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Ghrelin Has Partial or No Effect on Appetite, Growth Hormone, Prolactin, and Cortisol Release in Patients with Anorexia Nervosa

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Context: Anorexia nervosa (AN) is an eating disorder characterized by self-induced starvation. Gastric hormone ghrelin, potent orexigen, and natural GH secretagogue are increased in AN. Although exogenous ghrelin stimulates appetite, GH, prolactin, and cortisol release in humans, its effects have not been studied, during infusions, in AN patients.

Objective: The objective of the study was to determine the effects of ghrelin on appetite, sleepiness, and neuroendocrine responses in AN patients.

Design: This was an acute interventional study.

Setting: The study was based at a hospital.

Investigated Subjects: Twenty-five young women, including nine patients diagnosed with AN with very low body weight, six AN patients who partially recovered their body weight but were still amenorrheic, and 10 constitutionally thin female subjects, without history of eating disorder, weight loss, with regular menstrual cycles, were included in the study.

Intervention: Each patient received 300-min iv infusion of ghrelin 5 pmol/kg·min and was asked to complete Visual Analog Scale questionnaires hourly.

Main Outcome Measures: Visual Analog Scale scores for appetite and sleepiness, GH, prolactin, and cortisol responses were measured.

Results: At baseline, AN patients had significantly higher ghrelin, GH, and cortisol levels and significantly lower leptin than constitutionally thin subjects. GH responses to ghrelin infusion were blunted in patients with AN. Ghrelin administration did not significantly affect appetite but tended to increase sleepiness in AN patients.

Conclusions: Ghrelin is unlikely to be effective as a single appetite stimulatory treatment for patients with AN. Our results suggest that AN patients are less sensitive to ghrelin in terms of GH response and appetite than healthy controls. Ghrelin effects on sleep need further studies. **(*J Clin Endocrinol Metab* 91: 1491–1495, 2006)**

ANOREXIA NERVOSA (AN) is an eating disorder, mostly affecting young females, characterized by impaired visual body perception, fear of adiposity, and therefore chronically decreased caloric intake, resulting in self-induced starvation. Excessive physical activity and/or purging behavior in some patients further contribute to resistance of efforts to increase body weight. The prolonged starvation in these patients causes profound changes in their body composition inducing many adaptive endocrine changes in adipocytokines and reproductive, thyroid, adrenal, and somatotrope axes.

Ghrelin, a novel peptide secreted mainly by the stomach (1), is potent GH secretagogue, with orexigenic properties providing a new link between stomach and brain in the regulation of energy homeostasis. Ghrelin is secreted in a pulsatile manner, peaking at 2000 h and rising before meals, returning to baseline levels after the food ingestion, implicating its important role in the feeding behavior (2, 3). Ghrelin administered iv strongly stimulates GH secretion in both rats and humans (1, 4, 5), acting through GH secretagogue receptor type 1a in hypothalamus and pituitary. In pharmacological doses ghrelin also increases prolactin, ACTH, and cortisol secretion (5). Exogenous ghrelin increases adiposity in rodents (6) and appetite in healthy volunteers (7) and patients with cancer cachexia (8). Although ghrelin may be an efficient and promising therapeutic tool for patients suffering from anorexia due to various organic diseases, weight loss in anorexia nervosa is primarily psychiatric in origin, and effects of ghrelin intervention on appetite and food intake have not been studied so far in these patients.

Circulating ghrelin levels are elevated in patients with anorexia nervosa (2), compared with normal-weight control subjects, reflecting the state of negative energy balance. Acute administration of 1 μg/kg ghrelin iv injection on neuroendocrine response in AN patients has shown an inadequate GH response (9). Longer infusion studies have not

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Abbreviations: AN, Anorexia nervosa; BMI, body mass index; CTS, constitutionally thin subjects; ΔGHmax, difference between peak and baseline GH levels; PRAN, partially recovered AN; VAS, Visual Analog Scale.

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been performed in these patients. In our study, we aimed to investigate the effects of prolonged ghrelin infusion (5 h protocol) on appetite, sleepiness [through repeated Visual Analog Scale (VAS) assessment], and neuroendocrine responses in patients with AN. Test meals were avoided because AN patients with very low body weight were unwilling to consume them. Saline (placebo) studies were also avoided as cumbersome for the frail AN subjects.

Patients and Methods

All studies were performed according to the principles of the Declaration of Helsinki and approved by the local research and ethics committee. Written informed consent was obtained from all subjects. Twenty-five young female subjects were recruited: nine AN patients with very low body weight, six AN patients who partially recovered body weight but were still amenorrheic, and 10 healthy constitutionally thin female subjects with regular menstrual cycles were studied in follicular phase of the cycle.

All patients were diagnosed with AN on the basis of Diagnostic and Statistical Manual of Psychiatric Disorders-Fourth Edition criteria. Three study groups were formed: 1) nine AN patients (four with purging and five with restrictive type of AN) with very low body mass index (BMI) of 12.0 ± 0.4 kg/m^2 (range 10.6–13.8 kg/m^2) and body weight 34 ± 0.8 kg (range 30–39 kg); 2) six partially recovered AN patients (PRAN) with BMI of 17.2 ± 1.3 kg/m^2 (range 16.9–18.3 kg/m^2) and body weight 49.0 ± 3.8 kg (range 39–59 kg) without purging behavior who nearly normalized their body weight but were still amenorrheic; and 3) 10 constitutionally thin subjects (CTS) with subnormal body weight, 51.4 ± 2.4 kg (45–60 kg) and BMI 17.6 kg/m^2 (range 16.6–19.3 kg/m^2) but without history of eating disorder and weight loss and with regular menstrual cycles (Table 1.).

Ghrelin (5 pmol/kg·min) infusion has been reported to increase appetite in healthy volunteers (7) and patients with cancer-associated cachexia and impaired appetite (8). Human ghrelin was purchased from Bachem Ltd. (Merseyside, UK). The limulus amoebocyte lysate assay for pyrogen was negative and the peptide was sterile on culture. Fasted subjects had two iv cannulae placed, one for the infusion and the other for blood sampling. Ghrelin infusion (5 pmol/kg·min) started at 0900 h (0 min) and lasted for 300 min. Blood samples were taken at baseline (0 min) and every 15 min during first 2 h of the infusion and from that point every 30 min for ghrelin, GH, prolactin, and cortisol measurements. To assess the effects of ghrelin administration on appetite and sleepiness, we used the same VAS questionnaire as in previous studies with ghrelin infusions (7, 8). Investigated subjects were asked to complete VAS (possible scores 0–100 mm) rating hunger, satiety, palatability, sickness, and sleepiness before infusion and hourly during the infusion. Scores were measured by a blinded observer.

TABLE 1. Baseline clinical and hormonal characteristics of investigated subjects

Variable	AN (n = 9)	PRAN (n = 6)	CTS (n = 10)
Age (yr)	25.1 ± 1.7	24.8 ± 1.9	22.5 ± 1.4
Body weight (kg)	34.0 ± 0.8	49.0 ± 3.8[a]	51.4 ± 2.4[a]
BMI (kg/m^2)	12.0 ± 0.4	17.2 ± 1.3[a]	17.6 ± 0.4[a]
Leptin (ng/ml)	2.1 ± 0.2	4.6 ± 0.8[b]	9.6 ± 1.8[a]
Adiponectin (μg/ml)	33.5 ± 8.5	44.2 ± 3.8	37.2 ± 4.2
Ghrelin (pg/ml)	985.3 ± 165.4	685.2 ± 78.0[b,c]	443.7 ± 78.7[a]
GH (μg/liter)	8.5 ± 3.7	1.4 ± 0.4[b]	0.6 ± 0.2[b]
Cortisol (nmol/liter)	744.0 ± 59.9	502.7 ± 52.5[b]	425.8 ± 39.1[a]
Prolactin (mU/liter)	538.8 ± 266.6	426.3 ± 224.7	353.6 ± 75.5
Glucose (mmol/liter)	3.4 ± 0.2	3.7 ± 0.3	4.1 ± 0.2
Insulin	11.85 ± 2.30	11.03 ± 3.43	8.10 ± 3.20
C-peptide	0.33 ± 0.08	0.25 ± 0.04	0.36 ± 0.07

[a] $P < 0.01$ PRAN/CTS *vs.* AN.
[b] $P < 0.05$ PRAN/CTS *vs.* AN.
[c] PRAN *vs.* CTS $P < 0.05$.

Hormone assays

Ghrelin immunoreactivity was measured with a specific in-house RIA (Hammersmith Hospital, London, UK). The assay measures both octanoyl and des octanoyl ghrelin and does not cross-react with any known gastrointestinal or pancreatic peptide hormones. The assay detected changes of 25 pmol/liter plasma ghrelin with 95% confidence limit. Other hormones were measured by commercial kits: GH by immunoradiometric assay (CIS-US, Inc., Bedford, MA); prolactin by RIA (CIS-US); cortisol by RIA (CIS-US); insulin and c-peptide by RIA (Institute for the Application of Nuclear Energy, Zemun, Serbia and Montenegro); leptin by RIA (Linco, St. Charles, MO); and adiponectin by RIA (Linco). Blood glucose was measured using enzymatic glucooxydaze method (Randox, Antrium, UK).

Statistical analysis

Results are expressed as means ± SEM. Plasma hormone levels at baseline were compared using one-way ANOVA. Changes in the hormone levels during the infusion and VASs were analyzed using a general linear model. Values of $P < 0.05$ were considered statistically significant.

Results

No adverse events were observed or reported on any infusion day. Significant differences were observed at baseline between AN and two other groups, PRAN and CTS, in the levels of leptin, ghrelin, GH, and cortisol (Table 1.). AN patients had significantly lower leptin and significantly higher ghrelin, GH, and cortisol levels, compared with PRAN and CTS (Table 1). However, there were no significant differences between the studied groups in fasting glucose, insulin, c-peptide, and adiponectin levels at baseline (Table 1). Ghrelin levels were significantly higher with lower leptin in PRAN, compared with CTS, with the same BMI.

Plasma ghrelin was significantly elevated to the same extent by ghrelin infusion (5 pmol/kg·min) in all groups (Fig. 1). Significantly higher GH response to ghrelin infusion was observed in CTS [change in maximum GH (ΔGHmax) 22.0 ± 3.0 μg/liter], compared with AN (ΔGHmax 6.3 ± 1.3 μg/liter, $P < 0{,}0001$) and PRAN (ΔGHmax 14.8 ± 2.2 μg/liter, $P < 0.05$). PRAN showed better GH response to ghrelin than AN patients ($P < 0.05$). In all subjects the GH response was marked within the first 2 h of the infusion, resolving there-

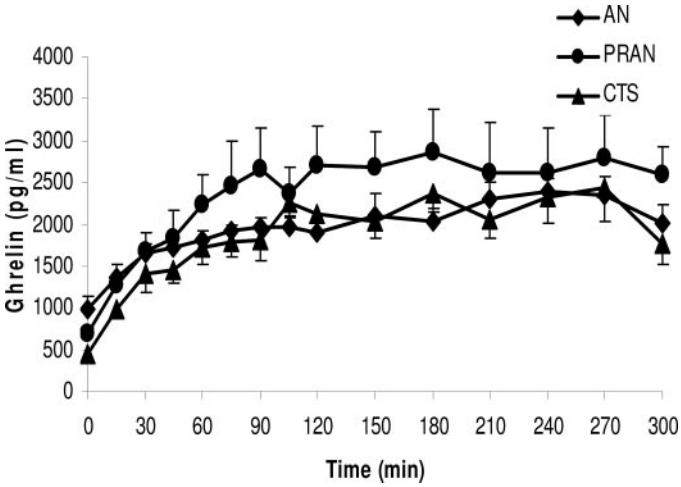

FIG. 1. Ghrelin levels (picograms per milliliter) during ghrelin infusion in patients with AN, PRAN, and CTS.

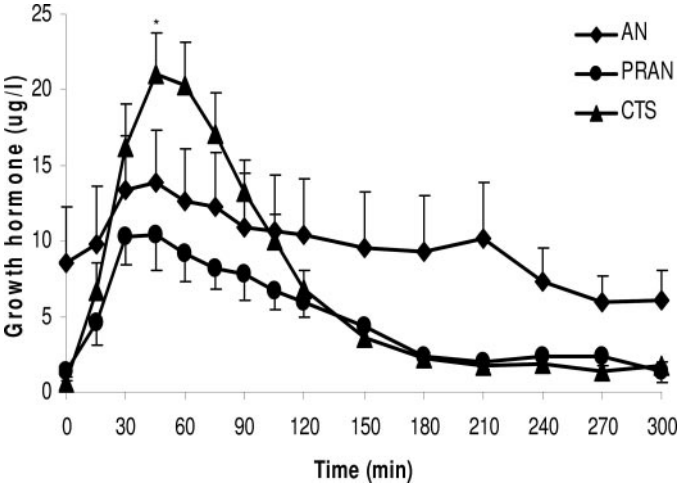

FIG. 2. GH (micrograms per liter) levels during ghrelin infusion in patients with AN, PRAN, and CTS. *, $P < 0.05$ CTS *vs.* AN/PRAN.

after (Fig. 2). Prolactin (Fig. 3) and cortisol (Fig. 4) levels were not significantly affected by ghrelin infusion.

Analysis of the VAS revealed significant differences in hunger scores after the first hour and sleepiness scores after the fourth and fifth hour of ghrelin infusion between patients with AN, both at low body weight and after partial recovery, and CTS (Figs. 5 and 6). AN and PRAN patients felt significantly less hungry (hunger score at 60 min: 34.4 ± 30.29 *vs.* 65.2 ± 23.19, $P < 0,05$) and more sleepy (sleepiness scores at 240 min: 43.4 ± 29.9 *vs.* 29.5 ± 30.5, $P < 0.05$; and 300 min: 40.78 ± 33.63 *vs.* 26.2 ± 32.75, $P < 0.05$), compared with CTS. There were no significant differences in how full and how sick anorectic patients (AN and PRAN), compared with CTS, felt during ghrelin infusions (results not shown).

Discussion

Our study shows for the first time that infusion of active ghrelin is incapable of inducing normal GH and appetite responses in patients with AN. Furthermore, persistence of alterations in baseline ghrelin and leptin levels and GH responses to ghrelin, in partially recovered anorectics in our study, suggest persistence of eating disorder.

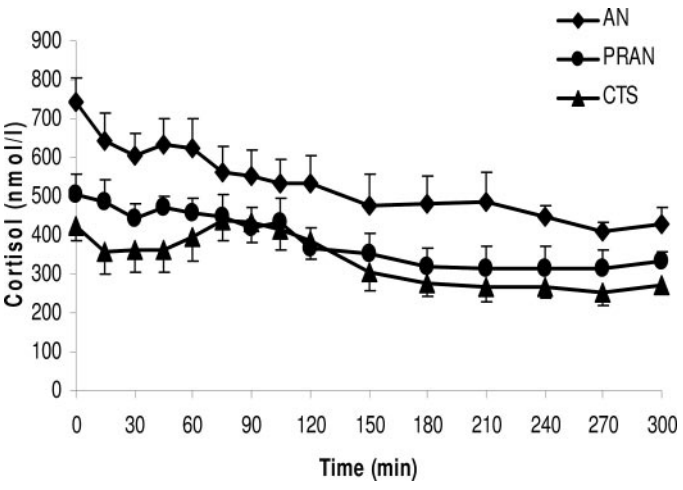

FIG. 3. Cortisol levels (nanomoles per liter) during ghrelin infusion in patients with AN, PRAN, and CTS.

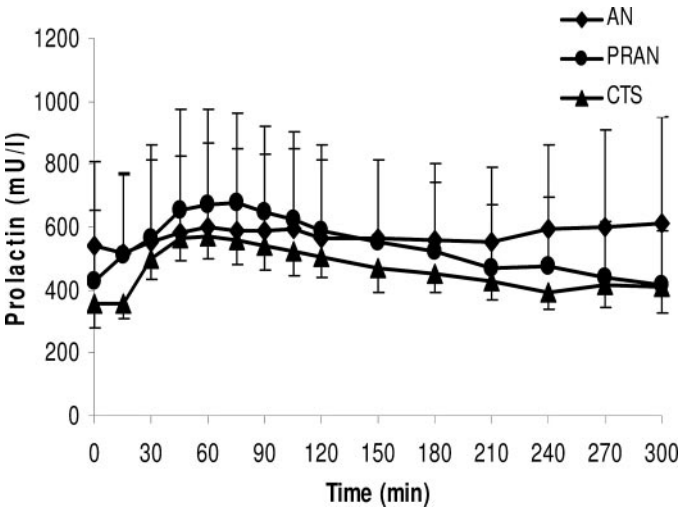

FIG. 4. Prolactin (milliunits per liter) response to ghrelin infusion in patients with AN, PRAN, and CTS.

Hyperghrelinemia, at baseline, in patients with low-weight AN, has been reported previously and at least partly explained by chronic self-induced starvation (2, 10, 11). Recently increased levels of ghrelin due to increase in inactive, *i.e.* nonacylated, ghrelin have been shown in patients with AN (12). Our results are in accord with findings of increased frequency and amplitude of ghrelin pulses in patients with AN (13). Significantly higher circulating ghrelin levels together with lower leptin levels, at baseline, in partially recovered anorectic patients, when compared with CTS, have also been shown by others (14–16).

At baseline, patients with AN and low BMI had significantly elevated GH levels and displayed a blunted GH response during ghrelin infusion. The same supraphysiological levels of ghrelinemia were achieved in all studied groups. GH responses to ghrelin infusions were time limited to the first 2 h of the infusion in all subjects, probably due to tachy-

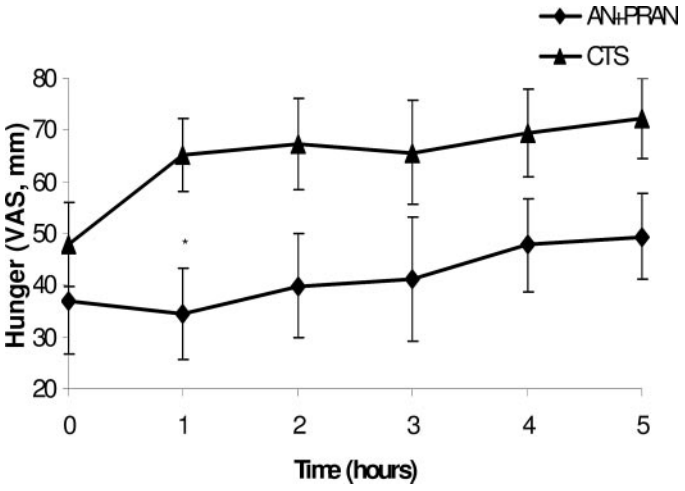

FIG. 5. VAS scores (presented in millimeters) rating hunger during ghrelin infusion in AN and PRAN (AN+PRAN) and CTS. *, $P < 0.05$ CTS *vs.* AN+PRAN.

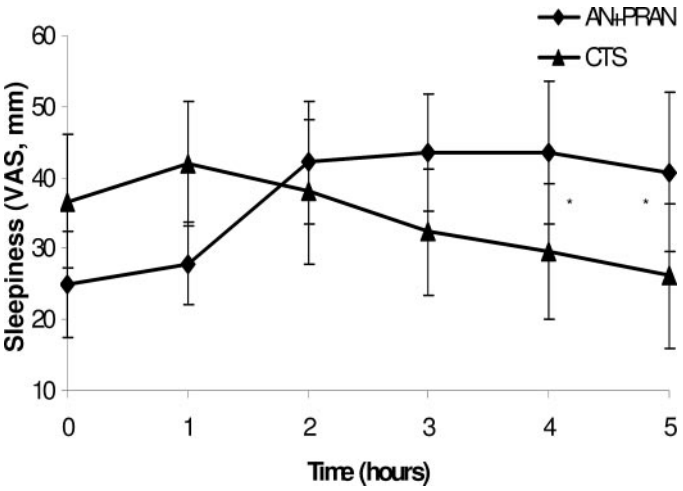

FIG. 6. VAS scores (presented in millimeters) rating sleepiness during ghrelin infusion in AN and PRAN patients (AN+PRAN) and CTS. *, $P < 0.05$ CTS *vs.* AN+PRAN.

phylaxis phenomenon. Blunted GH response in AN could at least be explained by the effects of prolonged exposure to endogenous hyperghrelinemia with consecutive desensitization to its actions, as has been reported for synthetic GH secretagogue, hexarelin (17), and ghrelin itself (9). We have previously shown, in the opposite situation, that chronic hypoghrelinemia due to gastrectomy renders these patients more sensitive to exogenous ghrelin in terms of GH response (18). Another explanation for the attenuated GH response to exogenous ghrelin infusion could be the hyperactivation of hypothalamo-pituitary-adrenal axis. Attenuated GH response to ghrelin has been reported for patients with Cushing's syndrome (19).

At baseline, cortisol levels were also significantly elevated in AN patients, compared with weight-recovered and CTS. It has been proposed that in patients with AN, there is a hyperactivation of the limbic-hypothalamic-pituitary-adrenal system as a response to chronic stressors (20). It can be hypothesized that low leptin and high ghrelin may also contribute to the increased GH and cortisol production because it has been shown that both ghrelin and leptin predict GH and cortisol burst frequency in AN (13, 21). Cortisol and prolactin levels were not significantly affected by ghrelin infusion in any of the studied groups, in contrast to the results obtained after acute bolus dose of ghrelin (9). Finally, Broglio *et al.* (22) have shown that nonacylated ghrelin counteracts the metabolic but not the neuroendocrine responses of acylated ghrelin in humans. Therefore, one could expect that neuroendocrine responses induced by intervention with acylated ghrelin would not be affected by increased nonacylated ghrelin levels in these patients. However, we have shown that infusion of active, acylated ghrelin failed to induce changes in neuroendocrine responses in anorectic patients.

When AN and PRAN were analyzed separately for hunger and sleepiness scores, there were no significant differences, and the two groups were therefore combined for purposes of analysis.

Although at baseline sleepiness scores were lower in AN (both at low body weight and after partial weight recovery) than CTS, increased sleepiness was observed in AN and PRAN patients, compared with healthy controls, after the fourth and fifth hour of ghrelin infusion. It has been shown previously that ghrelin promotes slow-wave sleep in humans (23). On the other hand, sleep curtailment has been shown to affect ghrelin and GH secretion (24–26). The mechanism of this action is unclear and warrants further investigations.

It was difficult to assess the effect of ghrelin on appetite in anorectic patients. The drawback of this part of the study was the inability to include a test meal and measure caloric intake as suggested (7, 8) because patients with AN and very low body weight refused to eat. Nevertheless, we assessed VAS hunger scores without meals and when compared with CTS, patients with AN showed less increase in their hunger scores, especially after the first hour of ghrelin infusion.

In conclusion, ghrelin infusions did not significantly affect appetite or change neuroendocrine responses but tended to increase sleepiness in patients with AN, warranting further studies in this field. Ghrelin is unlikely to be effective when used as single appetite stimulatory agent in patients with AN.

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All authors have nothing to declare.

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