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Ghrelin Increases Energy Intake in Cancer Patients with Impaired Appetite: Acute, Randomized, Placebo-Controlled Trial

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There is a pressing need for more effective appetite-stimulatory therapies for many patient groups including those with cancer. We have previously demonstrated that the gastric hormone ghrelin potently enhances appetite in healthy volunteers. Here, we performed an acute, randomized, placebo-controlled, cross-over clinical trial to determine whether ghrelin stimulates appetite in cancer patients with anorexia. Seven cancer patients who reported loss of appetite were recruited from oncology clinics at Charing Cross Hospital. The main outcome measures were energy intake from a buffet meal during ghrelin or saline infusion and meal appreciation as assessed by visual analog scale. A marked increase in energy intake (31 ± 7%; $P = 0.005$) was observed with ghrelin infusion compared with saline control, and every patient ate more. The meal appreciation score was greater by 28 ± 8% ($P = 0.02$) with ghrelin treatment. No side effects were observed. The stimulatory effects of ghrelin on food intake and meal appreciation seen in this preliminary study suggest that ghrelin could be an effective treatment for cancer anorexia and possibly for appetite loss in other patient groups. (*J Clin Endocrinol Metab* 89: 2832–2836, 2004)

THERE IS A pressing need for more effective, better-tolerated, appetite stimulatory treatments. Loss of appetite and loss of weight are major causes of morbidity and mortality affecting many patients, including those with cancer, HIV, cardiac cachexia, inflammatory conditions such as sepsis and burns, and postoperative patients. Weight loss also has an important impact on health economics. Undernutrition may account for an additional 5-d admission for 10% of hospital admissions costing approximately £266 million annually in Britain (1).

Up to 50% of cancer patients report changes in eating behavior at the time of diagnosis, leading to weight loss (2). Loss of appetite, decreased caloric intake, and associated symptoms are among the most frequent factors affecting the quality of patients' lives. These symptoms can be associated with cancer cachexia, a complex metabolic condition resulting in anorexia, weight loss, and skeletal muscle wasting, which adds significantly to morbidity and mortality (3). Cancer patients receiving chemotherapy also frequently experience debilitating loss of appetite and weight, which may limit the dose and duration of a potentially curative or disease-modifying treatment.

Currently prescribed appetite stimulatory drugs include steroids, progestogens such as megesterol acetate (megace), and prokinetic agents such as metoclopramide. Although steroids may improve quality of life and appetite, their metabolic, infectious, and psychiatric side-effects usually limit their use to the short term. Megestrol acetate has been found to improve appetite (3), but is associated with water retention and increases the already elevated risk of venous thromboembolism. A recent meta-analysis reported that megestrol acetate treatment produced a modest weight gain of 0.42 kg or 0.9 lb (4). Prokinetic agents have been shown to improve chronic nausea (5), but they have no proven effect on appetite and are associated with dose-limiting extrapyramidal side-effects. Clearly some patients are not helped by or cannot tolerate currently available treatments. There is a need for a safe appetite stimulatory treatment that can be commenced early in a patient's therapy to improve nutritional status before significant weight loss occurs.

Ghrelin is the only circulating appetite-stimulating hormone identified to date. Ghrelin is expressed in the stomach and activates neurons of the arcuate nucleus of the hypothalamus, an area of the brain known to be important in the regulation of feeding (6). Supraphysiological concentrations of other hormones, such as corticosteroids and thyroid hormones, may lead to metabolic changes associated with a secondary increase in appetite. In contrast, ghrelin appears to have a direct effect on appetite at concentrations within the normal fasting range (7).

Endogenous ghrelin levels peak before each meal and fall within 1 h of eating, thus supporting the hypothesis that ghrelin is a hormone that stimulates hunger (8). Plasma ghrelin is inversely proportional to body weight and fat mass and is increased by weight loss and decreased by weight gain

Abbreviation: CI, Confidence interval.

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(9). These findings suggest that ghrelin is part of a dynamic feedback system in the regulation of body weight.

We have previously reported that ghrelin infusion increases food intake by 28% (95% confidence interval, 19–37%) in male and female healthy volunteers in a double-blind, randomized, controlled trial (7). No adverse events were observed. However, subjects in negative energy balance, including patients with cancer and anorexia, have elevated endogenous plasma ghrelin (9, 10) and thus might be resistant to the appetite-stimulating effects of exogenous ghrelin. To determine whether ghrelin is effective pharmacologically in patients with appetite loss, we recruited a group of patients with cancer and anorexia. In this preliminary study we investigated the effect of ghrelin on energy intake and appreciation of food in cancer patients with appetite loss.

Patients and Methods

The aim of the study was to determine whether ghrelin stimulates food intake in cancer patients with anorexia. The primary outcome was energy intake from a buffet meal designed to be in excess. Secondary outcomes were visual analog scores of meal appreciation, 24-h food intake as assessed by food diary, and plasma ghrelin and GH levels.

Synthetic human ghrelin was purchased from Bachem (UK) Ltd. (Merseyside, UK). The *Limulus* amebocyte lysate assay test for pyrogen was negative (Associates of Cape Cod UK, Liverpool, UK), and the peptide was sterile on culture. The study was approved by our research ethics committee and was performed in accordance with the Declaration of Helsinki.

Cancer patients reporting appetite loss were recruited from oncology clinics at Charing Cross Hospital between September 10, 2002, and January 6, 2003, and assigned subject numbers in order of recruitment. Clinical reduction in appetite was confirmed by dietetic consultation using the Edmonton Symptom Assessment Scale, in which they were asked to rate the severity of the following nine symptoms on a 100-mm visual analog scale: pain, tiredness, nausea, depression, anxiety, drowsiness, lack of appetite, lack of well-being, and shortness of breath (11). Exclusion criteria were any of the following within the previous month: surgery, radiotherapy, and regular use of systemic steroids or progestins. Patients established on chemotherapy with sustained appetite loss were included in the study. At screening, subjects selected the food to be served to them in the study from four possible options and tasted it to confirm palatability.

Seven patients were recruited (six women and one man) with a mean weight loss from their precancer weight of 13% and mean current body mass index of 22.6 kg/m^2 (Table 1). All patients had metastatic cancer. At recruitment the mean Edmonton Symptom Assessment score for lack of appetite was 70 mm/100 mm, and the mean total score for all nine questions representing poor quality of life was 230 mm/900 mm. Thus, patients reported that lack of appetite was the main contributor to their overall poorer quality of life. Each patient gave their written, informed consent and attended for 2 infusion days at least 3 d apart (range, 3–21 d), 1 d for ghrelin and 1 d for saline control. Patients receiving chemotherapy attended for their first infusion as long after their chemotherapy cycle as possible (at least 17 d) and then the same number of days after their subsequent cycle. Although these patients took an antiemetic in the few days after their chemotherapy, this was no longer taken or required before ghrelin or saline infusion.

On infusion days, fasted patients had two iv cannulas (one for infusion and one for blood sampling) placed at 0900 h (t = −30 min). Pulse and blood pressure readings were taken every 30 min during the study. At 0930 h (time zero) a fixed breakfast was served (energy content, 703 KJ) to standardize food intake before infusion. Ghrelin or saline infusion was commenced at 1100 h (t = 90 min). The rate of ghrelin infusion (5 pmol/kg·min) was that which significantly increased food intake in healthy volunteers in our previous study (7). At 1230 h (t = 180 min) a buffet lunch was served of preweighed food in excess. After the meal, the remaining food was removed and weighed, and the infusion was discontinued. Blood samples (each 10 ml) were collected into plastic lithium heparin tubes containing 0.6 mg aprotinin. Samples were taken before breakfast (0 min) and at 45, 90, 150, and 180 min. Samples were immediately centrifuged, and plasma was separated and stored at −70 C until immunoassay. To assess meal appreciation, after lunch patients were asked to respond on a visual analog scale (possible score, 0–100 mm), to the prompt "how pleasant was this meal?" (11). Positions on the scale were measured in millimeters by a blinded observer. Patients completed a 24-h food diary after each infusion. One patient (patient 7) failed to complete a food diary after one of her infusions. Completed food diaries were assessed with Dietplan-5 nutritional analysis software (Forestfield Software, Horsham, West Sussex, UK).

Plasma ghrelin was measured by RIA (Phoenix Pharmaceuticals: intra- and interassay coefficients of variance, 5% and 14%, respectively). Plasma GH was analyzed using Advantage automated chemiluminescent immunoassay (Nichols Institute Diagnostics, San Juan Capistrano, CA). Glucose and triglycerides were measured using an Olympus AU640 clinical chemistry analyzer (Melville, NY), and insulin was measured using an automated microparticle enzyme immunoassay.

The study was randomized and double-blinded. Subjects were randomized to receive ghrelin then saline (four patients) or saline then ghrelin (three patients) using the statistics package, SigmaStat version 2.0 (SPSS, Inc., Chicago, IL). Vials of ghrelin and saline were indistinguishable visually; they were labeled by subject and infusion numbers and stored in a sealed container. Subjects, investigators, and dieticians were blinded to the infusion order until study completion.

Statistical comparisons between treatments for food intake, visual analog scores, and plasma ghrelin and GH levels were made using a paired *t* test, having ascertained that the data were normally distributed. Statistically significance was set at $P < 0.05$. Confidence intervals (CI) are reported at 95%.

Results

The mean fasting plasma ghrelin concentration was 538 (CI, 433–643) pmol/liter, with levels ranging from 350–938 pmol/liter. Ghrelin infusion achieved steady state within 60 min of infusion, with a mean plasma ghrelin of 1718 (CI, 1303–2132) pmol/liter (Table 2). The expected GH rise associated with acute ghrelin administration was observed (Table 3), confirming that the ghrelin infusion was biologically active. There was no significant change in plasma glu-

TABLE 1. Patient details

Patient no.	Age (yr)	Sex	Precancer weight (kg)	Current weight (kg)	Current BMI (kg/m^2)	Cancer	On chemotherapy?
1	52	F	58	44.3	17.3	Malignant melanoma	No
2	63	F	64	57.5	21.4	Breast	Yes
3	66	F	67	52.7	21.1	Breast	No
4	55	F	58	54.8	25.7	Breast	No
5	54	F	65	64.6	24.3	Breast	No
6	49	M	80	59	19.0	Colon	No
7	41	F	86	83.8	29.3	Breast	Yes

BMI, Body mass index; F, female; M, male.

TABLE 2. Plasma ghrelin levels with saline and ghrelin infusions at 0, 90, 150, and 180 min

Treatment	Ghrelin (pmol/liter)			
	0 min (prebreakfast)	90 min (infusion start)	150 min	180 min (prelunch)
Saline	545 ± 58	440 ± 59	509 ± 97	490 ± 63
Ghrelin	531 ± 83	505 ± 90	1718 ± 169	1840 ± 221
P value	0.7102	0.2004	0.0009	0.0006

Ghrelin values are the mean ± SEM. *P* values compare ghrelin levels at each time point.

TABLE 3. Plasma GH levels with saline and ghrelin infusions at 0, 90, 150, and 180 min

Treatment	GH (mIU/liter)			
	0 min (prebreakfast)	90 min (infusion start)	150 min	180 min (prelunch)
Saline	6.5 ± 3.3	6.5 ± 2.9	2.6 ± 1.0	3.8 ± 1.9
Ghrelin	10.9 ± 3.4	9.4 ± 3.3	72.5 ± 26.4	39.7 ± 12.4
P value	0.0810	0.0847	0.0341	0.0195

GH values are the mean ± SEM. *P* values compare GH levels at each time point.

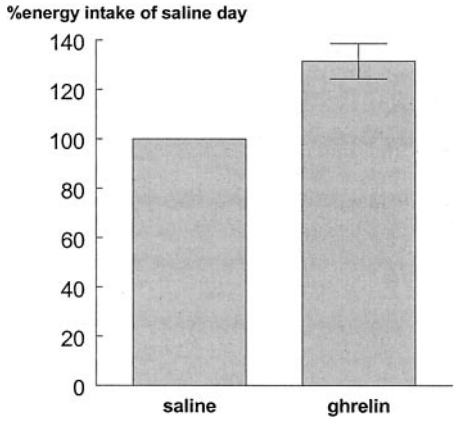

FIG. 1. Percentage increase in energy intake from a buffet meal after ghrelin compared with saline infusion.

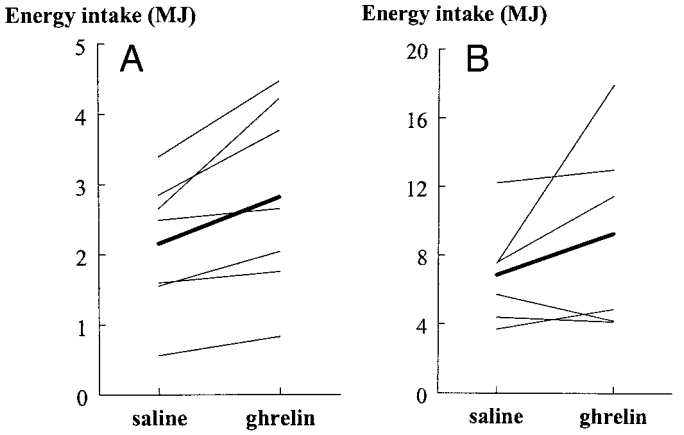

FIG. 2. Energy intakes (megajoules) in individual subjects receiving ghrelin compared with saline infusion. The *bold line* represents mean energy intakes. A, Energy intakes for the buffet meal (n = 7). B, Energy intakes for the 24 h after ghrelin or saline infusion (n = 6, as one patient failed to complete the diary).

cose, insulin, or triglycerides with ghrelin infusion at any of the time points studied (data not shown).

Energy intake from the buffet lunch was increased by 31% (CI, 14–49%; $P = 0.005$) during ghrelin infusion compared with the saline control (Fig. 1). Moreover, every patient consumed more on his/her ghrelin administration day (Fig. 2A) (range, 7–59% increase). No side effects were observed. In particular, there were no differences in pulse and blood pressure recordings between ghrelin and saline infusion days. There was no evidence of a compensatory decrease in food intake after ghrelin treatment as assessed by 24-h food diary (Fig. 2B). Total energy intake over the 24-h period including the buffet was 9,270 KJ (CI, 3,249–15,290 KJ) after ghrelin treatment *vs.* 6,854 KJ (CI, 3,634–10,070 KJ) after saline ($P = 0.09$).

Analysis of the visual analog score revealed a significant increase of 23% in the perceived pleasantness of the meal on the ghrelin administration day compared with the saline administration day (CI, 4–41%; $P = 0.02$).

Discussion

We demonstrated a 31% increase in energy intake with ghrelin infusion associated with a significant increase in meal appreciation in cancer patients with appetite loss. This is comparable with the 28% increase previously observed in healthy volunteers (7). Small daily increases in energy intake (~1%) are associated with significant weight gain when sustained (12). Thus, the 31% increase observed in this study represents a large increase in energy intake. Although baseline energy intake and plasma ghrelin varied among the patients studied, ghrelin stimulated appetite in all patients. There was a trend for an increase in 24-hr energy intake after ghrelin treatment from a mean of 6854 KJ with saline to 9270 KJ with ghrelin.

The effect of ghrelin on feeding appears to be more sustained than its effect on GH release. After peripheral ghrelin administration to rodents three times per day for 7 d, no attenuation in ghrelin-induced food intake was observed (13). However, after an initial rise, plasma GH and IGF-I were not significantly different from levels in saline-treated controls (13). Further, chronic ghrelin administration to animals with absent GH increased body weight (14). Thus, ghrelin's stimulatory effect on food intake appears to be independent of GH.

The effect of chronic ghrelin administration on body weight, morbidity, mortality, and quality of life in patients with loss of appetite remains to be investigated. Studies have

shown that when patients with cancer anorexia were given artificial enteral nutrition body weight, fat mass, and nitrogen balance improved (15). Thus, if ghrelin were to achieve long-term increases in voluntary food intake, it could increase body protein, fat, and total weight as well as improve quality of life.

It is not yet established whether ghrelin has any long-term adverse effects. A brief rise in GH was observed with ghrelin infusion. However, acromegalic patients who have chronically elevated GH only have a small increase in absolute risk of bowel cancer with no increased risk of other tumors (16). Data about the effect of ghrelin on cell lines is conflicting, with some studies suggesting an increase (17, 18) and some a decrease (19–21) in the rate of cell growth. Further work is needed to determine the effect of ghrelin on tumors *in vivo*.

In this acute study no changes were observed in plasma insulin, glucose, or triglycerides with ghrelin infusion. However, an iv bolus of ghrelin in humans has been reported to increase plasma glucose and decrease plasma insulin (22). Thus, chronic ghrelin could affect metabolic parameters such as insulin, glucose, and lipids.

Interestingly, fasting plasma ghrelin concentrations in the present study were higher than those reported in healthy reference populations of similar body mass index (8). This is consistent with a study performed by Wisse *et al*. (23) that found high ghrelin levels in rats with prostate cancer, although these levels were similar to those in pair-fed controls. This suggests that elevated ghrelin levels in cancer may reflect on-going negative energy balance. When ghrelin was administered directly into the intracerebroventricular space of these animals with prostate cancer, food intake increased (23). A human study reported that plasma ghrelin levels were higher in lung cancer patients with cachexia than in those without (10). Our study shows that peripheral ghrelin is effective in stimulating appetite in patients with various endogenous ghrelin baselines. Thus, sufficient exogenous ghrelin appears to overcome any resistance to the appetite-stimulating effects of ghrelin in these patients. The patients in this trial found the meal more pleasant with ghrelin infusion. In addition to stimulating appetite, ghrelin may improve appreciation of food and enhance quality of life.

Ghrelin has now been administered acutely to more than 100 human subjects worldwide at doses up to 6-fold higher than those used in the current study (24) with no reported side-effects other than hunger. It is also worthy of note that synthetic agonists of the ghrelin (GH secretagogue) receptor have been administered to adults with GH deficiency and children with idiopathic short stature for up to 2 yr with no reported adverse effects (25). Nonetheless, chronic ghrelin administration in patients with normal growth axis could lead to supraphysiological levels of GH, causing acromegaly and its associated complications, such as joint pain, headaches, and visual field defects. However, the normal phenotype, length, and weight of the ghrelin-null mouse (26) suggest that ghrelin is not the main regulator of GH release.

Unlike currently available appetite stimulatory treatments, administration of ghrelin directly boosts an endogenous appetite-regulating system. We have demonstrated that ghrelin stimulates appetite and food intake in both healthy volunteers and cancer patients with anorexia. In both groups food intake was increased in every individual studied. Therefore, it seems likely that ghrelin will be effective in other conditions associated with anorexia, and its potential therapeutic benefits need not be limited to patients with cancer. Preliminary studies suggest that ghrelin improves cardiac function and protects against cardiac ischemia (24), making a therapeutic role in cardiac cachexia particularly attractive. This acute study highlights the need for further investigations to establish whether long-term ghrelin can be used effectively in the palliation of appetite loss.

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