Ghrelin affects the hypothalamus-pituitary-thyroid (HPT) axis in humans
by increasing free thyroxine (fT4) and decreasing TSH in plasma

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Short title: Ghrelin affects the HPT axis in humans

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Abstract

Objective: Ghrelin promotes a positive energy balance, e.g. by increasing food intake. Stimulation of the activity of the hypothalamus-pituitary-thyroid (HPT) axis promotes a negative energy balance, e.g. by increasing energy expenditure. We therefore hypothesized that ghrelin suppresses the HPT axis in humans counteracting its energy-saving effect.

Design and Methods: In this single-blind, randomized, cross-over study, we determined secretion patterns of free triiodothyronine (fT3), free thyroxine (fT4), thyroid stimulating hormone (TSH), and thyroid binding globulin (TBG) between 2000 and 0700 h in 20 healthy adults (10 males, 10 females, 25.3±2.7 years), receiving 50 µg ghrelin or placebo at 2200, 2300, 0000, and 0100 h.

Results: FT4 plasma levels were significantly higher after ghrelin than placebo administration from 0000 until 0620 h except for the time-points at 0100, 0520, and 0600 h. TSH plasma levels were significantly lower from 0200 until study end at 0700 h except for the time-points at 0540, 0600 and 0620 h. The relative increase of fT4 (AUC 0130-0700 h [ng/dl x min]: placebo: 1.31±0.03; ghrelin: 1.39±0.03; \(P=0.001\)) was much weaker than the relative decrease of TSH (AUC 0130-0700 h [mIU/ml x min]: placebo: 1.74±0.12; ghrelin: 1.32±0.12; \(P=0.007\)). FT3 and TBG were not affected.

Conclusions: This is the first report that ghrelin affects the HPT axis in humans. The early fT4 increase was possibly induced by direct ghrelin action on the thyroid where ghrelin receptors have been identified. The TSH decrease might have been caused by ghrelin-mediated inhibition at hypothalamic level, through feedback inhibition by fT4, or both.
Introduction

Ghrelin is the endogenous ligand of the growth hormone secretagogue receptor (GHS-R). It is predominantly synthesized in the stomach but has also been detected in the bowels, kidney, pituitary, lung, lymphatic tissue, placenta, hypothalamus, and thyroid. Accordingly, a broad variety of endocrine, cardiovascular, immunological, reproductive and behavioral effects have been described (1). Still, most studies have focussed on ghrelin’s role in energy homeostasis and weight regulation: Ghrelin is an orexigenic hormone that increases appetite and food intake (2, 3) and induces adiposity in rodents by decreasing lipid oxidation and increasing lipogenesis (2, 4, 5). Furthermore, it was shown to shift food preference towards high-fat diet (6). There is also evidence that ghrelin decreases thermogenesis and energy expenditure (7, 8). Thus, ghrelin causes a positive energy balance. In humans, ghrelin plasma levels were found to be negatively correlated with weight and body fat (9, 10). Being decreased in obesity, plasma levels increased after weight loss (10). Conversely, plasma ghrelin levels were elevated in anorectic patients and decreased after weight gain (11).

Hormones of the hypothalamus-pituitary-thyroid (HPT) axis are crucially involved in maintaining body temperature and energy homeostasis in mammals. They stimulate the metabolic rate of most tissues such as liver, heart, skin, bone, muscle or adipose tissue, thereby increasing thermogenesis and energy expenditure (12-14). Consequently, hyperthyroid states are associated with weight loss and increased body temperature, whereas hypothyroid states are associated with weight gain and reduced body temperature (14). Taken together, ghrelin promotes energy saving effects and weight gain whereas the activation of the HPT axis is associated with increased energy expenditure and weight loss.

These findings suggest that ghrelin may affect the HPT axis. In fact, a recent study in male rats reported a decreased activity of the HPT axis after intracerebroventricular (icv)
injection of ghrelin or placebo every 24 hours for five days: Pituitary TSH cells were smaller and TSH plasma levels lower, and as a result thyroid follicles were less active and thyroxine plasma level reduced compared to placebo-treated rats (15). Furthermore, another study found significantly lower TSH plasma levels after a single icv injection of ghrelin than placebo after 20 minutes (16). But in studies in dogs (17, 18) and humans (19, 20) ghrelin did not change TSH levels. Also the synthetic GHS receptor agonist hexarelin was found to decrease TSH secretion after a single dose within two hours (21). However, hexarelin had no effects on TSH levels in the long term, i.e. injected subcutaneously for 16 weeks twice daily (22). There are other findings indicating a role for ghrelin in the regulation of the HPT axis: Ghrelin binding sites, possibly different from the GHS receptor, have been detected in the human thyroid (23, 24). In addition, ghrelin enhanced in vitro TSH-induced proliferation of rat thyrocytes (25) and diminished cell proliferation in human thyroid carcinoma cell lines (23).

We hypothesized that ghrelin suppresses the activity of the HPT axis in humans which counteracts its energy saving effects. We tested this hypothesis by determining secretion patterns of free triiodothyronine (fT3), free thyroxine (fT4), TSH and thyroid binding globulin (TBG) after administration of ghrelin and placebo.

**Research design and methods**

**Subjects**

20 healthy adults, aged 20 to 30 years (10 males, 10 females, 25.3 ± 2.7 years, BMI: 21.6 ± 1.6, range: 19.7 to 24.8) were included in this study. Exclusion criteria comprised a lifetime history of endocrine or psychiatric disorders, a pathological electroencephalogram (EEG) or electrocardiogram (ECG) or drug-intake during the 3 months prior to study entry. All subjects
had normal thyroid function as assessed by plasma levels of fT3, fT4 and TSH. The study was conducted in accordance with the guidelines in The Declaration of Helsinki. Written informed consent was obtained from all participants. Ethical review board approval was given.

**Study design**

This was a single-blind, placebo-controlled, randomized, cross-over study that comprised two blocks of two consecutive nights. In females, each block took place during the early follicular phase. Generally, both blocks occurred in two consecutive cycles, i.e. with an interval of about four weeks. In males, the two blocks were separated by at least one week. The first night of each block served for adaptation to sleep laboratory settings. During the second night, 50 µg acylated ghrelin (Clinalfa, Läufelfingen, Switzerland), or placebo was injected at 2200, 2300, 0000, and 0100 h. In addition, 4 ml of blood was drawn every 30 minutes (2000–2200 h) and 20 minutes (2200–0700 h) respectively from the adjacent room, using an iv cannula and a tubic extension. Furthermore, sleep-EEGs were conducted between 2300 and 0700. These data have been presented elsewhere (26, 27). Substances (e.g. coffee, alcohol) or activities (e.g. naps during the day, excessive exercises) potentially influencing vigilance were restricted or prohibited. Food intake was not controlled prior to the study period, but all participants reported normal eating patterns including breakfast, lunch and dinner. Apart from transient sweating in one female and one male subject in the ghrelin condition, no side effects occurred. None of the participants reported increased appetite.

**Hormone analysis**

Blood samples were centrifuged immediately and plasma was frozen at −25°C. Concentrations of fT3, fT4, TSH and TBG were determined using a solid phase, two-site, sequential chemiluminescent immunometric assay in an automated analyzer (Immulite 2005,
Siemens Medical Solutions, Erlangen, Germany). All samples of an individual were measured in the same assay run. Detection limits were 1.0 pg/ml for fT3, 0.12 ng/dl for fT4, 0.01 mIU/ml for TSH, and 1.6 µg/ml for TBG. Intra- and interassay coefficients of variance were below 9 and 12% (fT3, fT4, TBG), and 6 and 8% (TSH), respectively.

**Statistical methods**

Treatment effects on hormone concentrations were identified by means of a MANOVA for the whole study period (2000 to 0700 h), the two halves of the study period (1st half: 2000 to 0130 h; 2nd half 0130 to 0700 h), and the post-intervention period (2220 to 0700 h). Whenever significant treatment effects were found, three curve characteristics (area under the curve [AUC], mean location and delta [highest minus lowest value]) were calculated and tested for significant differences between treatment conditions with univariate F-tests. Differences of mean plasma levels of fT3, fT4, TSH and TBG at single time-points were tested for significance by test with contrasts in a MANOVA (level of significance: $\alpha = 0.05$). The Holm-Sidak method was used for correction for multiple testing.

Pulses and pulse characteristics of TSH secretion were determined using Cluster8 from PulseXP software (28) for the whole study period and the post-intervention period. Number of peaks, mean peak interval, mean peak width, mean peak height and mean nadir were analyzed. Less than two percent of all samples were missing which were not replaced. Metric demographic variables are given as mean ± standard deviation (SD), hormone variables as mean ± standard error of the mean (SEM).
Results

**fT3, fT4**

FT4 plasma levels were significantly ($P < 0.05$) higher after ghrelin than placebo administration from 0000 until 0620 h except for the time-points at 0100, 0520, and 0600 h (Figure 1). FT3 plasma levels did not differ at any point in time. Consequently, a significant treatment effect on fT4 secretion was observed during the whole study period ($P = 0.016$), the post-intervention period ($P = 0.019$) and the second half of the study period ($P = 0.005$) but not during the first half ($P = 0.063$) (Table 1). The AUC (fT4) was 1.1 % higher after ghrelin than after placebo injection during the post-intervention period, and 5.8 % higher during the second half of the study period. Significant treatment effects on secretion of fT3 were not observed during any of these periods (Figure 1).

**TSH**

Mean TSH plasma levels were almost identical in both treatment conditions until 0000 h showing a strong increase peaking at 2300 h. TSH plasma levels were significantly ($P < 0.05$) lower in the ghrelin than the placebo condition from 0200 h until study end at 0700 h except for the time-points at 0540, 0600 and 0620 h (Figure 2). A significant treatment effect was observed during the whole study period ($P = 0.004$), the post-intervention period ($P = 0.003$), and the second half of the study period ($P = 0.003$) but not during the first half ($P = 0.214$). During the whole study period, delta was significantly larger in the ghrelin than in the placebo condition (Table 2). AUC and mean location were numerically but not significantly smaller.

During the post-intervention period, all these findings reached statistical significance; AUC and mean location were about 15% smaller after ghrelin than after placebo administration (Table 2). During the second half of night, delta did not differ (placebo: $0.80 \pm 0.10$; ghrelin:
0.87 ± 0.09 mIU/ml), whereas AUC (placebo: 1.74 ± 0.18; ghrelin: 1.32 ± 0.12 mIU/ml x min; \( P = 0.007 \)) and mean location (placebo: 1.85 ± 0.19; ghrelin: 1.41 ± 0.13 mIU/ml \( P = 0.008 \)) were 24% smaller after ghrelin than after placebo administration.

The mean nadir was smaller after ghrelin than placebo injection (whole study period: \( P = 0.088 \); Post-intervention period: \( P = 0.040 \)). Other pulse characteristics, e.g. pulse frequency, did not differ (Table 2).

**TBG**

TBG plasma levels did not significantly differ at any time-point between treatment conditions. Significant treatment effects were neither observed during the whole study period (\( P = 0.832 \)), the post-intervention period (\( P = 0.738 \)), nor during one of the two halves of the study period (1\(^{st} \) half: \( P = 0.785 \); 2\(^{nd} \) half: \( P = 0.240 \)).

**Discussion**

Ghrelin caused a subtle increase of fT4 followed by a marked decrease of TSH approximately two hours after that in our study. This decrease occurred after the physiological TSH surge (29) which was not affected. FT3 plasma levels did not differ between placebo and ghrelin condition at any time.

Potential reasons for elevated fT4 plasma levels are an increased release from the thyroid or a decreased peripheral thyroid hormone metabolism, e. g. due to raised hepatobiliary clearance or reduced activity of deiodinases. In addition, reduced TBG plasma levels after ghrelin injection or T4 displacement from TBG by ghrelin could be associated with higher fT4 plasma levels. However, TBG plasma levels were similar with both treatments and displacement of T4 would have been probably accompanied by displacement of T3 being also
bound to TBG (30, 31). More likely, increased fT4 plasma levels could be caused by a decreased thyroid hormone metabolism: The hepatobiliary clearance of T3 and T4 occurs partly through different pathways, and substances which affect only the T4 clearance have been described (32-34). Considering an altered activity of deiodinases, changed T3 plasma levels might be actually expected since all deiodinases affect T3. Deiodinase 1 and deiodinase 2 catalyze the conversion from T4 to T3. Deiodinase 3 catalyzes the degradation of both T4 and T3 (35). Yet surprisingly, deiodinase 1 deficient mice had elevated T4 levels while T3 and TSH were normal (36). Accordingly, ghrelin could affect deiodinase 1 in humans. However, we assume that the increase of fT4 was rather caused by release from the thyroid than by an altered metabolism since it occurred already two hours after the first ghrelin injection. In contrast, acute exposure to substances which either induce or inhibit uridine diphosphoglucuronyl transferase (UGT), being crucially involved in thyroid hormone metabolism (37, 38), led to significant changes of UGT activity not before 24 h after exposure (39, 40).

Assuming that the increase of fT4 was due to release from the thyroid, it was apparently not induced by pituitary TSH since TSH plasma levels before the increase were similar for both treatments. We therefore suggest that ghrelin stimulated the fT4 release directly at the thyroid where GHS receptors were identified (24). A stimulatory action at thyroid level, namely a rapid activation of intracellular pathways involved in TSH-induced proliferation of thyrocytes, has been also described in rats (25). It can be argued that the TSH suppression observed in our study might be caused by a feedback inhibition by fT4. Both the plasma half life of TSH of roughly one hour and our finding that the relative increase of FT4 was about four times weaker than the relative decrease of TSH seem to be in line with this assumption since TSH and fT4 have been shown to have an inverse log-linear relationship (41, 42). However, it is questionable whether the small increase of fT4 can entirely explain the distinct
and sustained suppression of TSH as several times stronger increases of fT4 after administration of 125 or 250 µg T4 in healthy volunteers failed to be associated with a significant decrease of TSH (41).

In fact, there are several findings suggesting that ghrelin suppresses TSH secretion directly at hypothalamic level comparably to ghrelin’s suppressive effect on secretion of LH and FSH (43, 44): First, the same hypothalamic neurons that mediate ghrelin’s orexigenic action strongly affect the activity of thyrotropin releasing hormone (TRH) neurons, the hypothalamic releasing factor of TSH; ghrelin stimulates neurons containing the orexigenic peptides neuropeptide Y (NPY) (45-47) and agouti-related protein (AgRP) (45, 47) which decrease the activity of TRH neurons (48, 49). Furthermore, ghrelin probably inhibits neurons containing the anorexigenic peptides α-melanocyte stimulating hormone (α-MSH) (50) and cocaine and amphetamine regulated transcript (CART) (51) which increase the activity of TRH neurons (48, 49). Secondly, the hormone leptin that has antagonistic effects to ghrelin regarding appetite (decreasing) and TSH secretion (increasing) exerts these effects by an opposite action on NPY/AgRP neurons (inhibiting) (52, 53) and α-MSH/CART neurons (stimulating) (54, 55). Thirdly, TSH suppression in rats was induced by ghrelin injection in the CNS, suggesting a comparable mechanism in humans. In that study, ghrelin was given subchronically (5 days). TSH suppression was associated with a significant decrease of T4 and a decrease of T3 at a trend level (p < 0.1) (15).

Considering our and the other findings described we propose that the observed decrease of TSH was caused to a greater extent by direct inhibition of hypothalamic neurons and to a smaller extent by feedback inhibition by initially increased fT4. Yet, our study alone cannot definitely prove this assumption. The partly different findings in rats unequivocally showing a suppression of the HPT axis (TSH, T4, T3) (15) are probably caused by two factors; first, the central administration of ghrelin, rendering unlikely a direct stimulatory
effect on the thyroid; secondly, the markedly longer treatment and observation period (5 days versus 9 hours as judged from the first ghrelin injection in the present study). Taking the long half life of T4 of about seven days into account, our study was too short to capture effects on fT4 consecutive to TSH suppression. Therefore, our results do not exclude that ghrelin overall suppresses the activity of the HPT axis.

Why did fT3 plasma levels remain unchanged in our study? While regular administration of T4 causes an increase of T3 since more T4 will be deiodinased to T3 (56, 57), short term administration of T4 is not necessarily associated with changes in T3 (41). Comparably, the small T4 increase observed in our study was not followed by higher T3 plasma levels. The study was conducted at night-time for capturing the TSH surge because potential differences between treatments can be obviously more easily identified with higher plasma levels. In addition, potential inferences do more frequently occur during the day than the night. Ghrelin doses given in our study (50 µg corresponding to 0.6 to 0.8 µg/kg body weight) were lower than in most other studies investigating ghrelin’s effects in humans which were usually 1 µg/kg body weight (58, 59). As a result, no side effects occurred apart from sweating in two subjects. Of interest, not even appetite-induction of this actually appetite-inducing hormone (3) was reported. These clinical findings and the short half life of acylated ghrelin of about 10 minutes (60) rebut the possible concern that effects on the HPT axis observed in the present study might have been caused by an accumulation of ghrelin.

To our knowledge, this is the first study showing that ghrelin affects the HPT-axis in humans. Furthermore, it is the first study in mammals showing such an effect after peripheral administration of ghrelin. In rats, two groups reported a suppression of TSH plasma levels after icv injection (15, 16). However, most studies in animals and humans failed to detect an effect on the HPT axis possibly due to methodological limitations, e.g. lack of control.
condition (17-20), insufficient sample size and measurement period (17). In addition, several pulses of ghrelin might be required to elicit a suppressive effect since ghrelin physiologically exhibits a pulsatile secretion pattern (61).

In conclusion, we showed for the first time that ghrelin affects the HPT axis in humans. The early fT4 increase was possibly induced by direct ghrelin action on the thyroid where ghrelin receptors have been identified. The TSH decrease might have been caused by ghrelin-mediated inhibition at hypothalamic level, through feedback inhibition by fT4, or both.

**Declaration of interest**

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Figure legends

**Figure 1:** Secretion profiles of free triiodothyronine (fT3) and free thyroxine (fT4) (mean, SEM) in 20 healthy subjects receiving ghrelin or placebo

*significant difference between treatment groups

**Figure 2:** Secretion profile of TSH (mean, SEM) in 20 healthy subjects receiving ghrelin or placebo

*significant difference between treatment groups
**Table 1**: Curve characteristics of fT4 secretion in 20 adults receiving ghrelin or placebo; depicted are results (mean [SEM]) during the following periods: whole study (2000 to 0700 h), post-intervention (2220 to 0700 h), 1<sup>st</sup> half (2000 to 0130 h), 2<sup>nd</sup> half (0130 to 0700 h)

<table>
<thead>
<tr>
<th>Area under the curve</th>
<th>Mean location</th>
<th>Delta</th>
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<tbody>
<tr>
<td>(ng/dl x min)</td>
<td>(ng/dl)</td>
<td>(ng/dl)</td>
</tr>
<tr>
<td><strong>fT4</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>1.31 (0.03)</td>
<td>1.22 (0.02)</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>1.33 (0.03)</td>
<td>1.27 (0.03)</td>
</tr>
<tr>
<td></td>
<td><em>P</em></td>
<td>0.005</td>
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<tr>
<td>Placebo</td>
<td>1.27 (0.03)</td>
<td>1.21 (0.02)</td>
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<tr>
<td>Ghrelin</td>
<td>1.28 (0.03)</td>
<td>1.27 (0.03)</td>
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<td></td>
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<tr>
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<td>1.23 (0.03)</td>
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<tr>
<td>Ghrelin</td>
<td>1.27 (0.03)</td>
<td>1.28 (0.03)</td>
</tr>
<tr>
<td></td>
<td><em>P</em></td>
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<tr>
<td>Placebo</td>
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<td>Ghrelin</td>
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<td></td>
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Table 2: Curve and pulse characteristics (mean [SEM]) of TSH secretion during the whole study period (2000 – 0700 h) and the post-intervention period (2220 – 0700 h)

<table>
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<th>Post-intervention period</th>
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<td>1.82 (0.18)</td>
<td>Ghrelin</td>
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<tr>
<td>Mean location (mIU/ml)</td>
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<td>1.89 (0.18)</td>
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<tr>
<td>Delta (mIU/ml)</td>
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<td>1.28 (0.13)</td>
<td>Ghrelin</td>
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Pulse characteristics

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<tr>
<td>Number of pulses</td>
<td>3.95 (0.18)</td>
<td>4.25 (0.28)</td>
<td>n. s.</td>
</tr>
<tr>
<td>Mean peak interval (min)</td>
<td>126.4 (12.6)</td>
<td>114.2 (9.5)</td>
<td>n. s.</td>
</tr>
<tr>
<td>Mean peak width (min)</td>
<td>95.3 (7.6)</td>
<td>85.5 (9.4)</td>
<td>n. s.</td>
</tr>
<tr>
<td>Mean peak height (mIU/ml)</td>
<td>2.15 (0.21)</td>
<td>1.98 (0.17)</td>
<td>n. s.</td>
</tr>
<tr>
<td>Mean nadir (mIU/ml)</td>
<td>1.54 (0.15)</td>
<td>1.30 (0.14)</td>
<td>n. s.</td>
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</table>
Figure 2

216x279mm (600 x 600 DPI)