2.32	22.21 ± 9.95	<0.001	<0.001	<0.001
Ghrelin (ng/l)	320 ± 81	487 ± 110	750 ± 289	<0.001	<0.001	<0.001
Obestatin (ng/l)	44.3 ± 11.7	58.5 ± 10.3	71.1 ± 27.3	<0.001	<0.001	0.014
Ghrelin/obestatin	7.5 ± 2.0	8.5 ± 2.0	10.7 ± 1.7	0.045	<0.001	<0.001

Values are means ± SD.
NS: non-significant.
P-value < 0.05: significant.
a, column: Hypothyroid group vs control group.
b, column: Hypothyroid group vs hyperthyroid group.
c, column: Hyperthyroid group vs control group.

[21–23]. Therefore, it seems rational to investigate potential interactions between gut peptides and thyroid hormones.

The main objective of the study was to determine serum ghrelin and obestatin levels in different states of thyroid function. The second was to reveal correlations of gut and thyroid hormones. In addition, we hypothesize that there may be new regulatory relation between the hypothalamus–pituitary–thyroid axis and gut.

2. Materials and methods

2.1. Subjects and study design

The study groups were the following: 35 hypothyroid (females/males ratio 22:13), 35 hyperthyroid subjects and 35 healthy euthyroid volunteers (2.0 < serum TSH level < 4.5 mIU/l) served as the control group. All of them recruited from the outpatient clinic of Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran. The diagnosis of thyroid dysfunction was based on clinical assessment and biochemical findings. The study was performed at the time of diagnosis, before any treatment. In this study, subclinical hypothyroidism was defined as serum TSH level > 10 mIU/l with normal FT4 and subclinical hyperthyroidism was defined as serum TSH level < 0.1 mIU/l with normal FT4 [24–26]. Weight and height were measured and BMI was calculated in all subjects. On the basis of the influence of fat mass on ghrelin and obestatin values [27,28], serum concentrations of gut hormones were adjusted for body mass index (BMI) to evaluate directly the association between thyroid hormones and gut peptides. In order to eliminate the possible effect of sex and age on ghrelin and obestatin levels, the three groups were well matched. All participants did not have any hepatic or renal dysfunction, diabetes mellitus, cardio-vascular diseases, and did not take any medications. The study protocol was approved by the Ethical Committee of Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences. Signed informed consents were collected from all participants.

2.2. Hormone assays

Following an overnight fasting, blood samples were obtained from the antecubital vein in the morning. The serum was isolated and stored at −80 °C until assayed. Serum values of ghrelin, obestatin, free T3, free T4 and TSH were assessed. Serum levels of ghrelin and obestatin were measured by ELISA kit (Cusabio Biotech Co., Ltd., Japan). For obestatin, intra- and interassay CVs were less than 8% and less than 10%, respectively, the sensitivity of the assay was 1.2 pg/ml. For ghrelin, intra- and interassay CVs were less than 8% and less than 10%, respectively, the sensitivity of the assay was 0.16 pg/ml. Serum FT4 and FT3 were determined by commercially available electrochemiluminiscence immunoassays (ECLIA) (Cobas e 411, Roche Diagnostics GmbH, Mannheim, Germany). The sensitivity of the assays were 0.30 for FT3 and 0.40 for FT4 pmol/l. Interassay coefficients of variation were 3.5% at 0.68 ng/dl and 3.3% at 1.64 ng/dl for FT4 and 2.8% at 1.86 pg/ml and 2.7% at 2.51 pg/ml for FT3. Serum TSH was assayed by immunoradiometric assay method (TurboTSH [125I] IRMA kit, Institute of Isotopes Co., Ltd. (Izotop), Hungary), the sensitivity of the assay was 0.011 mIU/l.

2.3. Statistics

Kolmogorov–Smirnov test was used to test for normal distribution. Comparisons of means between groups were made using independent *T*-test, for normally distributed data. Correlations between variables were assessed by Pearson's correlation analysis. All data are expressed as mean ± SD. P-value < 0.05 was considered statistically significant for all analyses. All calculations performed using SPSS 16 for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

The main demographic, anthropometric, clinical and biochemical characteristics of the participants are presented in Table 1. The patients and control subjects were well matched in age, sex and BMI parameters.

3.1. Thyroid function

The hypothyroid group had high serum TSH concentrations (>10 mIU/l) and low FT3 and FT4 levels; while the hyperthyroid group showed decreased TSH (<0.1 mIU/l) and elevated FT3 and FT4 values, compared to the control group (Table 1).

3.2. Gut hormone levels

In subclinical hypothyroids, fasting ghrelin levels were significantly reduced; whereas in subclinical hyperthyroids, ghrelin values were higher than those of the healthy euthyroid subjects. In patients with subclinical hypothyroidism, fasting obestatin levels were also significantly lower than in their control group; while we observed increased obestatin concentrations in subclinical hyperthyroid individuals. Moreover, ghrelin and obestatin values were higher in hyperthyroid than hypothyroid state. Furthermore, the ghrelin to obestatin ratio was increased in hyperthyroids and reduced in hypothyroids, compared to controls (Table 1).