Thermogenic effects of sibutramine in humans

Dorte L Hansen, Søren Toubro, Michael J Stock, Ian A Macdonald, and Arne Astrup

ABSTRACT

Background: Sibutramine is an effective compound for the treatment of obesity, acting both on serotonergic and noradrenergic pathways. Animal studies have shown that sibutramine exerts its effect by enhancing satiety as well as by increasing thermogenesis.

Objective: We tried to compare the acute thermogenic effect of a single 30-mg dose of sibutramine with placebo on basal energy expenditure (EE) and diet-induced thermogenesis.

Design: The study was randomized, double-blind, and placebo controlled. Eleven healthy, normal-weight men underwent 4 distinct treatment regimens separated by washout periods of 6–10 d. EE was measured by indirect calorimetry before and for 5.5 h after sibutramine or placebo administration with or without a 2.1-MJ breakfast. Visual analogue scales for assessment of appetite were completed hourly.

Results: Sibutramine caused a significant increase in EE above that for placebo (over 5.5 h) during both the fed (34%, 0.15 kJ/min) and fasted (183%, 0.20 kJ/min) states (P < 0.02) as well as during the last 3.5 h of this 5.5-h period and in the fed (87%, 0.26 kJ/min) and fasted (152%, 0.22 kJ/min) states, respectively (P < 0.01). The sibutramine-induced increase in EE was accompanied by an increase in plasma epinephrine (P < 0.01), heart rate (P < 0.001), blood pressure (P < 0.05), and plasma glucose (P < 0.02). About 25% of the increased heart rate with sibutramine could be explained by increased thermogenesis. Sibutramine increased satiety more than did placebo (5-h area under the curve, P < 0.05).

Conclusions: Sibutramine caused a significant increase in both EE and satiety, which may both contribute to its weight-reducing properties.

KEY WORDS Thermogenesis, humans, sympathetic nervous system, obesity, satiety, sibutramine, epinephrine, men

INTRODUCTION

Obesity develops from an imbalance between energy expenditure and energy intake, and the physiologic approach to obesity treatment is to achieve a negative energy and fat balance. Sibutramine is a novel antiobesity agent that acts centrally as a serotonergic and noradrenergic reuptake inhibitor (1). In animal studies, sibutramine has been shown to exert its weight-reducing effect by a dual mechanism. It reduces food intake by enhancing the natural physiologic process of satiety and it stimulates thermogenesis, thereby producing an elevation in energy expenditure (2). In humans, sibutramine produces clinically significant weight loss in a dose-dependent manner (3–5) and, as in the animal studies, it reduces energy intake by increasing satiety and decreasing hunger (6). Whether sibutramine also possesses any thermogenic properties in humans has not, however, been examined.

The aim of the present study was to compare the acute thermogenic effect of a single (30 mg) dose of sibutramine or placebo on energy expenditure and diet-induced thermogenesis in 11 young, normal-weight, nonsmoking men, and to evaluate its effect on heart rate, body temperature, blood glucose, catecholamines, and hunger.

SUBJECTS AND METHODS

Eleven healthy, normal-weight, nonsmoking, nonathletic male volunteers were recruited by local advertisement. They all underwent a full medical history and physical examination including standard biochemical and hematologic tests of blood and urine. All were found to be in good health and none were taking any medication. Body weight was measured on a digital scale (model 707; Seca, Copenhagen). Body composition was estimated by bioimpedance using an Animeter (HST-Engineering Inc, Odense, Denmark). Anthropometric subject data are presented in Table 1. Fat mass and fat-free mass were calculated by using the equations given by Heitmann (7). Informed consent was obtained according to the Declaration of Helsinki II, and the study was approved by the Municipal Ethical Committee of Copenhagen and Frederiksborg.

The trial was designed as a randomized, double-blind, placebo-controlled, 4-way crossover study. Each subject underwent 4 distinct treatments separated by washout periods of 6–10 d, receiving 30 mg sibutramine (Meridia; Knoll Pharmaceuticals, Nottingham, United Kingdom) or placebo with or without a breakfast meal providing 2.1 MJ. The meal consisted of juice,
bread, butter, jam, cheese, and ham with a macronutrient composition of 48% of energy from carbohydrate, 37% from fat, and 15% from protein. The treatment order was in accordance with a computer-generated randomization list.

The subjects arrived at the research center at 0745 after an overnight fast and after a minimum of physical activity (on the test days). Consumption of alcohol and coffee was prohibited 48 and 24 h, respectively, before the assessment. After voiding their bladders, the subjects were fitted with sport testers (Diaescape 2 Arthema; S & W Medico Teknik A/S, Albertslund, Denmark) for heart rate monitoring and rectal probes (type 20923001; S & W Medico Teknik A/S) for measurement of core temperature. During a 30-min rest period preceding the start of the measurements, a catheter was inserted into a dorsal hand vein. The hand was placed inside a box with the air heated to 55–60°C (Department of Medical Physics, Queen’s Medical Centre, Nottingham, United Kingdom) to obtain arterialized venous blood samples; the catheter was kept open during the experiment by flushing it regularly with saline solution (8). The room was kept approximately thermoneutral at 25°C, and the subjects were allowed to watch light movies or listen to the radio to keep them relaxed.

Energy expenditure was measured by indirect calorimetry by using an open-air circuit ventilated hood (Jaeger Oxycon Champion; Jaeger, Zoelen, Netherlands). Basal metabolic rate (BMR) was measured before (0830–0850) and immediately after (0900–0920) medication was taken. Breakfast was consumed at 0930–0950 and gas exchange was measured for the next 5.5 h in 20-min blocks, each followed by a 10-min calibration period. The intraindividual day-to-day CV for BMR with this system was found previously to be 3.9% (S Toubro, unpublished results, 1997).

Blood pressure was measured automatically (model UA-743; Tadeka, Japan) every 30 min, heart rate and rectal temperature were calculated as means during 20-min periods, and visual analogue scales for hunger and satiety were completed hourly (9).

### Laboratory analyses

Blood samples for plasma glucose were taken at 30-min intervals starting at 0830 and samples for catecholamines were taken every 60 min starting at 0900. Blood was sampled without stasis through the indwelling hand cannula by using ice-cold syringes, collected in tubes with heparin, and centrifuged at 1300 × g, 4°C, for 15 min. Samples for plasma glucose determination were collected in tubes containing fluoride and EDTA, and plasma glucose was measured by standard enzymatic methods (10). Blood for determination of plasma catecholamines was collected in tubes containing EGTA and glutathione. These samples were centrifuged immediately at 3000 × g, 4°C for 10 min and plasma was stored at −80°C until catecholamine concentrations were determined by HPLC with electrochemical detection (11).

### Results

#### Respiratory data

The time course of energy expenditure responses to sibutramine plus meal (SM), sibutramine plus fast (SF), placebo plus meal (PM), and placebo plus fast (PF) is shown in Figure 1. We decided to use the second baseline period (0900–0920) to calculate responses because mean values and within-subject variability decreased significantly from the first (0830–0850) to the second period (0900–0920; P < 0.05). This phenomenon was probably due to the stress and discomfort associated with the insertion of the catheter. The posttreatment increment in energy expenditure was expressed as the AUC for the full 5.5 h as well as for the last 3.5 h for the 4 treatment groups (Table 2). Sibutramine caused a significant increase in energy expenditure above that of placebo, amounting to an average of 0.20 kJ/min (183%, SF compared with PF) and 0.15 kJ/min (34%, SM compared with PM) during the full 5.5 h (P < 0.05) and 0.22 kJ/min (152%, SF compared with PF) and 0.26 kJ/min (87%, SM compared with PM) during the last 3.5 h (P < 0.01). A comparison of the thermogenic response to sibutramine and to placebo using a simple t test showed a significant difference for SF compared with PF during both the full 5.5 h and the last 3.5 h (P < 0.01). The increases in energy expenditure corresponded to an increase in BMR of 3.6% (fast) and 2.7% (meal) during the whole 5.5 h, and 4.0% (fast) and 4.8% (meal) during the last 3.5 h. Compared with placebo, sibutramine did not cause any significant changes in the postprandial respiratory quotient in either the fed or the fasted state (Table 3).

#### Plasma catecholamines and glucose

The plasma epinephrine and glucose responses to the 4 treatment groups are shown in Figure 2. Compared with placebo, a significant increase in the plasma glucose concentration was found during the last 3.5 h after sibutramine administration (P < 0.05; Table 2), with the main difference being between SM and PM. The plasma epinephrine response, calculated as the AUC over the 5-h period, was higher after sibutramine than after placebo by 0.40 nmol/5 h in the fed state and 0.30 nmol/5 h in the fasted state (P < 0.01; Table 2). Sibutramine caused no significant changes in plasma norepinephrine in either the fed or the fasted state.

#### Heart rate, blood pressure, and rectal temperature

Changes in heart rate, blood pressure, and rectal temperature are shown in Figure 3. Compared with placebo, heart rate increased by 8.6 beats/min in the SM group (P < 0.05) and by 7.0 beats/min in the SF group (P < 0.05) during the full 5.5 h.

### Table 1

<table>
<thead>
<tr>
<th>Anthropometric data of the healthy, normal-weight men</th>
<th>x ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>24.4 ± 1.1</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>74.9 ± 2.0</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.83 ± 0.02</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.5 ± 0.5</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>13.3 ± 0.7</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>61.6 ± 1.7</td>
</tr>
</tbody>
</table>

Note: Means are shown as x ± SEM; n = 11.

Statistics

The statistical analyses were performed by using SIGMA-STAT statistical software (version 1.0; Jandel Scientific GmbH, Erkraft, Germany) and the results were expressed as means ± SEMs. The time course for the different responses showed a slow, sustained effect of sibutramine; consequently, mean differences from baseline and the areas under the response curves (AUCs) were calculated for both the full 5.5 h as well as the last 3.5 h. Responses of the treatment groups were compared by two-way analysis of variance for repeated measures with treatment and meal as the 2 factors. Post hoc comparisons of differences between the treatment groups were determined by using Bonferroni’s multiple comparisons test.
This effect was even more pronounced for the last 3.5 h, with an increase of 10.7 beats/min ($P < 0.05$) in the fed state and 7.5 beats/min ($P < 0.05$) in the fasted state (Table 3). Compared with placebo, sibutramine induced a significant increase in the mean diastolic blood pressure during the full 5.5 h ($P < 0.05$), whereas both the mean diastolic and the mean systolic blood pressure increased during the last 3.5 h ($P < 0.05$; Table 3). In the fed state, sibutramine induced a significantly greater increase in rectal temperature of 0.25°C than did the placebo for the full 5.5 h ($P < 0.05$) and 0.23°C for the last 3.5 h ($P < 0.05$; Table 3). No significant changes were observed in the fasted state.

When the data for the 4 different assessment days were pooled, it was found that the changes in energy expenditure tended to be positively correlated with the changes in plasma epinephrine concentrations ($r = 0.25$, $P = 0.05$) for the total (5 h) response, with the correlation being significant during the late (last 3 h) response ($r = 0.35$, $P < 0.05$). Also, the increase in energy expenditure was found to be positively correlated with the mean increase in heart rate for both the total ($r = 0.45$, $P < 0.01$) and the late response ($r = 0.55$, $P < 0.001$). For the total response, there was no significant correlation between the increase in rectal temperature and energy expenditure, but during the late response a significant correlation was found ($r = 0.32$, $P < 0.05$). No correlations were found between changes in plasma glucose and energy expenditure for either the total or the late response.

**TABLE 2**

<table>
<thead>
<tr>
<th></th>
<th>SM</th>
<th>PM</th>
<th>SF</th>
<th>PF</th>
<th>Two-way ANOVA ($P$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Energy expenditure</td>
<td>Epinephrine</td>
<td>Norepinephrine</td>
<td>Plasma glucose</td>
</tr>
<tr>
<td>SM</td>
<td>5.38 ± 0.17</td>
<td>5.46 ± 0.19</td>
<td>5.38 ± 0.18</td>
<td>5.41 ± 0.16</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PM</td>
<td>5.43 ± 0.19</td>
<td>5.46 ± 0.19</td>
<td>5.43 ± 0.18</td>
<td>5.41 ± 0.17</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SF</td>
<td>5.38 ± 0.18</td>
<td>5.38 ± 0.18</td>
<td>5.38 ± 0.18</td>
<td>5.41 ± 0.16</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PF</td>
<td>5.41 ± 0.16</td>
<td>5.41 ± 0.16</td>
<td>5.41 ± 0.16</td>
<td>5.41 ± 0.17</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

\footnote{\overline{x} ± SEM; area under the response curve. $n = 11$. SM, 30 mg sibutramine plus meal; PM, placebo plus meal; SF, 30 mg sibutramine plus fast; PF, placebo plus fast.}
Hunger and satiety

Sibutramine caused an increase in the satiety rating expressed as AUC (cm/5 h) when compared with placebo: 2.3 for SM compared with 2.2 for PM and 2.4 for SF compared with 9.6 for PF (P < 0.01; Table 4). No significant drug effect was found on the hunger ratings (P = 0.07).

DISCUSSION

We found that compared with placebo, sibutramine caused a significant increase in energy expenditure in both the fed and fasted states. Energy expenditure increased by a mean of 0.15 kJ/min during the whole 5.5 h and by 0.26 kJ/min during the last 3.5 h in the fed state, with the thermogenic effect being equiva-
lent to 3–5% of BMR. The present study is, to our knowledge, the first to report a thermogenic effect of sibutramine in humans. The magnitude of the thermogenic response was similar to that induced by ephedrine and the amount of caffeine in a cup of coffee, which are other sympathomimetic agents possessing weight-reducing properties in humans (12–14), as well as by other adrenergic thermogenic agents (15).

Sibutramine itself is pharmacologically rather inactive and its action depends on first-pass metabolism into 2 active metabolites that reach their plasma peak values 1–2 h after oral ingestion and have half-lives of 16 and 14 h, respectively (16). We took this pharmacokinetic profile into consideration when we designed this study. Consequently, measurement of energy expenditure was continued until 6.5 h after sibutramine ingestion, and the analysis was separated into a total and a late response. This approach seems justified because sibutramine caused a sustained increase in energy expenditure that showed no sign of declining by the time of the last measurement (Figure 1). The fact that the thermogenic response during the fed state (ie, sibutramine AUC compared with placebo AUC) was greater in the last 3.5 h than the in entire 5.5-h postprandial period indicates that its thermogenic activity is likely to be sustained for a considerable time. This suggests that the present study has, if anything, underestimated the impact of sibutramine on daily energy expenditure, and longer studies including more meals (eg, lunch) are warranted.

The pharmacokinetic profile of the active metabolites may explain the failure of a recent study to detect an acute thermogenic effect of 30 mg sibutramine. Seagle et al (17) measured thermogenic effect for only 3 h after intake and found no differ-

![Figure 3](image_url)

**FIGURE 3.** Changes in mean diastolic blood pressure, heart rate, and rectal temperature after sibutramine plus meal (SM), placebo plus meal (PM), sibutramine plus fast (SF), and placebo plus fast (PF). $\bar{x} \pm$ SEM; $n = 11$.

<table>
<thead>
<tr>
<th>SM</th>
<th>PM</th>
<th>SF</th>
<th>PF</th>
<th>Two-way ANOVA ($P$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satiety</td>
<td>2.3 ± 1.7</td>
<td>−2.4 ± 2.5</td>
<td>−2.6 ± 1.9</td>
<td>−9.6 ± 2.1</td>
</tr>
<tr>
<td>Hunger</td>
<td>0.5 ± 2.9</td>
<td>0.04 ± 2.1</td>
<td>1.5 ± 2.2</td>
<td>11.9 ± 3.2</td>
</tr>
</tbody>
</table>

$\bar{x} \pm$ SEM; area under response curve for 5-h period. $n = 11$. SM, 30 mg sibutramine plus meal; PM, placebo plus meal; SF, 30 mg sibutramine plus fast; PF, placebo plus fast. There were no significant treatment × meal (or fast) interactions.
ence between 30 and 10 mg sibutramine and placebo treatments (17). This finding agrees with our results because there was no significant thermogenic effect of sibutramine in the first 3 h after intake.

In animal studies, it has been shown that sibutramine stimulates sympathetic nervous system activity, and this in turn activates thermogenesis in brown adipose tissue (2). The thermogenic properties of sibutramine in humans are also likely to be due to a stimulatory effect on the sympathoadrenal system, as indicated by reports of increases in heart rate and blood pressure (4, 18). However, in the present study no consistent increase in plasma norepinephrine was found. By contrast, we observed that plasma epinephrine concentrations were increased by sibutramine both in the fed and fasted states, and that the late thermogenic response significantly correlated with the corresponding increase in plasma epinephrine. The failure to detect an increase in plasma norepinephrine concentration does not allow a firm conclusion about sympathetic activity to be made because plasma norepinephrine concentrations provide only a very approximate index of sympathetic activity (19). However, the results of the present study show that the sympathetic efferent pathways to the adrenal medulla were activated, causing increased epinephrine secretion, and the increased circulating epinephrine is likely to be at least partly responsible for the thermogenic effect (20, 21).

In accordance with previous animal and human studies (2, 7), we found an acute satiety-enhancing effect of sibutramine, the reverse effect on the hunger ratings compared with placebo was also seen when one subject, whose response to SM differed markedly from that of the other subjects, was excluded (P < 0.01).

Loss of body weight is often associated with a decrease in BMR, partly because of the loss of FFM and lower activity of the sympathetic nervous system (19). Moreover, several studies have found that the relative reduction in BMR is larger than the relative reduction in body weight (22, 23). Thus, if sibutramine has sufficient thermogenic activity to attenuate the decline in metabolic rate, it will help maximize its effect on food intake and energy balance, thereby resulting in more weight loss than could be achieved by energy restriction alone. Moreover, the thermogenic activity would allow body weight to become stabilized at a somewhat higher, more acceptable energy intake, and this should aid compliance during long-term weight maintenance.

Several studies have indicated that a low BMR for a given body size and composition may be involved in some cases of obesity. Ravussin et al (24) reported in a prospective study that subjects with a low adjusted BMR were at higher risk for subsequent weight gain than were individuals with a high adjusted BMR. Moreover, a meta-analysis of BMR in formerly obese subjects and matched control subjects found that the formerly obese had a 3% lower BMR and had a 5-fold higher risk of having a very low BMR than the never obese (25). Other studies have looked for possible explanations of the lower BMR of obesity-prone subjects and lower thyroid hormones and sympathoadrenal activity have been suggested (26). A recent prospective study found that low urinary norepinephrine excretion was associated with increased body weight gain and low epinephrine excretion, with an increased risk of abdominal obesity (27). Most studies have indicated that plasma epinephrine concentrations are normal or subnormal in obesity (28) and that the concentrations are not normalized by weight loss (29). Thus, in this context, it is possible that sibutramine may have a special role in the weight management of obese subjects with low BMRs and epinephrine concentrations.

The finding of increased heart rate agrees with the well-known pharmacologic profile of sibutramine (1). In the present study, we found that the changes in heart rate and thermogenesis caused by sibutramine correlated significantly (r = 0.45–0.55). It is well established that increased energy expenditure achieved by physiologic and pharmacologic stimulants is accompanied by increased heart rate in acute studies (30). In field studies, heart rate monitoring is often used as a surrogate measure of energy expenditure (31). The increased heart rate is supposed to reflect the increased metabolic activity and heat production of various organs and tissues, which require hemodynamic homeostatic alterations to maintain a normal body temperature. The present findings indicate that ≥25% (r² = 0.53) of the increased heart rate induced by sibutramine may be secondary to increased heat production. The increased heart rate and blood pressure increase cardiac work, which may contribute to the thermogenic effect of sibutramine. However, cardiac thermogenesis induced by sympathomimetic agents with thermogenic and cardiovascular effects similar to sibutramine has been estimated to account for <5% of their whole-body thermogenic effect (32). The major sites of sibutramine-induced thermogenesis remain to be determined. The acute cardiac effects of sibutramine may not be desirable in obese subjects. However, during chronic treatment, the accompanying weight loss markedly reduces cardiac work so that the net result is a reduction in blood pressure and heart rate in most patients (33).

In summary, we found that sibutramine caused a significant 3–5% increase in energy expenditure as well as a significant increase in satiety ratings in normal-weight men. This reciprocal relation between pharmacologic suppression of food intake and stimulation of thermogenesis agrees with the results of other studies (14, 34, 35). The increased metabolic rate correlated with a significant increase in plasma epinephrine and heart rate, and may indicate involvement of the sympathetic nervous system, which would be consistent with its activity in animals.

REFERENCES


