Short-Term Continuous Enteral Tube Feeding Schedules Did Not Suppress Appetite and Food Intake in Healthy Men in a Placebo-Controlled Trial[1,2]

Rebecca J. Stratton,[3] R. James Stubbs* and Marinos Elia

*Institute of Human Nutrition, University of Southampton, Southampton, UK and *Rowett Research Institute, Aberdeen, UK*

ABSTRACT Tube feeding (TF) provides a model with which to study appetite when nutrient delivery bypasses the upper gastrointestinal (GI) tract and associated cephalic phase response. Nocturnal, diurnal and 24-h TF schedules are used clinically, but their effects on satiety have not been distinguished. This study tested two hypotheses: *1*) bypassing the upper GI tract with TF has little satiating effect, and *2*) diurnal TF suppresses appetite and food intake more than nocturnal or 24-h schedules. Six healthy men, residing in a metabolic suite, each received three continuous TF schedules (diurnal 12-h, nocturnal 12-h and 24-h; 6.86 ± 0.51 MJ/d) in random order for 3 d over separate 10-d periods. Two days before and after TF, a placebo feed (<0.4 MJ/d) was given. Weighed measurements of ad libitum food consumption, hourly tracking of appetite and metabolic and hormonal measurements were undertaken. Compared with placebo feeding, there was a nonsignificant reduction in oral intake (1.01–2.49 MJ reduction), little change in appetite sensations with TF and an increase in total energy intake from 14.88 to 20.42 ± 3.25 MJ. The schedules did not differ although diurnal TF was the most satiating. Changes in a variety of mediators (including leptin, insulin, cholecystokinin, metabolites and respiratory quotient) did not relate to immediate assessments of appetite and food intake. This trial suggests that continuous TF has little effect on satiety in healthy men over a period of 3 d, irrespective of the timing of the schedule. This could not be explained by changes in a variety of metabolic and hormonal signals within the time frame studied. J. Nutr. 133: 2570–2576, 2003.

KEY WORDS: • *tube feeding* • *appetite* • *food intake* • *healthy men*

Tube feeding (TF)[4] directly into the stomach provides a useful model with which to study what happens to appetite and satiety when nutrient delivery bypasses the oropharyngeal/esophageal region of the gastrointestinal (GI) tract and the associated cephalic phase response. Investigation of the effect of TF on satiety is physiologically relevant, helping to further establish the processes that control appetite in humans. In addition, such study has clinical relevance because this is a method of feeding that is widely used in the nutritional support of those with disease in both hospital and community settings (1). Despite the widespread and increasing use of TF in clinical practice (2), the effect of this artificial method of feeding on appetite and food intake (and mediators implicated in their control) in humans is poorly understood (3). Patients fed artificially by tube experience disturbances in appetite sensations (3,4). In addition, although TF is used in conjunction with food intake in ~50% of patients receiving nutrition by tube at home (5), it is unclear whether the energy given by this method of feeding suppresses appetite and simply replaces energy taken orally or whether it provides additional energy. The effect of TF on appetite and food intake may vary depending on the timing of the feeding schedule (e.g., diurnal, nocturnal, 24 h). Although previous studies in a variety of patient groups alluded to the effect of continuous TF on food intake [summarized in (1)], interpretation of these results has been hampered by uncontrolled study designs, the confounding variables of disease and its treatment, and unusual feed compositions. Formal assessment of appetite sensations and controlled investigations comparing the effects of differently timed continuous schedules on appetite, food intake and potential appetite mediators (e.g., metabolites, insulin, leptin, gastrointestinal hormones, markers of energy utilization/fuel selection) are also lacking. Overall the data from existing clinical (6) and experimental studies in humans (7) and animals (8) suggest that nutrients delivered by continuous TF schedules may have little suppressive effect on appetite and food intake. This could be due to the liquid consistency of feeds, slow continuous infusion rates (instead of intermittent feeding) and the administering of feed at physiologically unusual times (e.g., overnight during sleep). Also, nutrients delivered by tube bypass the oropharyngeal and esophageal regions of the GI tract and in doing so, may fail to elicit the full cephalic phase response.

[1] Presented in abstract form at the British Association for Parenteral and Enteral Nutrition (BAPEN) [Stratton, R. J., Stubbs, R. J. & Elia, M. (1998) Effect of nasogastric tube feeding regimens on voluntary food intake and hunger in healthy volunteers. Proc. Nutr. Soc. 108A (abs.)].

[2] Funded by the Medical Research Council, UK.

[3] To whom correspondence should be addressed.
E-mail: R.J.Stratton@soton.ac.uk.

[4] ANCOVA, analysis of covariance; CCK, cholecystokinin; DEBQ, Dutch Eating Behavior Questionnaire; GI, gastrointestinal tract; NG, nasogastric; NEFA, nonesterified fatty acids; REE, resting energy expenditure; RQ, respiratory quotient; TF, tube feeding.

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Although a new general model of intake regulation was proposed recently (9), which considers the influence of compensated and uncompensated factors on energy intake, the role of artificial feeding methods requires investigation. We reported previously on the relationship between leptin concentrations and changes in hunger and food intake with diurnal TF (10), but there has not been a controlled, comparative trial of the effects of bypassing the cephalic phase response with different tube feeding schedules on food intake, a variety of appetite sensations and a wide range of putative appetite mediators. Therefore, this placebo-controlled study in healthy subjects aimed to compare the effects of differently timed continuous TF schedules on appetite and food intake and on some of the potential mediators of appetite control. Two main hypotheses were addressed: *1*) bypassing the upper GI tract (and associated cephalic phase response) with TF has little suppressive effect on oral energy intake, appetite sensations and on a number of mediators implicated in their control; and *2*) the extent to which TF suppresses appetite (hunger, desire to eat) and food intake is greater when the feed is given only during the day (diurnal TF schedule) than when administered only overnight (nocturnal TF schedule), i.e., the satiating order of TF schedules is proposed to be: (most satiating) diurnal >24 h >nocturnal (least satiating). In addressing these hypotheses, it should also be possible to assess another clinically relevant issue, i.e., the extent to which TF increases total energy intake. To obtain insights into these processes, circulating concentrations of metabolites, hormones and other peripheral putative appetite signals are measured.

SUBJECTS AND METHODS

Ethical approval for this study was obtained from the Local Research Ethics Committee and subjects gave their informed consent before taking part. Six healthy adult nonsmoking men [age 26 ± 8.3 y; BMI 21.9 ± 2.21 kg/m^2 (values are means ± SD)], none of whom were taking medication, were recruited from a volunteer database and from advertisements in the local university. For the duration of the studies, subjects were resident in a metabolic suite. To control for the effect of physical activity on appetite and food intake, subjects were not permitted to exercise.

Protocol. The study was a single-blind, Latin-square design. Each subject received three different continuous TF schedules (diurnal 12 h, nocturnal 12 h, 24 h), in random order, separated by at least 2 wk. Each TF schedule lasted for 3 d within a 10 d study period. A fine bore nasogastric (NG) tube (Freka 8F, 120 cm; Fresenius, Cheshire, United Kingdom) was inserted at the start of each 10 d study period. For the first 2 d, subjects were allowed to become accustomed to the tube. Thereafter, feed was administered through the NG tube diurnally (0900–2100 h), nocturnally (2100–0900 h) or over 24 h (0900–0900 h) at a constant rate using a portable Kangaroo Enteral Delivery System (pump with dose delivery accuracy ± 10%, 1600 mL, contained within a rucksack for portability; Sherwood Medical, West Sussex, United Kingdom). For 3 d (d 5–7), a standard commercial tube feed was given (6.86 ± 0.51) MJ; 15% energy from protein, 49% carbohydrate, 35% fat; 4.18 kJ/mL; Nutrison, Nutricia Clinical Care, Wiltshire, United Kingdom); the daily energy content of the feed was equivalent to each individual's predicted basal energy expenditure (11). During the two days preceding (d 3–4) and following (d 8–9) tube feeding, a placebo feed consisting of water colored with a small amount of feed (energy provision < 0.4 MJ) was infused. This placebo feed was similar in appearance to the tube feed and was given in identical volumes, at the same rate and for the same period of time as tube feeding. When questioned at the end of the study, subjects were unaware that a placebo had been used.

Measurements

During each 10-d period, the following measurements were undertaken.

Food intake. For the first 2 d (d 1 to 2) of each study period, subjects were given a fixed "maintenance" diet [energy content equivalent to 1.5× predicted basal energy expenditure (11)] to facilitate energy balance. Thereafter (d 3–9 of each study schedule), subjects consumed ad libitum covertly manipulated food items that were isoenergetically dense (550 kJ/100g), and had the same macronutrient composition (40% energy from fat, 47% from carbohydrate and 13% from protein) [see (12) for methods]. There were 11 different food items available daily as part of a 3-d rotating menu cycle, including a variety of cereals, milkshakes, soups, puddings and savory meals (e.g., pasta dishes, casseroles, curry) and a milk allowance. All food was preprepared in excess and kept in a refrigerator designated to each subject; a microwave oven was available for heating food when required. The men also had free access to caffeine-free beverages throughout the study period. Subjects were asked to record the timing of food and drink consumption in a food diary. All foods were weighed before being placed in the refrigerator and all leftovers were weighed [see (13) for method] daily to assess oral energy intake. There was no evidence that leftovers were disposed of by other means. Dietary analysis was undertaken using the RONA computer package, created by the Rowett Research Institute, Aberdeen, UK and based on the Royal Society of Chemistry's Composition of Foods database (14). Assessment was made of the pleasantness and satisfying nature of the food after each meal using visual analog scales (scored from 0 to 100 mm for the least to the most pleasant and satisfying) (15). The Dutch Eating Behavior Questionnaire (DEBQ) (16) was completed by all subjects at the end of the study to assess dietary restraint.

Appetite sensations. Subjects rated appetite sensations each waking hour using a paper questionnaire consisting of six visual analog scores with which to rate "hunger," "fullness," "desire to eat," "how much can you eat now?" "urge to eat" and "preoccupation with thoughts of food" (15,17). Each subject was given a booklet of questionnaires (containing one questionnaire for each hour) and a small hourly timer to remind them to complete it.

Anthropometry. Height was measured at the start of the study using a stadiometer (Karrimetre, Raven Equipment, Dunmow, Essex, UK) and body weight was measured (using a digital platform scale, Sauter, West Germany, accurate to within 0.001 kg) at the same time on each morning of the study after voiding urine. BMI (kg/m^2) was calculated, measurements of skinfold thickness at four sites were undertaken on d 1, 3, 5 and 8 and the percentage of fat calculated (18). Subjects were unaware of these results.

Indirect calorimetry. *Respiratory quotient (RQ) and resting energy expenditure (REE).* REE was measured on d 3 (after maintenance period), d 5 (after placebo feeding period), d 8 (after TF period) and d 10 (after second placebo feeding period) at the same time in the morning (0815 h) in subjects after waking. The ventilated hood technique was used with a Deltatrac Metabolic Monitor (MBM-100; Datex Instrumentarium, Helsinki, Finland). All measurements were conducted over a 30-min period at room temperature (23 ± 1°C). Oxygen consumption (VO_2) and carbon dioxide production (VCO_2) were measured so that RQ and REE could be calculated (19). The analyzers were calibrated using standard gases before and after each measurement. The accuracy of the Deltatrac (98–100% of predicted values) was checked periodically using nitrogen (80%) and carbon dioxide (20%) infusions [measured using an oil-filled gas meter type DM3A (Alexander Wright, London)] (20). Nocturnal and 24-h continuous TF schedules, which ended at 0915 h, continued during the measurement.

Blood sampling for the measurement of metabolites and hormones. After measurement of the REE on d 3, 5 and 8, venous blood was taken for the measurement of plasma concentrations of the following metabolites: glucose (Gluc HK, Unimate 5); nonesterified fatty acids (NEFA; Wako Alpha Laboratories, UK) triacylglycerol (Unimate 5 TRIG kit); glycerol (Boehringer Mannheim kit, GmbH); lactate (21); β-hydroxybutyrate (21); and for the hormones insulin (Enzyme Amplified Sensitivity Immunoassay, Biosource Europe S.A., Belgium), leptin (RIA; Linco Research Inc. St Louis, MO), cholecystokinin (CCK; RIA, Euro-Diagnostica, Malmo, Sweden) and glucagon (RIA). Nocturnal and 24-h continuous TF schedules, which ended at 0915 h, were ongoing during the taking of blood samples.

Statistical methods. Two-way repeated-measures ANOVA was used to analyze the effects of the individual schedules and the differences between schedules on oral energy intake (main dependent variable), body weight and appetite. The two within-subject factors were time (day) and schedule (nocturnal, diurnal, 24 h). Using daily measurements, a planned analysis involving polynomial contrasts was undertaken to assess *1*) the linear effects across the study (d 3–9) and the individual study periods (d 3–4; d 5–7; d 8–9); and *2*) the quadratic effect [comparison of the tube feeding period (d 5–7) with the placebo periods (d 3–4 and d 8–9 collectively)]. A further analysis, using the same statistical techniques, examined the extent to which the reduction in oral energy intake compensated for the infused energy from TF (d 5–7) compared with the placebo feeding (d 3–4 alone and in combination with d 8–9). Results are presented as means ± SD. Repeated-measures ANOVA with deviation contrasts was used to compare the individual, within-day, hourly ratings of hunger and fullness, with the daily grand mean. Changes in metabolic measurements with TF were assessed using repeated-measures ANOVA with simple contrasts. To calculate the correlation coefficients for repeated metabolic measurements, energy intake and appetite, analysis of covariance (ANCOVA) was used. These analyses were undertaken on normally distributed data and are presented as means ± SD. Leptin concentrations, which were log transformed to normalize the positively skewed distribution, are presented as geometric means + SD (the antilog of the "mean of logged data + 1 SD of logged data"). For nonnormally distributed data, analyses were carried out using Friedman's k-related samples and Wilcoxon signed-ranks test (paired comparisons); data are presented as medians (range). Statistical analysis was conducted using SPSS, version 7.5 (SPSS, Woking, Surrey, UK).

RESULTS

All subjects ($n = 6$) completed the study without experiencing adverse gastrointestinal side effects from TF.

Oral energy intake. TF (all schedules combined, d 5–7) did not reduce oral energy intake compared with the control periods before and after administration of a placebo feed (d 3–4 and d 8–9, **Fig. 1**). There was also no reduction in oral intake with each of the individual continuous TF schedules (nocturnal, diurnal, 24 h, d 5–7) and no differences among schedules; for simplicity, the results are presented as means ± SD data for the three study periods in **Table 1**. Although there were no differences between the effects of the different TF schedules on oral energy intake, the greatest reduction in oral energy intake occurred with diurnal TF [TF period (d 5–7) vs. placebo periods (d 3–4 and d 8–9), $P < 0.054$; $F_{(1,5)}$ 6.254], which had the lowest oral energy intake during TF (d 5–7) of all three schedules (Table 1). Compared with only the first placebo period (d 3–4), the reduction in oral intake with diurnal TF of 2.49 ± 2.27 MJ (equivalent to 36 ± 32% of the tube feed energy given) was significant ($P < 0.043$; $F_{(1,5)}$ 7.24). The equivalent reductions in oral intake with nocturnal and 24-h schedules were 1.01 ± 2.27 and 1.06 ± 1.34 MJ, respectively, equivalent to 14 ± 31 and 16 ± 21% of the tube feed energy given. As a consequence, total energy intake (oral and tube energy combined) with all feeding schedules was markedly increased from 14.88 ± 3.5 MJ [during the placebo period (d 3–4)] to 20.43 ± 3.25 MJ during 3 d of TF [mean combined tube and oral intake during the 3-d TF period (d 5–7) all schedules combined; 37% (5.55 MJ) increase, see Fig. 1].

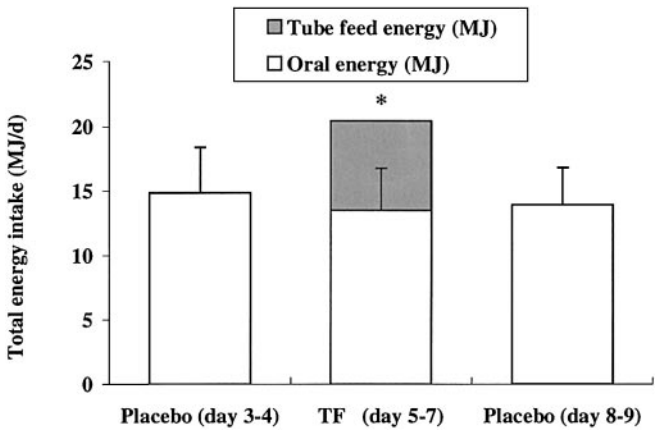

FIGURE 1 Total energy intake during continuous tube feeding (TF; all schedules combined) and ad libitum oral consumption in healthy men. Values are means ± SD, $n = 6$. *Different from the placebo periods before (d 3–4) and after (d 8–9) TF, $P < 0.001$; $F_{(1,11)}$ 198.

TABLE 1

Oral energy intakes during diurnal, nocturnal and 24 h continuous tube feeding (TF) and placebo feeding in healthy men[1]

Schedule	Placebo (d 3–4)	TF (d 5–7)	Placebo (d 8–9)
		MJ/d	
Diurnal[2,3]	14.95 ± 2.06	12.46 ± 2.57	13.40 ± 2.84
Nocturnal	14.37 ± 3.96	13.88 ± 3.78	13.91 ± 2.68
24 h	15.32 ± 4.31	14.26 ± 3.72	14.46 ± 3.18

[1] Values are means ± SD, $n = 6$.
[2] Interindividual responses were significantly different, $P < 0.04$, $F_{(6,30)}$ 7.24.
[3] There was a nonsignificant reduction in oral intake, $P < 0.054$, $F_{(1,5)}$ 6.254.

During all of the individual TF studies (nocturnal, diurnal, 24 h), there were no changes in oral energy intake within the TF period (d 5–7) or within the two placebo periods, which also did not differ from each other (d 3–4 vs. d 8–9). The mean daily oral energy intakes during TF were not affected by the order of feeding schedules (first: 14.56 ± 3.73 MJ, second: 12.91 ± 2.78 and third: 13.13 ± 2.43 MJ periods, d 5–7). There were also no linear changes across the study periods (d 3–9). Results from the DEBQ suggested that three subjects were restrained eaters (dietary restraint score > 20) (16).

Food pleasantness and satisfaction ratings. Throughout all of the study periods (d 3–9), there was little change in the daily pleasantness and satisfaction ratings obtained for the food items ingested; there were also no differences among the studies. The pleasantness and satisfaction ratings of the food ingested from each of the three menus (used on a rotating basis) were similar [e.g., pleasantness ratings (mm): menu d 1, 68 ± 13; d 2, 72 ± 11; d 3, 66 ± 13; satisfaction ratings (mm): menu d 1, 72 ± 7; d 2, 69 ± 11; d 3, 69 ± 13].

Appetite sensations during enteral tube feeding. The h 1 rating of the day for all the appetite sensations (hunger, desire to eat, fullness, urge to eat, preoccupation with thoughts of food and "how much can you eat now?") did not differ within the 3 d of feeding of each of the schedules (diurnal, 24 h or nocturnal TF). In addition, compared with the ratings for the preceding period of placebo feeding, each TF schedule produced similar changes (no significant interindividual differences). The alteration in daily appetite sensations with TF (d 5–7), compared with placebo feeding (d 3–4), did not differ irrespective of whether the feed was administered during the day, overnight or for 24 h (e.g., h 1 hunger: 1 ± 12 mm diurnal; 2

± 9 mm nocturnal; −2 ± 11 mm 24 h; no difference among schedules).

Within-day temporal changes in hunger and fullness sensations during the waking hours of the TF period (d 5–7) did not differ, irrespective of the timing of the schedule (**Fig. 2**, mean values from normally distributed data). Hunger and fullness sensations differed significantly from the group mean at 0900, 1200, 1700 and 2000 h, which often coincided with oral meal ingestion.

Relationships between the metabolic and hormonal changes associated with TF and appetite and food intake shortly after the time of measurement. The range of metabolic measurements, which were made after an overnight fast during the diurnal TF schedule and during feed delivery with the nocturnal and 24-h TF schedules, is shown in **Figure 3** (RQ and REE) and **Table 2** (metabolites and hormones). During all three study periods, the changes in RQ and REE (see Fig. 3), circulating metabolites, insulin and leptin concentrations were related to the preceding day's total energy intake (e.g., leptin and total energy intake, r values ranged from 0.87 to 0.92, $P < 0.001$; ANCOVA). However, the RQ and REE, circulating metabolites, insulin, leptin, glucagon and CCK concentrations did not relate to and thus predict appetite (e.g., h 1 hunger) or food intake (morning energy intake) assessed shortly after the measurements were made (there was also no relationship with mean daily oral energy intake or hunger). The three different TF schedules produced similar changes in RQ and REE (Fig. 3), leptin, CCK, glucagon and metabolite concentrations but not insulin concentrations, which showed a greater increment with nocturnal TF (Table 2).

Anthropometry. The initial weight of subjects at the start of the three study periods did not differ (d 1: nocturnal 69.9 kg; diurnal 69.1 kg; 24 h 69.6 kg) and weight remained stable during the maintenance period (d 1–2). During the 3 d of TF, all schedules were accompanied by weight gain ($P < 0.01$ $F_{(1,5)}$ 16), whereas during the placebo infusion periods, no changes were observed. Although the greatest change in weight was observed with nocturnal TF (+2.4 ± 0.71 kg), the difference among schedules was not significant (24 h +1.88 ± 0.45 kg; diurnal +1.84 ± 0.59 kg). The percentage of fat (18) did not differ at the start of the three study periods [nocturnal 21.4%; diurnal 20.5%; 24 h 20.0% (median)] and no detectable changes occurred throughout any of the studies (diurnal, 24 h, nocturnal).

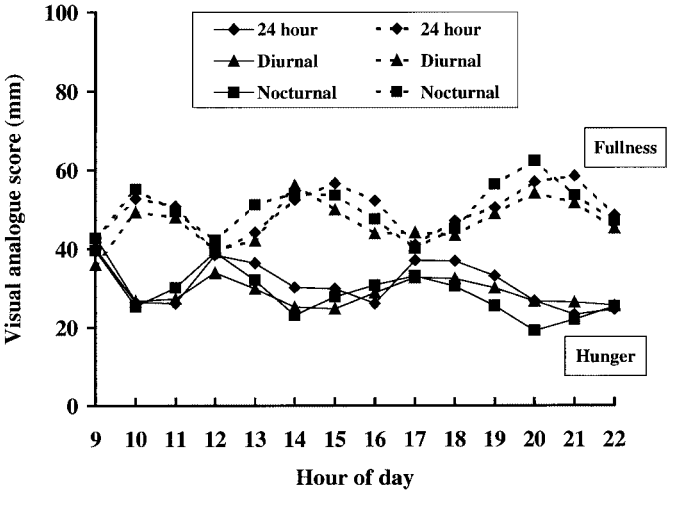

FIGURE 2 Temporal changes in feelings of hunger and fullness according to a visual analog score during diurnal, 24-h and nocturnal tube feeding (TF) schedules in healthy men. Values are means ± SD, n = 6.

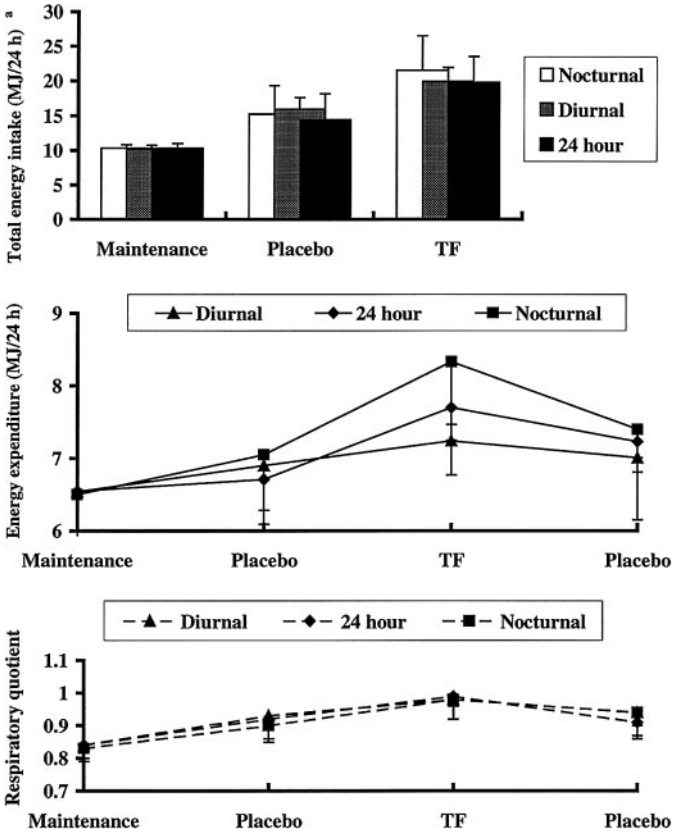

FIGURE 3 Increment in preceding day's total energy intake (*upper panel*) related to subsequent measurements of resting energy expenditure (REE, *middle panel*) and respiratory quotient (*lower panel*) with tube feeding in healthy men (maintenance: maintenance diet; placebo: placebo feeding via tube; TF: tube feeding). Values are means ± SD, n = 6. [a]The changes in energy expenditure (*middle panel*) and respiratory quotient (*lower panel*) were related to the preceding day's total energy intake (*upper panel*) (r = 0.92; $P < 0.001$).

DISCUSSION

This placebo-controlled pilot study presents the first small comparative investigation of the effect of differently timed continuous TF schedules on appetite, food intake and their potential mediators in the same healthy subjects. The first notable finding of this study was that continuous TF, at least over the duration of this study, had remarkably little effect on appetite sensations (e.g., hunger, desire to eat, fullness), measured by visual analog scales. In contrast, visual analog scale-appetite ratings were responsive to food ingestion (see Fig. 2 for changes in hunger and fullness ratings), as was shown in previous studies (22,23). In the current investigation, both h 1 and mean daily ratings of a variety of appetite sensations did not differ throughout the study, including periods when placebo (d 3,4 and 8,9) or feed (d 5–7) was infused by tube. Clinical observations also suggest that the delivery of nutrients solely via a tube may not be satiating. Many patients with chronic disease, in whom food intake is contraindicated, may remain hungry despite receiving their estimated nutritional requirements in full by TF (24,25).

The second finding of this study was that oral energy

TABLE 2

Circulating metabolite and hormone concentrations during three studies of different tube feeding schedules (diurnal, 24 h, nocturnal) in healthy men[1]

	Maintenance (d 3)	Placebo (d 5)	TF (d 8)	Placebo vs. TF[2]
Metabolites				
Glucose, *mmol/L*				
Diurnal	5.15 ± 0.46	5.40 ± 0.58	5.41 ± 0.47	NS
24 h	5.13 ± 0.47	5.27 ± 0.32	5.58 ± 0.53	NS
Nocturnal	5.23 ± 0.43	5.53 ± 0.61	6.03 ± 1.46	NS
Nonessential fatty acids, *μmol/L*				
Diurnal[3]	322 ± 108	175 ± 107	146 ± 85	$P < 0.04$ F 8.5
24 h	266 ± 97	210 ± 55	209 ± 90	NS
Nocturnal	261 ± 154	168 ± 93	147 ± 107	NS
Triacylglycerol, *mmol/L*				
Diurnal	1.28 ± 0.4	1.01 ± 0.26	1.38 ± 0.37	$P < 0.02$ F 12.8
24 h	0.98 ± 0.23	1.03 ± 0.49	1.35 ± 0.79	NS
Nocturnal	1.21 ± 0.41	1.07 ± 0.25	1.85 ± 0.34	$P < 0.003$ F 27.9
Glycerol, *μmol/L*				
Diurnal[3]	129 ± 31	109 ± 47	94 ± 30	NS
24 h	114 ± 20	139 ± 43	130 ± 40	NS
Nocturnal	109 ± 28	89 ± 32	168 ± 66	NS
Lactate, *μmol/L*				
Diurnal[3]	813 ± 170	1151 ± 174	1300 ± 202	NS
24 h	862 ± 155	953 ± 109	1177 ± 187	$P < 0.007$ F 26.6
Nocturnal[3]	863 ± 191	1202 ± 152	1194 ± 220	NS
β-Hydroxybutyrate, *μmol/L*				
Diurnal	40 ± 25	36 ± 26	29 ± 26	NS
24 h	43 ± 23	47 ± 27	34 ± 22	NS
Nocturnal	37 ± 22	38 ± 24	21 ± 23	NS
Hormones				
Insulin,[4] *pmol/L*				
Diurnal[3]	33.8 ± 9.65	44.6 ± 13.4	64.7 ± 9.86	$P < 0.007$ F 18.5
24 h[3]	30.8 ± 11.3	41.0 ± 13.0	80.8 ± 21.7	$P < 0.001$ F 14.5
Nocturnal[3]	32.2 ± 10.1	52.2 ± 14.4	158.3 ± 53.6	$P < 0.003$ F 27.3
Leptin,[5] *μg/L*				
Diurnal	2.82 ± 2.09	3.43 ± 1.89	4.23 ± 1.80	$P < 0.05$ F 6.89
24 h	2.57 ± 2.09	3.39 ± 1.95	4.90 ± 2.14	$P < 0.012$ F 14.8
Nocturnal	2.51 ± 2.00	3.72 ± 1.58	6.03 ± 1.62	$P < 0.01$ F 16.6
Cholecystokinin, *pmol/L*				
Diurnal[3]	18.8 ± 4.49	21.1 ± 3.09	17.4 ± 4.88	NS
24 h[3]	17.3 ± 4.09	18.2 ± 4.16	20.3 ± 6.45	NS
Nocturnal[3]	16.6 ± 3.74	18.6 ± 3.85	28.9 ± 4.92	$P < 0.002$ F 47.1
Glucagon, *pmol/L*				
Diurnal[3]	31.6 ± 10.03	31.7 ± 7.18	35.0 ± 11.53	NS
24 h[3]	31.9 ± 9.24	31.0 ± 11.14	36.1 ± 11.41	NS
Nocturnal[3]	30.5 ± 11.94	30.5 ± 10.17	31.8 ± 10.03	NS

[1] Values are means ± SD, $n = 6$ unless noted. Maintenance: measurement on d 3 after maintenance diet; Placebo: measurement on d 5 after placebo feeding via tube; TF: measurement on d 8 after tube feeding. NS, not significant, $P > 0.05$.
[2] Repeated-measures ANOVA with simple contrasts ($F_{0.05(1,5)} = 6.61$).
[3] Significant interindividual responses ($P < 0.007$).
[4] Significant difference between schedules (diurnal, 24 h, nocturnal) $P < 0.001$; F 15.9.
[5] Values are geometric means (±1 geometric SD).

intake did not compensate for the energy provided by continuous TF (d 5–7), resulting in a marked increase in total energy intake during the TF period (Fig. 1). The reduction in oral energy intake with 3 d of TF was equivalent to <40% of the tube feed energy (6.86 MJ), producing a significant increase in body weight but no detectable change in the percentage of fat. Compared with the first control period when only the placebo was given (assuming potential carry-over effects in the second control period), a reduction in oral energy intake of 2.49 MJ (36% of TF energy), 1.01 MJ (14%) and 1.06 MJ (16%) occurred with diurnal, nocturnal and 24-h TF schedules, respectively (TF energy 6.86 ± 0.51). Similar reductions were suggested by previous less controlled studies of nocturnal TF in the clinical setting (26,27), although the variable effects of disease during the course of studies may confound interpretation. Last, the findings of the present investigation were unable to confirm fully the original hypothesis that the timing of the TF schedule (nocturnal, diurnal, 24 h) would be an important determinant of the effect on appetite and voluntary food intake. In contrast, this investigation suggested that differently timed continuous TF schedules had largely similar effects on a variety of appetite sensations, on food intake and on potential metabolic and hormonal mediators of appetite (with the exception of insulin), at least over the duration of the study period. Furthermore, a relationship between the concentrations of the putative mediators of appetite with subsequently measured appetite and food intake was not evident, at least within the time frame of this investigation.

There was a small degree of variation in the extent to which different TF schedules replaced oral energy intake, and hence the degree to which total energy intake was increased (in the order hypothesized: diurnal > 24 h > nocturnal) but this was not significant ($P = 0.42$). One possibility is that the study could not detect small differences in the effects of the schedules because of insufficient power associated with small sample sizes (type II error). Simple power calculations (28), based on the intraindividual variability in food intake for 2-d periods, similar to that observed in the present study and in other investigations by our group (SD 12%, 1.67 MJ), suggested that a sample size of six subjects would be sufficient to detect a 20% change in daily oral energy intake (~2.8 MJ) with 80% power and a significance of $P < 0.05$. Such calculations were not possible before the start of these studies because the variability in oral energy intake from covertly manipulated food items during TF had not previously been documented.

There are several potential explanations for the lack of change in appetite and food intake with TF. The effect of social conditioning on food intake (29) may have overridden changes in the putative satiety signals induced by TF, particularly because the period of feeding was only 3 d. Indeed, preliminary work would suggest that greater suppression of food intake occurs if the duration of TF is increased (4,30). Alternatively, it could be that nutrients delivered by TF, in bypassing the upper gastrointestinal tract, fail to elicit the full cephalic phase and other GI responses that may provide feedback in the control of appetite and food intake (31). In addition, the liquid consistency of the feed may have a different satiating effect than that of solid-liquid meals (32), and the slow, continuous rate at which nutrients are delivered (0.28–0.57 MJ/h) may not produce the same satiety signals as those produced by intermittent meal ingestion. Indeed, after TF, changes in the measured metabolic and hormonal mediators implicated in the control of satiety did not relate to or predict appetite or food intake assessed shortly after measurement (or over the subsequent day as a whole). Greater insights into the underlying mechanisms of appetite control during TF are likely to be obtained by tracking profiles of metabolites and other signals over longer periods of time.

This study also provides the first data on the temporal patterns of appetite during the day in subjects receiving different TF schedules. Not only is this an issue of physiologic interest (e.g., no suppression of h 1 hunger ratings despite overnight TF of 6.9 MJ) but one of clinical relevance because such information may enable more effective targeting of oral and other nutritional therapy (e.g., supplementation) at times when patients are more hungry and more likely to eat. Alternatively, in those patients receiving TF who are unable to eat and are distressed by hunger or other appetite sensations, treatments (e.g., pharmacologic or psychologic interventions) could also be targeted at the most appropriate times. However, the results of this study in healthy subjects found that the temporal patterns for hunger and fullness sensations (see Fig. 2) and the distribution of oral energy intake through the day were remarkably similar for all three TF schedules.

In summary, this investigation provides the first placebo-controlled pilot comparison of the effects of differently timed TF schedules (diurnal, nocturnal, 24 h) on food intake and on a variety of different appetite sensations and potential mediators of satiety in the absence of confounding factors such as disease (33), dietary and other factors (34–38). This study suggests that the energy from all 3-d continuous TF schedules (6.86 ± 0.51 MJ) is largely additional to that taken orally, having little effect on appetite sensations. It also suggests that all schedules (diurnal, nocturnal, 24 h) have similar effects on appetite and food intake, at least within the time frame studied. The effect of longer continuous TF schedules (>3 d) or intermittent bolus TF schedules on appetite and food intake and the metabolic and hormonal mediators involved in the control of appetite and food intake remain to be elucidated in humans.

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