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Metabolic Support

Interrelationship Between Circulating Leptin Concentrations, Hunger, and Energy Intake in Healthy Subjects Receiving Tube Feeding

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ABSTRACT. *Background:* Tube feeding is an unphysiological route of nutrient delivery, and yet there is a lack of controlled trials examining its effects on appetite, food intake, and factors involved in their control. This study aimed to investigate the relationship between diurnal tube feeding, hunger, food intake, and circulating concentrations of leptin (a putative satiety factor). *Methods:* Six healthy lean men received a continuous nasogastric infusion (9:00 AM to 9:00 PM) of colored water (2 days), liquid feeding (4.2 kJ/mL, energy provision 1× the initial predicted basal metabolic rate; 3 days), and colored water (2 days). Measurements of hunger (visual analog scales), weighed food intake, and fasting circulating leptin concentrations were made while the subjects were allowed free access to isoenergetically dense food items. *Results:* Three days of diurnal nasogastric feeding (mean, 6.9 MJ/d) significantly increased total energy intake (to 19.4 MJ/d; $p < .001$; analysis of variance [ANOVA]), suppressing oral energy intake by only 17%, with no significant effect on mean daily hunger. Higher levels of energy intake led to a universal rise in circulating leptin concentrations (2.82 to 4.23 ng/mL; $p < .004$; ANOVA) that was not significantly related to subsequent breakfast energy intake, first rated hunger of the day, timing of morning food consumption, or subsequent mean daily oral energy intake or hunger. *Conclusions:* This study suggests that 3 days of diurnal tube feeding (equivalent to basal metabolic rate) failed to suppress hunger and reduced food intake by only 17%. The rise in circulating leptin concentrations, associated with tube feeding and the increase in total energy intake, failed to predict subsequent hunger or oral energy intake. (*Journal of Parenteral and Enteral Nutrition* **22:**335–339, 1998)

The 1996 British Artificial Nutrition Survey (BANS) reported that at any one time approximately 13% of hospitalized patients need some form of artificial nutrition support (ANS),[1] including parenteral (IV nutrition) and enteral (nutrition supplements taken orally and tube feeding) nutrient provision. The continued existence of malnutrition in hospitals,[2] together with the documented benefits of nutrition support, particularly in undernourished patients[3–5] has led to widespread and increasing use of ANS, in both the hospital and the community setting.[6] Despite this, research has yet to reach a consensus as to the effect of these unphysiological methods of nutrient provision, which bypass part or all of the gastrointestinal tract, on appetite and voluntary oral energy intake. Studies in patients receiving parenteral feeding suggest disturbances in the control of energy intake and appetite[7–10] may occur. A few studies of nocturnal tube feeding in patients and healthy subjects suggest that even the delivery of nutrients via a nasogastric tube, bypassing only part of the gut, may result in little suppression of oral energy intake,[4,11,12] although the effects on appetite in particular are less well documented.

Little is known about potential mediators that control appetite and energy intake during different methods of ANS. For example, leptin, the 16-kDa protein, secreted by adipose tissue[13] and the product of the *ob* gene,[14] has been implicated as a possible mediator of satiety in the regulation of food intake. As yet, most of the work on leptin's role in energy balance regulation has been undertaken in animals;[15,16] the relationship between changes in circulating leptin concentrations, energy intake, and hunger in humans has not yet been fully ascertained. The hypothesis examined by this study was that elevations in circulating leptin concentrations, as a result of overfeeding in humans, reduce hunger and food intake. More specifically, the study aimed to investigate the effects of 3 days of diurnal nasogastric (NG) tube feeding in healthy subjects on hunger and voluntary oral energy intake and to assess whether circulating concentrations of leptin (a putative satiety factor) could predict the changes in energy intake and hunger that were observed. Nasogastric feeding was administered diurnally because this was considered more likely to suppress food intake during the day than overnight feeding.

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MATERIALS AND METHODS

Subjects

Six healthy, nonsmoking males, with a mean age of 36 ± 8 years and mean weight of 69.1 ± 10.3 kg (with

stable weight for 1 year [±2 kg]) and who were within the ideal body mass index (BMI) range (mean, BMI 22.1 ± 2.27 [kg/m^2]), were resident in the metabolic suite at the Dunn Clinical Nutrition Center for the duration of this study. None were taking medication. Ethical approval was obtained from the Ethical Committee for the Dunn Clinical Nutrition Center, and all subjects gave informed consent before starting the study.

Volunteers were intubated on day 1 of the study with a fine bore NG tube (Freka 8F, 120 cm; Fresenius, Runcorn, Cheshire, United Kingdom). The NG tube remained *in situ* for the duration of the study and was kept patent with regular flushing. With the NG tube *in situ*, for days 1 and 2, subjects consumed a fixed diet (47% carbohydrate, 40% fat, and 13% protein; energy equivalent to 1.5× the initial predicted basal metabolic rate[17] [BMR]; 6.9 ± 0.47 MJ) to standardize energy and macronutrient intakes. Thereafter, through the NG tube, volunteers received 2 days (days 3 and 4) of water (colored to look like feeding), 3 days (days 5 to 7) of feeding (commercial, 4.18 kJ/mL, 49% carbohydrate, 35% fat, and 15% protein; energy provision 1× initial predicted BMR[17]), and a further 2 days (days 8 and 9) of colored water. The feeding was delivered diurnally for 12 hours, from 9:00 AM to 9:00 PM, at a constant infusion rate using the portable Kangaroo Enteral Delivery System (with dose delivery accuracy of ±10%; a 1600-mL giving set, and a carrying case; model 2100 portable pump; Kangaroo, Crawley, West Sussex, United Kingdom). Throughout days 3 to 9, volunteers were allowed *ad libitum* access to covertly manipulated food that was isoenergetically dense (energy density of each food item, 550 kJ/100 g, 13% protein, 47% carbohydrate, and 40% fat).[18] Eleven different food items were available each day as part of a 3-day rotating menu cycle. All food was preprepared in excess and kept in a refrigerator designated to the individual subject, and a microwave oven was available for heating food when required. Subjects had free access to caffeine-free beverages throughout the study period: water, tea, coffee, and diet drinks. The subjects were asked to record the timing of food and drink consumption but were not informed that a weighed food inventory was carried out. Assessment was made of the pleasantness and the satisfying nature of the food 15 minutes after meals[19] and The Dutch Eating Behavior Questionnaire (DEBQ)[20] was completed by all subjects at the end of the study to assess dietary restraint.

Hunger

Throughout the study 100-mm visual analog scales were completed hourly during waking hours by subjects for the assessment of hunger.[19,21] These were measured and scored from 0 mm (not at all hungry) through to 100 mm (as hungry as I have ever felt).

Blood

Blood was taken after an overnight fast and at the same time on the following mornings for the measurement of circulating leptin concentrations: (1) day 3, after fixed diet; (2) day 5, after *ad libitum* access to food; and (3) day 8, after *ad libitum* access to food and 3 days of tube feeding. After centrifugation, plasma was stored at −80°C before analysis of leptin (within-assay coefficient of variation, 3.4% to 8.3%; between-assay coefficient of variation, 3.0% to 6.2%, human leptin radioimmunoassay kit; Linco Research, St Louis, MO).

Anthropometry

Body weight was measured daily, after voiding, at the same time each morning, by a digital platform scale (Sauter, GmbH, Ebingen, Germany), but the result was not divulged to the subjects. Height was measured using a Stadiometer (Karrimetre, Raven Equipment Limited, Dunmaw, Essex, United Kingdom), and body mass index (kg/m^2) was calculated. Percent fat was calculated from measurements of four skinfold sites (triceps, biceps, suprailiac, and subscapular), using the equations of Durnin and Womersley[22] on days 1, 3, 5, and 8.

For the duration of the study, the men were restricted to the Centre, and exercise was not permitted (to control for the effect of physical activity on appetite and food intake).

Statistical Analysis

Repeated measures analysis of variance (ANOVA), with polynomial (quadratic) contrasts for *post hoc* analysis, where appropriate, and Pearson's correlation coefficients, was used to analyze normally distributed data, which for leptin required log transformation to normalize the positively skewed distribution. Plasma leptin concentrations are presented as geometric mean + SD (the antilog of the mean of logged data + 1 SD of logged data).

RESULTS

NG Tube Feeding, Energy Intake, and Hunger

Within each period, when either colored water (days 3 and 4 and days 8 and 9) or feeding (days 5 to 7) was nasogastrically administered, there was no significant change in either hunger or oral energy intake. For example, no significant change in oral energy intakes (12.4, 11.9, and 13.1 MJ) or mean daily rated hunger (28, 29, and 31 mm) occurred during the 3 days (days 5 to 7) of tube feeding administration (mean feeding provision, 6.9 ± 0.47 MJ/d). Resulting mean total energy intakes during the period of tube feeding administration were equivalent to 2.8× the initial predicted BMR[17] (19.4 ± 2.45 MJ), with an overall significant and universal increase in total energy intake, between the start of the study (days 1 and 2) and the tube feeding period (days 5 to 7) (ANOVA; $p < .001$; Fig. 1). This was accompanied by a 1.9 ± 0.9 kg gain in weight but no detectable change in percent body fat (as calculated from skinfold anthropometry).

After the initial period of colored water administration (days 3 and 4), oral energy intakes over the 3 days of diurnal tube feeding (days 5 to 7) were reduced by 17% (equivalent to 35% of the tube feeding energy). Comparison of the daily oral energy intakes during

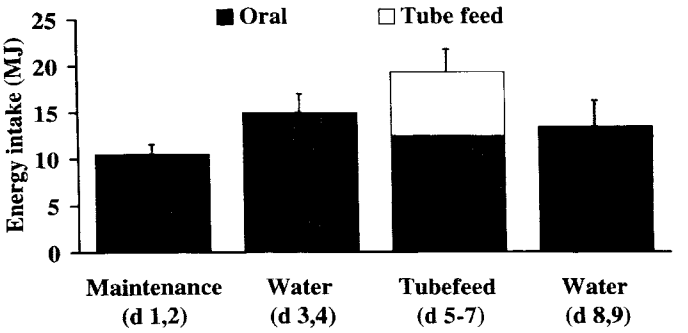

FIG. 1. Oral and total energy intake during each period of the study. Results are expressed as means; error bars, +SD; d, days.

tube feeding (days 5 to 7) with the intakes during the days before (days 3 and 4) and after (days 8 and 9), when colored water was administered, did not reach statistical significance ($p = .054$; ANOVA with quadratic contrasts; see Fig. 1 for mean intakes during the different periods). Furthermore, there was no significant change in the mean daily hunger ratings during tube feeding (days 5 to 7) compared with the colored water periods (days 3 and 4 and days 8 and 9) (ANOVA).

Leptin and Changes in Energy Intake and Hunger

An increase in fasting concentrations of circulating leptin was observed in all subjects (mean 50% increase in leptin, from 2.82 ng/mL [day 3] to 4.23 ng/mL [day 8]; geometric mean [$p < .004$; ANOVA]), whereas the increment in total energy intake (10.2, 15.2, and 20.2 MJ) on the 3 days preceding the measurement of leptin (days 2, 4, and 7) was also significant ($p < .001$; ANOVA; Table I). However, subsequent daily hunger ratings and subsequent oral energy intakes on the day of leptin measurement remained unaltered despite the increments in circulating leptin concentrations. Indeed, the increase in leptin within the study (taken on days 3, 5, and 8; Fig. 2) did not significantly relate, and hence did not predict, subsequent mean daily rated hunger or subsequent oral energy intakes on the days of leptin measurement (Pearson's correlation coefficients). Furthermore, there was no significant relationship between plasma leptin concentrations and either the energy content of breakfast (food consumed up to 12:00 PM; mean intakes 2.5, 2.0, and 2.4 MJ on days 3, 5, and 8, respectively), the timing of the first meal (47, 155, and 62 minutes, respectively, after the leptin measurement), or the first hunger rating of the day (recorded shortly after the leptin measurement; mean hunger scores, 47, 43, and 43 mm, respectively).

TABLE I
Circulating leptin concentrations and previous 24-hour total energy intake

	Day 3	Day 5	Day 8
Leptin (ng/mL)*	2.82 ± 2.09	3.43 ± 1.89	4.23 ± 1.80
Previous 24-hour total energy intake (MJ/d)†	10.2 ± 0.52	15.2 ± 2.18	20.2 ± 2.24

ANOVA, analysis of variance.
* Leptin; $p < .004$; ANOVA. Values are geometric means ± SD.
† Includes tube feeding energy, days 5 to 7, $p < .001$; ANOVA. Values are means ± SD.

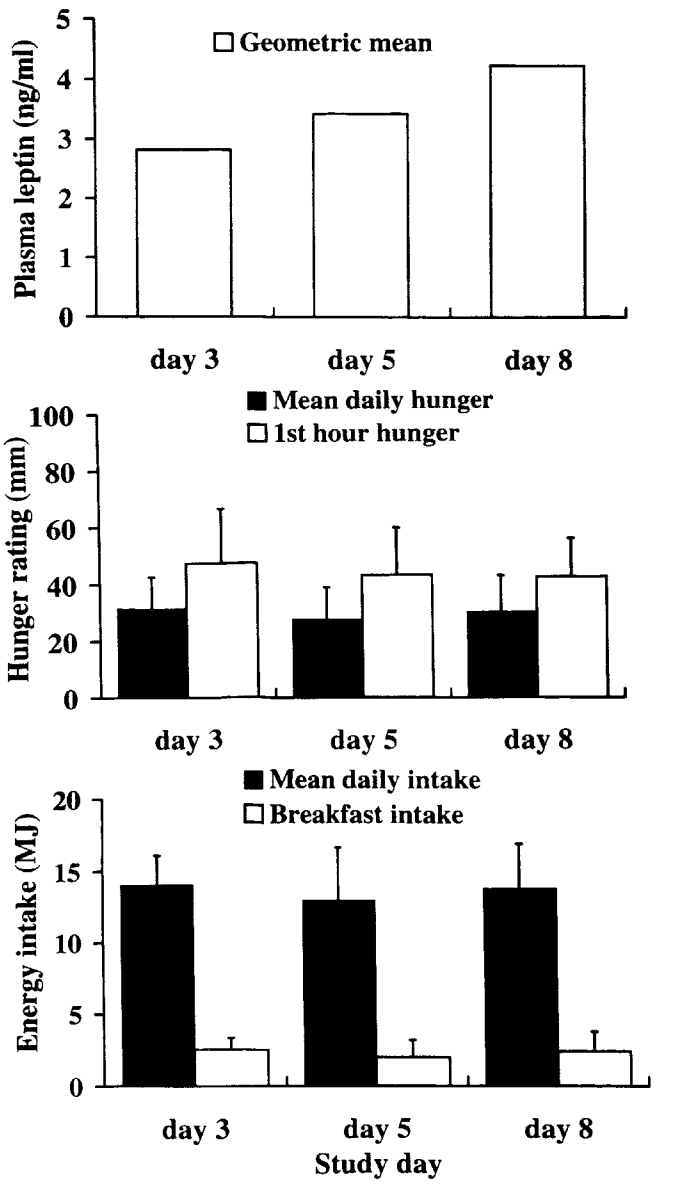

FIG. 2. Plasma leptin concentrations (geometric mean), subsequent first hour and mean daily hunger, and breakfast and mean daily oral energy intake on days 3, 5, and 8. Results are expressed as mean; error bars, +SD.

As in previous studies, visual analog scales for the rating of hunger were sensitive to the oral consumption of covertly manipulated food items and to overnight fasts in all subjects (see Fig. 3 for a typical result). No significant difference was found in the mean rated pleasantness scores for each of the menu days (73, 66, and 69 mm for days 1, 2, and 3, respectively). Two subjects exhibited restrained eating behavior, with a DEBQ[19] score >20.

DISCUSSION

This is the first study to report the relationships of leptin with food intake and hunger sensations in

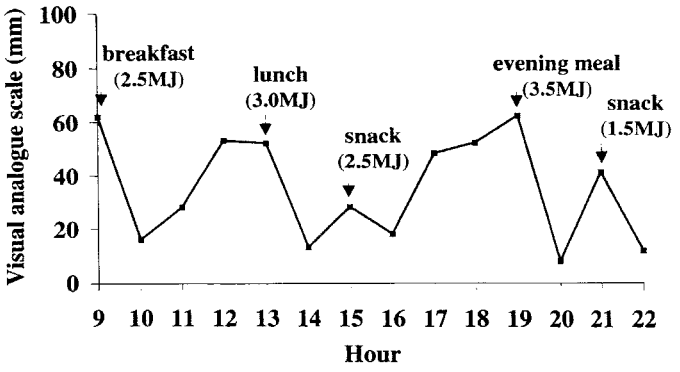

FIG. 3. Typical diurnal pattern in hunger ratings illustrating the responsiveness to oral food ingestion

humans receiving tube feeding. Three issues emerged. First, an increase in circulating leptin concentrations with overfeeding, as demonstrated in animals[23] and humans,[24] was observed during the study. Three days of diurnal tube feeding (energy provision 1× the initial predicted BMR[17]), in addition to *ad libitum* food intake, resulted in total energy intakes of nearly 3× the initial predicted BMR, weight gain, and an associated 50% increase in circulating leptin concentrations. Because leptin concentration is related to adipose tissue mass, it is possible that some of the observed rise in leptin concentrations was due to the increased deposition of fat. However, on the basis of differences in leptin concentrations with differing BMI or percentage of body fat between healthy individuals,[25,26] if the energy balance was positive by as much as 40 MJ over the study period, and all was stored as fat, leptin concentrations would be expected to rise by only 15%. This is analogous to the large reduction in leptin concentrations during fasting, which is out of proportion to the amount of fat lost[27] (where as much as a 50% to 70% reduction in leptin can occur after a 24-hour fast).

Second, despite the significant rise in the circulating concentrations of the putative satiety factor leptin, subsequently rated hunger and oral energy intakes after leptin measurement were not significantly suppressed, even during the period when diurnal tube feeding was administered. This suggests that within the time frame of the study, the circulating leptin concentrations alone (2.82, 3.43, and 4.23 ng/mL) do not predict subsequent hunger or oral energy intake in healthy men receiving NG infusions of tube feeding or colored water. Therefore, our findings do not lend support to the hypothesis that an increase in circulating leptin concentration is associated with a reduction in hunger and food intake. This information also has clinical relevance to stable patients receiving long-term enteral tube feeding, a third of whom appear to be distressed by hunger despite receiving an adequate energy intake.[28]

Third, this study in healthy men provides evidence that the short-term, diurnal delivery of artificial nutrition (via an NG tube) largely provides additional energy to that taken orally, with only a partial suppression (17%) of oral energy intake. Although this observation may not be unique to enteral tube feeding, the slow rate of continuous nutrient infusion (12 hours) and the liquid nature of the tube feeding may be factors. Bypassing the oropharyngeal and esophageal sensory inputs to central regulatory processes[29,30] by the delivery of nutrients via an NG tube also may be important. Our observations are consistent with those of Ashworth et al,[12] who observed little reduction in mean voluntary food intake during NG feeding (1000 to 2000 kcal). However, their study differed from ours in that NG feeding was administered as a bolus at night under less controlled conditions and there was no assessment of appetite. Indeed, there has been little documentation of the effects of enteral nutrition on hunger and other aspects of appetite in the literature, and further controlled studies are required to assess the impact of altering the rate, mode, timing, and the duration of artificial feeding delivery on both appetite and food intake. Although tube feeding in healthy subjects provides an excellent experimental model to learn more about the regulatory processes of appetite and food intake, more importantly it facilitates examination of the effects of different tube feeding regimens in the absence of disease, which can then be applied to the clinical setting where the use of enteral tube feeding (enterostomy, and to a lesser extent, nasoenteric feeding) is widespread and increasing in prevalence in both hospitals and the community.

In summary, this study suggests that 3 days of diurnal NG tube feeding in healthy men has no significant effect on hunger and only partially (17%) replaces energy taken orally. Circulating leptin concentrations, which rise after an increase in nutrient intake associated with tube feeding, fail to predict subsequent hunger or subsequent food intake.

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