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Individual plasma ghrelin changes in the same patients in hyperthyroid, hypothyroid and euthyroid state

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ABSTRACT

Ghrelin is a multifunctional peptide of widespread expression. Since it has been shown to influence energy homeostatis, its potential role in thyroid dysfunction may have clinical significance. In this study, plasma ghrelin changes have been analyzed in the same patients in three different thyroid states for the first time. The study group consisted of 16 patients who had been diagnosed with hyperthyroidism, were treated with radioiodine, developed hypothyroidism after treatment, and finally became euthyroid on L-thyroxine substitution. In the initial state of hyperthyroidism plasma ghrelin levels correlated negatively with fT_3 and fT_4. In hypothyroidism ghrelin concentration increased significantly ($p < 0.05$). Although the mean value of plasma ghrelin tended to decrease in the euthyroid state, the individual difference between hypothyroidism and euthyroidism was not significant. Plasma ghrelin in euthyroidism was still significantly higher than in hyperthyroidism ($p < 0.05$), and correlated positively with ghrelin levels in hyperthyroidism and hypothyroidism. In our opinion, plasma ghrelin fluctuations may reflect metabolic changes in patients with thyroid dysfunction. Moreover, it cannot be excluded that in thyroid disorders ghrelin acts as a compensatory factor, helping to balance metabolic disturbances.

1. Introduction

Ghrelin is a multifunctional peptide that was discovered in 1999 as the first natural ligand for the growth hormone – secretagogue receptor (GHS-R) [22]. GHS-R has two subtypes: GHS-R1a – a functional ghrelin receptor and GHS-R1b, whose role still needs to be analyzed [15,18]. A unique modification (n-octanoylation at Ser 3) enables acylated ghrelin to bind GHS-R1a and exert biological activity [17,22]. Des-acyl ghrelin was previously considered to be inactive, but recent studies have demonstrated that it may also have a biological function [9,11].

Ghrelin is produced mainly in neuroendocrine cells (X/A cells) of the gastric mucosa [3]. However, to a lesser extent, it is also secreted in the intestine, hypothalamus, pituitary and many other tissues [15,40].

Ghrelin was initially described as the first endogenous growth hormone secretagogue, and proved to be a strong stimulator of growth hormone release [36]. Furthermore, it has been described as an essential regulator of metabolic processes, as it increases food intake, acts as an adipogenic factor, stimulates gastric emptying and reduces energy expenditure [35,43,44]. As a result, ghrelin causes energy saving effects, positive energy balance and weight gain [21].

Ghrelin secretion is regulated mainly by the metabolic state. Its plasma concentration is high during fasting and decreases in response to food intake [7]. Similarly, long-term negative energy balance states (anorexia, cachexia) increase ghrelin production while obesity, on the other hand, decreases ghrelin secretion [12,37,42].

It is well known that thyroid hormones play an important role in energy homeostasis. They increase the metabolic rate, thermogenesis and energy expenditure. Thus, hyperthyroidism as a hypermetabolic state is associated with increased appetite, but also with increased energy expenditure and weight loss. In contrast, hypothyroid patients present a decreased metabolic rate and weight gain.

The presence of ghrelin receptors has been demonstrated in the thyroid [5,15,27,40]. Furthermore, exogenous ghrelin uptake in thyroid tissue has been shown to be notably high in rats [32].

Previous studies have revealed that in hyperthyroidism plasma ghrelin levels are decreased [1,4,10,13,16,23,30,31,38,39] and rise

Abbreviations: BMI, body mass index; EDTA, ethylenediaminetetraacetic acid; fT_3, free triiodothyronine; fT_4, free thyroxine; GHS-R, growth hormone – secretagogue receptor; NIS, sodium/iodide symporter; RIA, radioimmunoassay; TSH, thyrotropin.

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after treatment [10,13,30,31,38,39]. These observations were surprising in view of such symptoms as increased appetite and weight loss in hyperthyroid patients. Hypothyroidism has been predominantly associated with a high ghrelin level [4,14,23] that decreases after treatment [14]. Some authors did not notice any difference [13,33,38], or observed low plasma ghrelin levels in hypothyroid patients [2].

To the best of our knowledge, none of the previous studies evaluated plasma ghrelin concentrations in three different thyroid functional states in the same patients. Various individual factors influence plasma ghrelin levels, i.e. metabolic rate, kidney function, or lipoprotein concentration [8,42,45]. Thus, it seems that a comparison of three different groups of hyper-, hypo- and euthyroid patients may not always be accurately objective. Consequently, the aim of the study was to evaluate the fluctuations of plasma ghrelin concentrations in the same patients during their hyperthyroid, hypothyroid and euthyroid state. We assume that such an analysis may help to understand the dynamic changes of ghrelin concentration based only on the thyroid state at a given time, without the interference of other individual features.

2. Materials and methods

2.1. Study group

The study group consisted of 16 patients who had been diagnosed with hyperthyroidism (13 women and 3 men), were treated with radioiodine, developed hypothyroidism after treatment, and finally became euthyroid on L-thyroxine substitution. Plasma ghrelin concentration was assessed in these patients during the hyperthyroid, hypothyroid and euthyroid state. Blood samples were collected after a 10-h overnight fast and placed in polyethylene tubes containing plasma enzymes inhibitors (aprotinin and ethylenediaminetetraacetic acid – EDTA).

2.2. Laboratory methods

Total plasma ghrelin levels were measured in duplicate with a commercially available radioimmunoassay (RIA) (Phoenix Pharmaceuticals Inc.). Radioactivity of the samples was assessed in an automatic LKB-Wallace gamma counter. The technique of plasma ghrelin measurement has been already described [24].

Free thyroxine (fT_4), free triiodothyronine (fT_3) and thyrotropin (TSH) levels were assessed using an electrochemiluminescence method.

2.3. Statistical methods

Plasma ghrelin changes in the hyperthyroid, hypothyroid and euthyroid state were analyzed using the non-parametric Friedman test, and the post hoc multiple comparison tests. Correlations were assessed with the use of Spearman's rank correlation coefficient.

2.4. Ethics

The study was conducted with the permission of Poznan University of Medical Sciences Ethical Committee.

3. Results

In the initial state of hyperthyroidism plasma ghrelin level (ghrelin 1) (160.1 ± 90.5 pg/ml) correlated negatively with fT_3 ($r = -0.67$, $p < 0.05$) and fT_4 ($r = -0.83$, $p < 0.05$). In hypothyroidism (ghrelin 2) (364.6 ± 269.4 pg/ml) it increased considerably ($p < 0.05$)

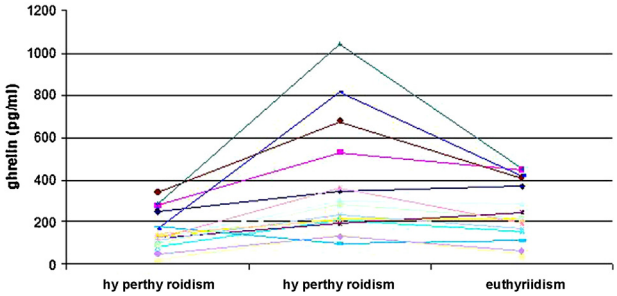

Fig. 1. Individual plasma ghrelin changes in each patient. Plasma ghrelin levels evaluated in hyperthyroidism, hypothyroidism and euthyroidism.

(Fig. 1). Although the mean value of plasma ghrelin concentration tended to decrease when the patients achieved euthyroidism, the individual difference between hypothyroidism (ghrelin 2) and euthyroidism (ghrelin 3) (251.8 ± 132.9 pg/ml) was not significant. Plasma ghrelin in euthyroidism was still significantly higher than in the initial state of hyperthyroidism ($p < 0.05$) and correlated positively with plasma ghrelin concentrations measured in hyperthyroidism ($r = 0.65$, $p < 0.05$) and hypothyroidism ($r = 0.93$, $p < 0.05$).

At the moment of submitting this manuscript two patients were still characterized by increased TSH levels (5.9 μIU/ml and 5.1 μIU/ml). However, they presented a major clinical improvement and notable decrease of TSH concentrations in comparison to the hypothyroid state (hypothyroid TSH 59.9 μIU/ml and 50.81 μIU/ml, respectively). One patient was evaluated during hyperthyroidism, then in euthyroidism after radioiodine treatment, and finally in hypothyroidism that developed afterwards (Table 1).

4. Discussion

In our study, in the initial state of hyperthyroidism plasma ghrelin levels correlated negatively with free thyroid hormones (fT_3 and fT_4). Hyperthyroid patients presented a low ghrelin level, which increased rapidly in hypothyroidism after radioiodine treatment. Normalization of thyroid hormone levels due to L-thyroxine replacement did not alter the plasma ghrelin level significantly. When euthyroidism was achieved, plasma ghrelin levels correlated positively with the concentrations observed in hyperthyroidism and hypothyroidism, which may suggest individual parallel fluctuations of plasma ghrelin in the same patient.

The relationship between thyroid function and ghrelin secretion has not been established yet. The presence of ghrelin and GHS-R has been demonstrated in the thyroid. However, the differences between their expression in parafollicular and follicular cells, as well as in benign and malignant thyroid diseases are still the subject of discussion [19,20,27,29,40,41,46]. Since ghrelin is expressed mainly in parafollicular cells and GHS-R was observed in follicular cells, it has been suggested that ghrelin may influence follicular cells in a paracrine manner [29]. Since then, various studies

Table 1
Biochemical and clinical characteristics of the patients in hyperthyroid, hypothyroid and euthyroid states (normal ranges: TSH, 0.27–4.2 μIU/ml; fT_4, 11.5-21 pmol/l; fT_3, 3.9–6.7 pmol/l) (*statistically significant difference in comparison to hyperthyroidism).

	Hyperthyroidism	Hypothyroidism	Euthyroidism
TSH (μIU/ml)	0.008 ± 0.002	35.3 ± 19.6	2.6 ± 1.5
fT_4 (pmol/l)	66.4 ± 29.1	5.7 ± 3	18.3 ± 5.4
fT_3 (pmol/l)	29 ± 12.6	3 ± 1.8	4.8 ± 0.9
BMI (kg/m^2)	24.4 ± 6	25.9 ± 6.1	26.2 ± 6.9
Ghrelin (pg/ml)	160.1 ± 90.5	364.6 ± 269.4*	251.8 ± 132.9*

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