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The effects of sibutramine on the microstructure of eating behaviour and energy expenditure in obese women

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Abstract

Given the suggestion that many potential anti-obesity drugs may enhance within-meal satiation, few studies have directly measured the effects of any drug on the microstructure of human eating behaviour. The effects of 7 days dosing with sibutramine 10 mg and 15 mg a day on appetite and energy balance were determined in 30 obese women (BMI 34.6 ± 3.3 kg/m², age 46.0 ± 12.9 years) using a Universal Eating Monitor (UEM) and indirect calorimetry, in a double-blind, placebo-controlled crossover study. At day 7, sibutramine 10 mg and 15 mg reduced food intake by 16.6% and 22.3%, respectively ($p < 0.001$), compared with placebo. Sibutramine reduced eating rate compared with placebo rather than meal length (10 mg $p < 0.05$; 15 mg $p < 0.001$). In addition, sibutramine 10 mg significantly reduced hunger later in the meal ($p < 0.05$) and sibutramine 15 mg increased fullness early in the meal

($p < 0.01$), both of which are consistent with enhanced within-meal satiation. Sibutramine had little effect on resting metabolic rate, although 15 mg did significantly reduce respiratory quotient at several time points during the test day. These results provide novel evidence that decreased consumption of a test meal induced by sibutramine is primarily because of reduced eating rate, enhancing the deceleration in cumulative food intake within a meal associated with the development of satiety. Changes in within-meal appetite ratings appear particularly sensitive to drug-induced enhancement of satiation, and may provide key indices for assessing the therapeutic potential of novel anti-obesity drugs.

Key words

cumulative intake; eating rate; obesity; satiety; sibutramine

Introduction

The effect of anti-obesity drugs on the pattern and structure of human eating behaviour is likely to be critical to their efficacy. However, many potential anti-obesity drugs have undergone significant clinical development, often into Phase 3 clinical trials, with little detailed examination of this effect. With the exception of serotonergic drugs such as d-fenfluramine, little

is known about the effects of many drugs that affect food intake on the macrostructure (meal intake and patterns across the day) of human eating behaviour. These effects can provide useful indications of a drug's potential efficacy, as well as elucidating mechanism of action and providing early indications of any undesirable side effects.

When the effects of serotonergic drugs on eating behaviour in humans have been studied, the focus has been on the

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macrostructure of eating, that is, the effect of drugs on total food intake during meals and appetite ratings before and after these meals. However, effects on the microstructure (structure of individual eating episodes) of human food intake could potentially be crucial to our understanding of the nature of a drug's hypophagic effect (Rogers and Blundell, 1979; Yeomans and Gray, 1997). For instance, although amphetamine and fenfluramine both reduce food intake, the increase in eating rate produced by amphetamine is secondary to the stimulant effects of the drug, whereas the reduction in eating rate produced by fenfluramine is due to enhanced satiety (Rogers and Blundell, 1979).

To measure eating rate, some researchers have developed automated means of assessing intake, that generate cumulative intake curves, from which within-meal changes in eating rate can be identified. A key development was Kissileff's Universal Eating Monitor (UEM), designed to continually measure food intake through the use of hidden scales placed underneath the participants' plate or bowl (Kissileff, *et al.*, 1980; Kissileff, *et al.*, 1982; Guss and Kissileff, 2000), linked to a computer to allow continuous recording of the intake of solid and semi-liquid meals. Further developments have enabled the UEM to automatically solicit subjective ratings of appetite from participants at regular intervals during the meal (Wentzlaff, *et al.*, 1995; Yeomans, 1996).

Despite the sensitivity of UEM measures, the microstructure of eating behaviour has not been routinely used as an assay for potential anti-obesity drugs. Obesity is currently one of the most active areas of research and development in the pharmaceutical industry, and many novel neurotransmitter and neuropeptide targets are being explored. Approval of a new anti-obesity drug by regulatory authorities such as the Food and Drug Administration (FDA) requires efficacy to be demonstrated in clinical trials over a 2-year treatment period. Inevitably, many late phase candidates fail, and each failure can cost companies several hundred million pounds. Hence, we designed a study to show that UEM-derived measures of meal intake may provide a valuable measure of the potential efficacy of appetite-reducing anti-obesity drugs. For this validation study, a drug currently licensed for weight loss was needed. Sibutramine hydrochloride monohydrate (9*N*-[1-[1(4-chlorophenyl)cyclobutyl]-3-methylbutyl]-*N,N*-dimethylamine hydrochloride monohydrate), marketed as Reductil and Meridia (Abbott Laboratories Ltd, Maidenhead, UK), is a nor-adrenaline and serotonin re-uptake inhibitor (Heal, *et al.*, 1998). Sibutramine is marketed worldwide for the treatment of obesity and thus is a good candidate drug with which to establish the utility of within-meal analyses of eating behaviour.

Although some studies have used UEM equipment to measure human food intake with sibutramine (Barkeling, *et al.*, 2003), no study to-date has reported in detail the effect of sibutramine on the microstructure of human eating behaviour. Given that the anti-obesity effects of sibutramine have been reported to be due to satiety and thermogenesis (Stock, 1997; Heal, *et al.*, 1998), an outpatient, randomised, double-blind, placebo-controlled crossover study was designed to evaluate the effects of sibutramine on food intake and energy expendi-

ture in obese female participants. The aims of this study were firstly to assess the effects of the two licensed doses of sibutramine on the microstructure of eating behaviour using a test meal given via the UEM, and secondly to determine the efficacy of these doses of sibutramine at reducing appetite. These data provide the most complete characterisation of the anti-obesity effects of sibutramine to-date and validate new measures (i.e., within-meal changes in appetite) against which novel anti-obesity drugs can be compared in subsequent studies. It was predicted that both doses of sibutramine would significantly reduce energy intake at a test meal. These changes in intake will be accompanied by changes in eating rate and ratings of hunger and fullness during the meal.

Methods

Participants

Thirty-nine obese but otherwise healthy female volunteers were recruited from existing databases of obese volunteers and by advertisement in the local press and posters around The University of Liverpool and University Hospital Aintree. The poster advertisement asked for overweight female volunteers, who wished to take part in a project investigating how a medicine used to help people lose weight affects appetite and metabolism. The study commenced in November 2005 and was completed in June 2006. Individuals who called the study centre underwent a standardised telephone interview to assess their age, height, weight, smoking status and food restrictions. Those who were aged over 65, with a body mass index (BMI) <30 kg/m² or >40 kg/m², who disliked/could not eat the study foods, and those pregnant, or who were of childbearing potential and not using a reliable form of contraception were not studied further. Following this, each participant attended the study centre for a screening visit at which a full medical history was taken and a physical examination carried out by a qualified General Practitioner (GP). In addition, an electrocardiogram was performed, blood samples were taken to test for thyroid function, height and weight measurements were taken, blood pressure and heart rate were checked and the Three Factor Eating Questionnaire (Stunkard and Messick, 1985) was completed. Other exclusion criteria were any major medical illnesses such as diabetes, untreated thyroid disease and known contraindications to sibutramine as listed in the Summary of Product Characteristics. Three Factor Eating Questionnaire (TFEQ) scores for restraint, hunger and disinhibition were used to characterise eating behaviour within the sample and potentially to remove those with contaminant eating behaviour from the analysis. The complete inclusion and exclusion criteria can be found in Table 1. The protocol and consent form were approved by Sefton Research Ethics Committee, Liverpool, UK. Informed consent was gained from all participants and the study was conducted in accordance with the Declaration of Helsinki. Clinical trial registration (EudraACT) number 2005-2080-88.

Study design and medication

This was an outpatient, double-blind, placebo-controlled, two-dose (10 mg and 15 mg sibutramine) study using a crossover design with each treatment period lasting 1 week. Participants attended a pre-study familiarisation day (day 0) before the first day (day 1) of the first dosing period to familiarise them with using Visual Analogue Scales (VAS), the UEM, and to experience the indirect calorimetry equipment. The three 7-day dosing periods started on day 1, day 22 and day 43. The participants returned to the laboratory on day 7, day 28 and day 49 for the assessment of drug effects on food intake, appetite and energy balance. Using blinded randomised allocation, the study pharmacist dispensed medication for three 1-week dosing periods. Each treatment was separated by a 2-week washout (non-treatment) period for a total study duration of 7 weeks. Two weeks were considered sufficient as the half life of sibutramine and active metabolites is 14–19 h (Hind, *et al.*, 1999).

Sibutramine 10 mg, 15 mg and placebo were supplied by Abbott as matching white capsules in coded bottles to ensure the double-blind status of the study. At baseline (day 0), participants were given a bottle containing a supply of study medication for the subsequent 7 days (dosing period 1). Participants were instructed to take their daily dose before breakfast each morning with water, and to delay the last capsule until they attended the study centre for the test day (day 7). Participants attended the study centre on day 7 and took their study medication at 8.30 a.m. before breakfast being served at 9 a.m. A bottle containing the new study medication for the next treatment period was given to participants at the end of day 7 and participants were given the date on which to take the first cap-

sule of dosing period 2 (following a 2-week washout) before the second test day (day 28). Participants were also contacted by telephone the day before this date, to be reminded to begin the medication. The same procedure was followed for dosing period 3 before the third test day (day 49). Any unused medication was to be retrieved for inventory on each test day.

Measures and materials

Measurements of metabolic rate and post-prandial thermogenesis were taken regularly throughout the test days using a ventilated hood system (Deltatrac Metabolic II Monitor™; Datex-Ohmeda Ltd, Hertfordshire, UK). Data were collected from the participants in a recumbent position for 20 min before blood sampling, at baseline and 60, 120, 180, 240, 300 and 360 min post-prandially. The first 5 min of each recording was discarded to allow for complete acclimatisation to the hood and the recumbent position. Energy expenditure was calculated using the equations from Benporat, *et al.* (1983). Changes in appetite across the test day were measured with a series of six 100 mm Visual Analogue Scale (VAS) questions to rate their degrees of hunger, fullness, satisfaction, desire to eat, perception of how much they could eat (prospective consumption) and nausea. To do this, they were asked to place a mark on each 100 mm VAS. For example, hunger was rated along a 100 mm line that was preceded by the question 'how hungry do you feel at this moment?', and the scale ranged from 'not at all hungry' to 'extremely hungry'.

To measure the effects of both doses of drug and placebo on the microstructure of eating behaviour, a UEM (The Sussex

Table 1 Study inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
BMI >30 kg/m ² or <40 kg/m ²	Diabetes
Female, otherwise healthy	Use of weight loss medication/any drug that might affect body weight or appetite (inc. antidepressants, antipsychotics, β -blockers, corticosteroids)
Aged 18–65 years	
Postmenopausal/sterilised/using reliable contraception	Hyperthyroidism
	Hypothyroidism (except if with normal TSH and free T ₄ , and on stable dose of thyroxine >3 months)
	Blood pressure >145/90 mmHg
	History of ischemic heart disease/stroke
	Significant cardiac dysrhythmias
	Known chronic liver disease
	Known renal failure
	Gilles de la Tourette syndrome
	Known phaeochromocytoma
	History of seizures or unexplained syncope
	Pregnancy
	History of intolerance to sibutramine or any of its constituents
	Recent major change in body weight (>3 kg gained or lost in preceding month)
	History of malignancy
	Presence of any other medical condition that, in the opinion of the investigator, precludes safe participation in the study

Meal Patterning System) was used (Yeomans, 2000). Test meal intake was continuously monitored using the UEM equipment, which consisted of a digital balance (Sartorius Model BP 8100; Sartorius Ltd, Epsom, UK; 0.1 g accuracy) positioned beneath, but protruding above, the table surface. The balance was obscured from participants view by a blue plastic place mat (circular, 37 cm in diameter), and was connected to an Apple Macintosh computer (model G4). The UEM software was custom-programmed to interrupt the participant after each 150 g of test meal consumed, to ask the participant to complete on-screen VAS ratings of hunger and fullness, providing a measurement of within-meal satiety processes (Yeomans, 2000). The UEM software measured intake every 1 min of the test meal and generated cumulative intake (in grams) curves by treatment group (placebo, sibutramine 10 mg, sibutramine 15 mg). Eating rate was calculated as total amount eaten (grams) divided by time taken (seconds). Additionally, both intake (gram and kilocalorie) and within-meal VAS parameters (hunger and fullness) were extrapolated to provide data on five incremental stages of the test meal (0%, 25%, 50%, 75% and 100% intake) for all participants. The extrapolation was undertaken using a simple interpolation rule. All scores were set against percentage intake scores and then scores for 25%, 50% and 75% were interpolated from the scores given by the participants at every 150 g consumed.

Kissileff, *et al.* (1982) reported the relationship between UEM measures and self-reported real world intakes (i.e., external validity). Various data show that UEM curves are influenced by gender and food deprivation, as well as the composition and palatability of test meals, showing that they are valid representations of the changes in appetite that occur within meals (Guss and Kissileff, 2000; Westterp-Plantenga, 2000; Yeomans, 2000; Gray, *et al.*, 2002; Robinson, *et al.*, 2005). With regard to the reliability of these various microstructural measures, many authors have commented on the consistency and stability of cumulative intake curves. In the early work of Jordan, *et al.* (1966) and Meyer and Pudal (1972), consecutive trials showed that individual's intake possessed large inter-individual but small intra-individual variability. Modern UEM systems also possess good test-retest reliability within individual UEM curves (Barkeling, *et al.*, 1992; Westterp-Plantenga, 2000; Hubel, *et al.*, 2006).

Test day procedure

On test days, participants attended the study centre at 8 a.m. and confirmed that they had had nothing to eat or drink other than water from midnight the previous evening. Participants were seated for a minimum of 5 min before heart rate, blood pressure and weight were recorded. Heart rate was recorded over 1 min, after the participant had been seated for at least 5 min. Blood pressure was measured according to the guidelines of the British Hypertension Society. The subject was seated for 5 min and blood pressure taken from the left arm using a cuff size appropriate for the participant. The first reading was discarded, and the mean of the three subsequent read-

ings was recorded. Participants were then asked to take the final dose of double-blind study medication for that study period (with the exception of day 0). At 8.30 a.m. of each test day, a basal metabolic rate measurement was taken. For each such measurement, the room temperature was maintained at 21°C, the subjects were lying down and readings were taken for 25 min (only data for the final 20 min after 5 min rest were included in the analysis). Further measurements of metabolic rate and post-prandial thermogenesis were taken at 10 a.m., 11 a.m., 12 noon, 2 p.m. and 4 p.m.

Following the initial indirect calorimetry session, participants were seated in individual cubicles and were asked to complete the first set of VAS questions to rate their degrees of hunger, fullness, satisfaction, desire to eat, perception of how much they could eat (prospective consumption) and nausea. Participants completed these ratings before and after breakfast and lunch as well as at 10 a.m., 11 a.m., 12 noon, 3 p.m., 4 p.m. and 5 p.m.

On test days, participants were instructed to entirely consume a fixed load breakfast consisting of cornflakes (30 g), whole milk (125 g), two slices of toasted white bread (70 g), low-fat margarine (10 g), jam (20 g), a glass of orange juice (125 g) and a cup of tea or coffee. The energy content of the breakfast was 2173 kJ [protein 14.4 g (11 E%), fat 13.2 g (23 E%) and carbohydrate 86.1 g (66 E%)]. Participants remained in the study centre to complete post-breakfast sets of VAS ratings and indirect calorimetry sessions at 10 a.m., 11 a.m. and 12 noon.

At 1 p.m., participants were seated in the UEM laboratory to complete a pre-lunch VAS set before being presented with the test meal and requested to eat as much or as little as they liked, and to complete the on-screen VAS when prompted. Participants were also told that there would be no time limit and to signal the investigator when they had finished. The *ad libitum* lunch meal consisted of pasta with a tomato-based sauce, with a total energy content of 5776 kJ [protein 47.2 g (14 E%), fat 10.7 g (7 E%) and carbohydrate 272.7 g (79 E%)].

Participants remained in the study centre until 5 p.m., completing indirect calorimetry sessions at 2 and 4 p.m. and VAS ratings at 3, 4 and 5 p.m.. Participants were allowed to leave the study centre at 5 p.m. and were not given any food restrictions for the evening of a test day. The same procedure was followed on all test days. Day 0 was virtually identical to the three other test days, with the exceptions that participants took a dose of single-blind placebo tablet rather than the double-blind study medication and were given full explanations of the VAS, the UEM and the indirect calorimetry equipment.

Adverse events

Participants were asked to report any adverse events they experienced while taking study medications. The type, severity, date of onset and resolution were recorded.

Statistical analysis

Data were analysed by Analysis of variance (ANOVA) using SPSS for Windows, Version 14 (SPSS Inc., Chicago, Illinois, USA). Order effects for caloric intake were assessed across drug and placebo conditions. The assumptions of the ANOVA model were tested and if homogeneity of variance was not found, multivariate tests were adopted for that variable. All data fit parametric assumptions, including normal distribution, therefore no data transformation procedures were required and parametric analyses were used. All post-hoc Dunnett's *t*-tests were corrected for number of contrasts. Resting metabolic rate (RMR) and respiratory quotients (RQ) were calculated using the Weir equation (Benporat, *et al.*, 1983; Mansell and Macdonald, 1990).

Cumulative intake data were initially analysed for between-condition differences at each time point (every minute). These Dunnett's *t*-tests were corrected conservatively for multiple comparisons ($p < 0.001$). A standard technique for the examination of individual cumulative intake curves, relying on the visual judgement of deceleration by raters blinded to condition, was used (Kissileff, *et al.*, 1996). Other studies have used curve-fitting software; however, differing mathematical assumptions such as that of a linear relationship can affect findings. However, in this study, this assessment was quantified by the raters calculating the co-efficient of the start and end of individual cumulative intake curves to confirm their initial assessment. Curves whose coefficients were not lower at the end of the meal than at the start were classified as non-decelerating. The between-participant difference was tested using a within-subjects chi-squared test (McNemar test).

The second criterion used for assessing the deceleration in individual cumulative intake curves was based on methods used by Lindgren, *et al.* (2000). If the linear coefficient decreased by half, the participant was considered to have significantly decelerated during the consumption of the meal and therefore returned to a normal significantly decelerated eating rate (Lindgren, *et al.*, 2000). The difference between the participants coefficients were assessed by a repeated-measures ANOVA on the three drug treatment groups.

The satiety quotient (SQ) was used to assess the satiating effect of each eating episode (Green, *et al.*, 1997). The SQ examines the relationship between the changes in subjective sensations of appetite that result from the consumption of a meal and the calories consumed during that meal (pre-test meal hunger rating – post-meal hunger rating/test meal caloric intake). Statistical significance was taken at $p < 0.05$.

Results

Participants

In total, 39 women were enrolled into the study. Of them, 32 completed two conditions, and 30 participants completed all three treatment periods. Of the two participants to complete

two treatment periods only, both missed a test day because of an adverse event, one was an unrelated illness and the other was an upset stomach, which was resolved upon discontinuation of the study medication. No other adverse events were reported in any of the treatment conditions during the trial. The other seven women discontinued prematurely: three withdrew without giving a reason, two for scheduling problems, one for family illness and one on the advice of her GP. Mean demographic and anthropometric characteristics (mean \pm SD) of the 30 participants included in the analysis were: mean age 46.0 ± 12.9 years, mean weight 92.6 ± 10.3 kg, mean height 1.6 ± 0.1 m and mean BMI 34.6 ± 3.3 kg/m². Compliance was confirmed by a tablet count at each visit. Participants returned no study medication, indicating that they had complied with study medication procedure. The mean (\pm SEM) scores for the study sample on the TFEQ subscales were: cognitive restraint 11.3 ± 0.9 , disinhibition 9.7 ± 0.5 and hunger 7.1 ± 0.7 . A *z*-score analysis showed that no participants were greater than ± 2 standard deviation scores away from the group mean on any TFEQ subscale, therefore none were excluded from the analysis on the basis of abnormal eating behaviour for this population.

Baseline

There was no significant difference in total food intake between baseline and placebo treatment groups (463.6 vs 459.8 g; $t(29) = 0.190$, $p = 0.851$). However, there was a significant difference in eating rate (0.63 g/min at baseline; 0.69 g/min at placebo; $t(30) = 2.300$, $p = 0.029$) showing the importance of the UEM familiarisation given at day 0. No significant order effects were found between the three non-baseline conditions. Means (\pm SEM) are shown in Table 2.

Appetite ratings taken throughout test day

With regard to ratings of appetite taken across the test day, sibutramine did not affect self-reported hunger ($F(3,27) = 1.619$; $p = 0.208$), fullness ($F(3,87) = 2.208$; $p = 0.093$), desire to eat ($F(3,27) = 2.196$; $p = 0.112$), prospective consumption ($F(3,27) = 2.879$; $p = 0.054$), satisfaction ($F(3,87) = 0.913$; $p = 0.438$), thirst ($F(3,27) = 1.821$; $p = 0.167$) or nausea ($F(3,27) = 0.413$; $p = 0.261$).

UEM measures of intake

The UEM measured changes in food intake and appetite ratings within the lunch test meal. Data from the UEM confirms that sibutramine significantly reduced energy intake at the test meal ($F(3,84) = 12.574$; $p < 0.001$). Means (\pm SEM) are shown in Table 2. The reduction in intake compared with placebo was 16.6% (76.5 g) at the 10 mg dose ($t(29) = 4.394$; $p < 0.001$) and 22.3% (102.4 g) at the 15 mg dose ($t(29) = 5.158$, $p < 0.001$). There was no significant difference in the amount of food consumed between the 10 mg dose compared with the 15 mg dose (3.8 kcal; $t(29) = 1.22$; $p = 0.233$). Post-hoc tests showed that

Table 2 Mean (\pm SEM) food intake, eating rate and blood pressure; and number of normal and decelerating satiety curves in all three conditions ($n = 30$)

Variable	Condition			
	Baseline	Placebo	Sib 10 mg	Sib 15 mg
Food intake (g)	463.6 (\pm 30.2)	459.8 (\pm 31.1)	383.3 (\pm 27.0)***	357.4 (\pm 30.7)***
Food intake (kcal)	1992.3 (\pm 152.2)	1987.2 (\pm 160.2)	1656.3 (\pm 155.1)***	1544.9 (\pm 169.2)***
Eating rate (g/min)	0.627 (\pm 0.03)	0.692 (\pm 0.04)	0.598 (\pm 0.03)**	0.541 (\pm 0.04)***
Blood pressure (mmHg)				
Systolic	123.1 (\pm 1.9)	123.8 (\pm 2.0)	123.8 (\pm 1.8)	123.8 (\pm 2.2)
Diastolic	66.8 (\pm 1.4)	67.9 (\pm 1.5)	69.9 (\pm 1.3)	70.7 (\pm 1.7)
No. normal satiety curves	Not analysed	12 (40%)	14 (47%)	18 (60%)
No. decelerating curves	Not analysed	7 (23%)	10 (33%)	10 (33%)

Significance from placebo: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

significant differences from placebo in mean cumulative intake were apparent by 12 min after starting the meal at the 10 mg dose ($t(28) = 3.302$; $p = 0.001$) and by 4 min with the 15 mg dose ($t(27) = 3.110$; $p = 0.002$).

In addition to reducing overall amount of food consumed, sibutramine also significantly reduced eating rate during the test meal ($F(2,58) = 9.699$, $p < 0.001$). Eating rate was significantly reduced at both the 10 mg ($t(30) = 2.721$, $p = 0.011$) and the 15 mg dose ($t(29) = 4.383$, $p < 0.001$) compared with placebo (a reduction from 0.69 to 0.60 g/min and 0.54 g/min, respectively). There was no significant difference in the eating rate between the 10 mg and the 15 mg doses ($t(30) = 1.763$, $p = 0.088$).

Figure 1 shows the classic deceleration curves associated with the development of normal satiety within each treatment group. However, data from individuals showed the marked individual differences in cumulative intake curves. It is clear that not all the study population exhibited the classical deceleration of eating associated with biological satiation (Meyer and Pudiel, 1972). To examine the prevalence of decelerating curves in each condition, individual cumulative intake curves were characterised as either decelerating or accelerating, using the techniques described by Kissileff, *et al.* (1996) and Lindgren, *et al.* (2000).

Visual ascription of the data to groups (decelerating or non-decelerating) showed that only 12 of the 30 participants (40%) had normal satiety curves (Meyer and Pudiel, 1972; Kissileff, *et al.*, 1996) in the placebo treatment group. Sibutramine increased the expression of normal satiety curves within those individuals who did not have normal satiety when receiving placebo. This was a dose-dependent effect, with 14 of 30 (47%) having normal satiety curves at the 10 mg dose and 18 of 30 (60%) at the 15 mg dose. This was an observable but not statistically significant difference ($p > 0.05$). Of the 18 individuals who did not have normal satiety curves with placebo, seven did with sibutramine. Two were returned to normal satiety curves by the 10 mg dose and the remaining five by the 15 mg dose. Of the 12 participants who had normal satiety

curves on placebo, seven showed deceleration in eating rate. Ten of 14 participants showed significant deceleration at the 10 mg dose, whereas 10 of 18 participants showed significant deceleration at the 15 mg dose.

Using Lindgren, *et al.*'s (2000) more stringent criteria, 23% of the participants in our sample showed significant deceleration at placebo, and 33% of participants showed significant deceleration at both the 10 and 15 mg doses. Again, this was

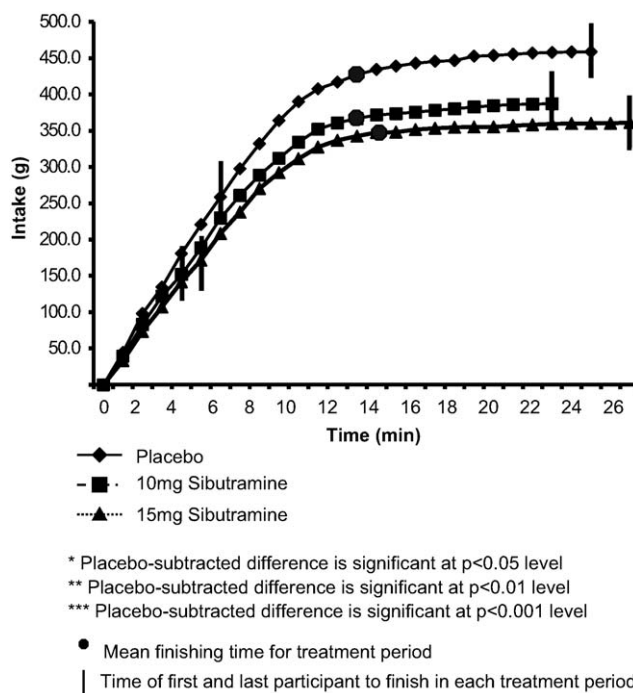


Figure 1 Mean ($n = 30$) cumulative intake curves from the test meal lunch measured by the UEM for whole sample at the end of each treatment period.

an observable but not statistically significant difference ($p > 0.05$).

UEM within-meal measures of appetite

The UEM also collected within-meal VAS measures of appetite (hunger and fullness). With regard to hunger, a significant interaction was found between dose (placebo, sibutramine 10 mg, sibutramine 15 mg) and stage of meal (25%, 50%, 75% and 100% intake) ($F(6,24) = 2.854$, $p = 0.03$). Hunger was found to be significantly lower at the 75% stage of the meal in the 10 mg sibutramine group compared with placebo (13.5 vs 17.3; $t(30) = 2.108$, $p = 0.043$). With regard to the differences in within-meal hunger between the 10 and 15 mg conditions, it appears that pre-meal hunger was lower (but not significantly so) before consumption in the 15 mg condition. Considering fullness, a significant interaction was found between dose and stage of meal ($F(6,24) = 4.726$, $p = 0.003$). Fullness was found to be significantly higher in the 15 mg sibutramine group compared with placebo at both the 25% (22.8 vs 17.0; $t(29) = 3.104$, $p = 0.004$) and 50% stage of the meal (28.4 vs 24.1; $t(29) = 2.358$, $p = 0.025$) (see Figures 2 and 3).

Satiety quotient

Given the changes in both overall intake and within-meal measures of appetite detected using the UEM, SQs, a means of examining the relationship between the amount consumed and its impact on appetite were calculated (Green, *et al.*, 1997).

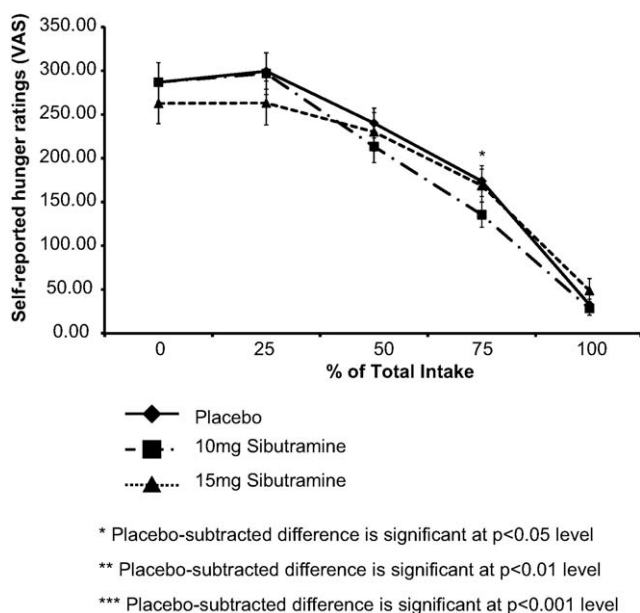


Figure 2 Mean within-meal VAS ratings of hunger from the test meal lunch measured by the UEM for whole sample at the end of each treatment period ($n = 30$).

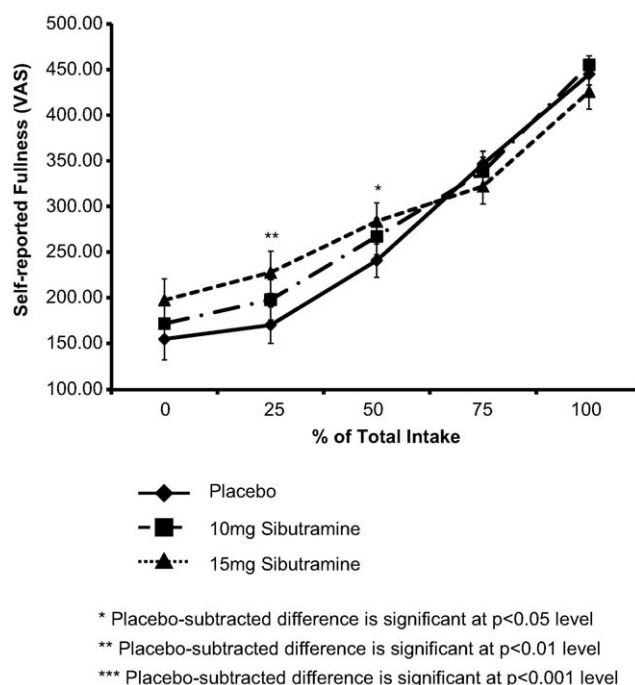


Figure 3 Mean within-meal VAS ratings of fullness curves from the test meal lunch measured by the UEM for whole sample at the end of each treatment period ($n = 30$).

Pre- and post-meal hunger ratings were used for the 'motivation to eat' variable in the equation. A paired t -test showed that the SQ of the test meal in the sibutramine 10 mg treatment group was significantly higher than in the placebo group (0.14 vs 0.11; $t(30) = 2.339$, $p = 0.026$). However, the SQ for 15 mg was similar to placebo, there was a smaller change in hunger rating pre- to post-test meal because of a proportionally greater reduction in food intake in this condition.

Energy expenditure across the test day

Overall, sibutramine did not have a significant effect on RMR ($F(3,75) = 2.458$; $p = 0.069$) despite an apparent trend for RMR to be lower following both doses of sibutramine compared with placebo. However, at 4 p.m. only, sibutramine 15 mg reduced metabolic rate significantly from 1682.2 to 1634.8 kcal/day, a reduction of 2.8% ($t(29) = 3.388$, $p = 0.002$). Sibutramine significantly reduced RQ ($F(3,72) = 8.305$; $p < 0.001$) across the day. RQ was significantly lower following the 15 mg dose of sibutramine when compared with placebo ($t(31) = 2.497$; $p = 0.017$) at several time points; 10 a.m. (0.88 vs 0.91, 3.0% reduction; $t(28) = 2.305$, $p = 0.029$), 11 a.m. (0.87 vs 0.90, 2.7% reduction; $t(29) = 2.959$, $p = 0.006$), 2 p.m. (0.87 vs 0.90, 2.7% reduction; $t(29) = 2.271$, $p = 0.031$) and 4 p.m. (0.86 vs 0.89, 3.7% reduction; $t(29) = 3.388$, $p = 0.002$) (see Figure 4).

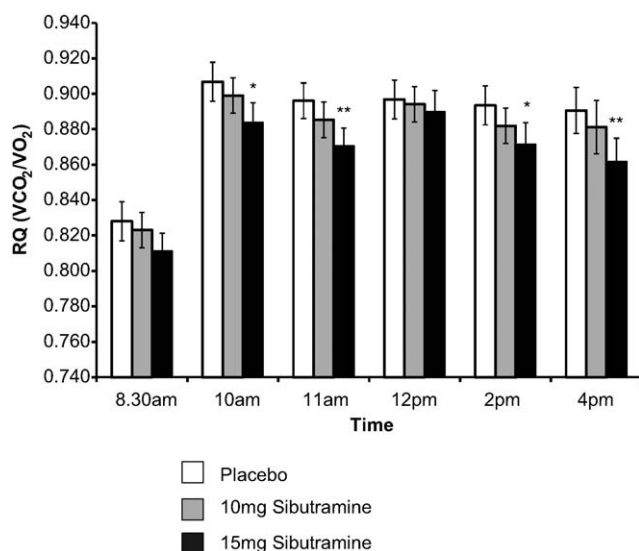


Figure 4 Changes in respiratory quotient measures across the test day for each treatment period ($n = 30$).

Blood pressure

Sibutramine had no effect on either systolic ($F(2,54) = 0.073$; $p = 0.930$) or diastolic ($F(2,54) = 2.395$; $p = 0.101$) blood pressure (see Table 2).

Discussion

The development and clinical evaluation of novel anti-obesity drugs is a lengthy and expensive process, with many potential anti-obesity treatments reaching large-scale clinical trials before lack of efficacy is detected (Zelissen, *et al.*, 2005; Erondur, *et al.*, 2006). Drug effects on human appetite and food intake are generally observed after initial dosing (e.g., for amphetamine and the fenfluramines), allowing initial determination of efficacy to be made during Phase 1 (in normal weight volunteers) or early Phase 2 (in a small sample of the patient population) studies. Therefore, efficacy (i.e., drug effects on eating behaviour) can be assessed together with safety, tolerability, pharmacokinetics and pharmacodynamics early in clinical development.

In this study, sibutramine produced robust hypophagic effects in obese women when compared either against their pre-treatment baseline measure of intake or placebo control. The normal therapeutic dose of sibutramine (10 mg) caused a marked reduction in caloric intake of 16.6% after 7 days of dosing. Surprisingly, only one other food intake study has used the standard dose of 10 mg (Rolls, *et al.*, 1998). However, whereas our study found a significant drug effect on caloric intake on day 7, Rolls, *et al.* (1998) found that 10 mg sibutramine failed to produce a significant reduction in caloric intake, despite a 10.9% difference in lunch intake between the drug condition and placebo.

In the current study, 15 mg sibutramine produced a reduction in caloric intake of 22.3%, which was significantly different from placebo but not from 10 mg sibutramine. This result is consistent with a number of previous studies using the same drug dose. Chapelot, *et al.* (2000) originally reported that 15 mg sibutramine produced a reduction in daily intake of 12%, including a significant reduction in caloric intake at lunch. This study, however, was not conducted in an obese population. More recently, Barkeling, *et al.* (2003) observed that the 15 mg dose significantly reduced lunch time intake in obese patients by 16% (compared with placebo). Barkeling, *et al.* (2003) also found that the hypophagic effects produced by 15 mg sibutramine in the initial crossover trial predicted patients' weight loss in a subsequent open-labelled study. This is the only study to examine if drug effects on caloric intake predict long-term weight loss, and these findings support the concept that laboratory measurement of food intake is a useful indicator of the clinical efficacy of an anti-obesity drug.

The cumulative intake curves produced by the UEM show clear effects of treatment group on eating rate, as well as total caloric intake, during the course of the meal. As the cumulative intake curves showed little indication of change in meal length, reductions in eating rate appear to account for the decreased intake. This reduction in eating rate indicates that sibutramine strengthened the satiating properties of the test meal. This is not the first study to use a UEM to measure the effects of sibutramine on food intake and appetite. Barkeling, *et al.* (2003) also measured meal intake automatically with a system capable of measuring meal duration and eating rate but found no significant effects. A difference in eating rate between baseline and placebo conditions was observed in this study, such an effect of placebo on eating rate has also been reported previously (Barkeling, *et al.*, 2003). Such differences would be expected because of habituation to the equipment, moreover the placebo effect would lead us to expect differences in behaviour. Previous studies show that once participants are familiarised with the UEM, their UEM-derived measures display intra-subject reliability over time (Hubel, *et al.*, 2006).

In the present study, the change in the structure of within-meal intake was also associated with a significant reduction in hunger later in the meal with 10 mg sibutramine, and a significant increase in fullness early in the meal with 15 mg sibutramine. These changes in appetite ratings are consistent with enhanced within-meal satiation. These data suggest that the use of subjective appetite ratings during a meal provide critical evidence on the nature of drug-induced hypophagia and provide strong support of the hypothesis that sibutramine acts selectively on mechanisms of satiety.

The failure of eating rate to decrease toward the end of a meal, that is, no occurrence of Meyer and Pudel's (1972) natural deceleration of eating behaviour, has been considered a key behavioural characteristic of some obese individuals (Stunkard and Kaplan, 1977; Stunkard, *et al.*, 1980). Subsequent studies have shown a greater frequency of non-decelerating cumulative intake in obese children (Laessle, *et al.*, 2001a,b), in syndromes characterised by severe obesity such as Prader-Willi (Lindgren,

et al., 2000), in the morbidly obese (Näslund, *et al.*, 1998) and in obese highly restrained adults (Westerterp-Plantenga, 2000), but not always in obese adults *per se* (Westerterp-Plantenga, 2000; Barkeling, *et al.*, 2003). Thus, increased eating rate and a failure to reduce eating rate at the end of a meal does not necessarily characterise the eating style of every obese individual (or at least this may not be evident in a laboratory setting).

The mean cumulative intake curves in our study showed the classical deceleration of eating associated with biological satiation (Meyer and Pudiel, 1972; Barkeling, *et al.*, 2003). Using the established method of assessing deceleration (Kissileff, *et al.*, 1980), only 40% of the participants had a control curve, which could be described as classically decelerating in the placebo condition (Meyer and Pudiel, 1972). Similarly, using the stricter criterion of Lindgren, *et al.* (2000), the same pattern emerged with only 23% displaying normal deceleration with placebo. These data suggest that failure to decelerate intake during a meal constitutes a key behavioural risk factor for over consumption but may not constitute a useful indices of pharmacological efficacy.

Measures of appetite were not only taken during the test meal but also across the study day. Near significant main effects were found for fullness and prospective consumption using a two-way analysis (both would have reached significance using a one-way analysis). Before the test meal, there was a significant increase in fullness in both conditions, suggesting that sibutramine had extended the satiating effects of the fixed-load breakfast, decreasing hunger before the onset of lunch. Similar effects of sibutramine have been reported in normal weight volunteers (Hansen, *et al.*, 1998; Chapelot, *et al.*, 2000). Significant effects of sibutramine on the appetite of the obese, however, have been more difficult to observe. Rolls, *et al.* (1998) failed to find any significant effect of 10 mg sibutramine on appetite after 7 days of drug treatment. It took 14 days before effects of 30 mg sibutramine became apparent, and only when data were transformed to exclude all other time points from the analyses. Barkeling, *et al.* (2003) also found no overall significant effects of 15 mg sibutramine on appetite ratings of the obese. Consequently, the authors limited their analysis to the second phase of their crossover study, excluding the data from the first phase, which allowed them to detect a significant effect of the drug on desire to eat.

In the present study, despite the reduction in food intake during the test meal, there was no evidence of any compensatory increases in post-lunch appetite (i.e., decreased fullness or increased hunger). Thus, the increase in within-meal satiation was not compensated for by any rebound reduction in post-lunch satiety. In fact, fullness was significantly higher with 10 mg sibutramine immediately after lunch. In addition, the SQ was increased with 10 mg sibutramine compared with placebo. This indicates that sibutramine increases the extent to which the test meal reduces subjective hunger per unit of intake (kilocalorie).

The effects of sibutramine on the expression of human appetite, that is, changes in eating rate and subjective ratings of appetite were similar to those produced by satiety-enhancing

serotonergic drugs such as fenfluramine, d-fenfluramine, fluoxetine and mCPP (1-(*m*-chlorophenyl)-piperazine) (Halford, *et al.*, 2007). Although human psychopharmacological studies rarely provide insight into the precise neurochemical mechanisms underpinning drug-induced changes in behaviour, they do provide critical data on the behavioural characteristics of drug effects. The changes in eating behaviour produced by sibutramine are consistent with a serotonergic enhancement of satiety (Blundell, 1977).

With regard to measures of energy expenditure, sibutramine produced little effect on RMR, but 15 mg sibutramine produced significant effects on RQ across the study day. Critically, these were reductions rather than increases. Although sibutramine has been shown to increase energy expenditure in lean volunteers (Hansen, *et al.*, 1998), studies conducted in the obese have failed to report a clear effect (Seagle, *et al.*, 1998). There is some evidence to suggest that sibutramine may, in part, reverse compensatory reductions in energy expenditure normally produced by weight loss (Hansen, *et al.*, 1998; Walsh, *et al.*, 1999). Given the possibility of sibutramine-induced weight loss (not measured in this study) to decrease metabolic rate and sibutramine-induced hypophagia to reduce dietary-induced thermogenesis, the lack of any drug increase in the measures of energy expenditure may not be entirely unexpected. Therefore, these findings replicate previous research, suggesting the therapeutic effect of sibutramine with the greatest clinical significance is a reduction in energy intake. Nonetheless, the fall in RQ with sibutramine treatment is consistent with previous observations and suggests a shift from carbohydrate to fat metabolism, consistent with participants being in negative energy balance. The treatment period was too short to be able to assess effects on body composition.

To summarise, this is the first study to report that both 10 and 15 mg sibutramine significantly reduce caloric intake during a test meal after only 7 days of treatment. These changes in caloric intake were accompanied by the first evidence that sibutramine modifies the microstructure of eating behaviour by causing a reduction in eating rate. Together with accompanying reductions in within-meal hunger and fullness, this indicates that sibutramine enhances the satiating properties of a test meal. This study is also the first to report clear effects of sibutramine on subjective measures of appetite in an *ad libitum* intake study in the obese. Sibutramine produced no significant increases in energy expenditure in the obese, which is consistent with some previous findings. Non-deceleration of eating rate during the meal, a characteristic often associated with obesity, was also observed in this study. Although this confirms the validity of our model, the utility of deceleration as an analysable behavioural characteristic in experimental studies may be limited, and examination of within-meal changes in appetite may be a more sensitive measure of drug effects.

A more general limitation of UEM-based studies is that researchers are limited to offering participants homogenous liquid or semi-solid set meals such as yogurts, soups, casseroles, pasta meals and Swedish hashes preventing any study of food choice (Hill, *et al.*, 1995). Moreover, researchers have to be

mindful of the potential impact of interrupting participants while eating. In fact, interrupting intake may perhaps slightly increase consumption but does not otherwise appear to alter the expression of appetite in humans (Yeomans, *et al.*, 1997). Perhaps one of the more basic problems with the automated analysis of eating behaviour is the cost, the space required for the study equipment and complexity of the set up. This requires laboratories to have permanently dedicated UEM facilities (including individual test and control rooms). Consequently, most eating behaviour laboratories only possess a small number of working UEM set ups (these generally range between one to three per laboratory). It is, therefore, unsurprising that these limitations have previously restricted the microstructural analysis of eating behaviour to smaller scale experimental studies (Hill, *et al.*, 1995).

This study reports that an experimental medicine model, which measures the microstructure of eating behaviour, is sufficiently sensitive to detect hypophagic and satiety-enhancing effects of novel compounds. Moreover, in this model of eating behaviour, changes were detected at doses not previously reported to affect food intake and eating behaviour, but that have showed weight loss efficacy. The effects of sibutramine on eating behaviour in this study provide a reference standard against which novel, appetite-reducing, anti-obesity compounds can be assessed. If we accept the concept that drug-induced changes in food intake and appetite are a valid indicator of potential weight-reducing efficacy, the potential for failure in later clinical phases could be significantly reduced by the use of such models early in clinical testing.

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