Methylphenidate reduces energy intake and dietary fat intake in adults: a mechanism of reduced reinforcing value of food?1–3

Gary S Goldfield, Claudio Lorello, and Éric Doucet

ABSTRACT

Background: Dopamine mediates the reinforcing value of food, and low concentrations of dopamine are related to increased feeding. Thus, administering a drug that increases dopamine may reduce energy intake, possibly by reducing food reinforcement.

Objectives: We tested whether short-acting methylphenidate (MPH), a drug that increases the availability of dopamine by blocking its reuptake, reduces energy intake and alters macronutrient preference and whether these effects are due to a mechanism of reduced hunger or food reinforcement.

Design: Fourteen adults were given placebo or short-acting MPH (0.5 mg/kg) in a randomized, double-blind, placebo-controlled crossover fashion. One hour after ingestion, hunger and the relative reinforcing value of snack food were measured, followed immediately by energy intake and macronutrient preference during a buffet-style lunch.

Results: MPH reduced energy intake by 11% (P = 0.024) as well as intake of fat by 17% (P = 0.003) relative to placebo. Despite similar levels of prebuffet hunger, subjects taking MPH reduced their energy intake more than those taking placebo, which suggests that hunger may not mediate the effects of MPH on energy intake. MPH showed a trend toward reducing the reinforcing value of high-fat food relative to placebo, but reduced food reinforcement was not significantly correlated with energy intake.

Conclusion: MPH reduced overall energy intake with a selective reduction in dietary fat. Findings are consistent with a reward deficiency model of obesity whereby low brain dopamine predicts overeating and obesity, and administering agents that increase dopamine results in reduced feeding behavior. Am J Clin Nutr 2007;86:308–15.

KEY WORDS Methylphenidate, dopamine, eating, energy intake, food reinforcement, obesity

INTRODUCTION

Food is very reinforcing (1, 2), and there are individual differences in the reinforcing value of food whereby obese persons find food more reinforcing than do nonobese persons (3–6) and show a stronger preference for highly palatable foods with a high-fat, high-carbohydrate content (7–9). Given food reinforcement predicts food intake (10–12), individual differences in the reinforcing value of food may play a role in the development of positive energy balance leading to obesity.

Dopamine was implicated in mediating the reinforcing value of food (1, 13), which was noted to be a strong determinant of excessive food intake and obesity (3, 4). Animal (14–17) and human (18–22) data suggest that low availability of circulating dopamine caused by rapid dopamine transport or reduced brain dopamine signaling may be related to the development of obesity. Ingesting palatable food, especially those high in sugar and simple carbohydrates, stimulates the release of dopamine in the accumbens shell and results in repeated self-administrative behavior typically observed in drugs of abuse (23, 24). Thus, raising brain dopamine concentrations should reduce the reinforcing value of food and the motivation to eat, making it easier to reduce energy intake essential for weight loss. Moreover, given that polymorphisms associated with reduced brain dopamine are associated with increased craving (25) and overconsumption of high-fat, high-carbohydrate foods (26), increasing synaptic dopamine may alter macronutrient preference, in addition to reducing caloric intake.

Several theoretical and clinical reasons are available to consider methylphenidate (MPH) as an agent to increase brain dopamine. MPH is a dopamine transport or reuptake inhibitor (27–29) currently indicated for the treatment of childhood and adult attention-deficit hyperactivity disorder (ADHD) (30, 31). Moreover, a common side effect is reduced hunger and weight loss in children and adults (31, 32), especially in those with highest body mass index (BMI; in kg/m2) at baseline (31–33).

Recently, Leddy et al (34) found that a single moderate dose of MPH (0.5 mg/kg) produced a 23% reduction in caloric intake (pizza) compared with placebo in 9 obese adult men, with a 21% decrease in energy intake relative to placebo with a high dose (1.0 mg/kg). Moreover, reported side effects from the single MPH doses were mild, not significantly different from placebo, and unrelated to food intake (34). However, that study did not explore

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putative mechanisms linking MPH and reduced food intake or the effects of MPH on macronutrient preference.

The purposes of this study were 1) to examine the effects of short-acting MPH on hunger, caloric intake, satiety, and macronutrient consumption during a buffet lunch and 2) to evaluate the effects of MPH on food reinforcement. We also evaluated the relation between changes in the reinforcing value of high-fat, high-carbohydrate foods (dessert or snack food) and changes in energy intake of these high-fat, high-carbohydrate foods to elucidate whether food reinforcement may be a mechanism by which MPH reduces energy intake and macronutrient preference.

SUBJECTS AND METHODS

Participants

Participants were recruited by posting flyers in local universities and in the community; ∼50 persons called to inquire about the study. Thirty-one were screened, 17 met inclusion criteria, and 3 participants did not complete testing, leaving 14 young adults (7 male and 7 female) for data analysis. Inclusion criteria included men or women between the ages of 18 and 40 y; BMI ≥ 20 (normal weight or higher) and body weight < 120 kg to accommodate the recommended maximum dosage of MPH of 60 mg/d; nonsmoker or tobacco users; body weight that has not varied >2 kg in the previous 6 mo; no known food allergies; no history of previous MPH use or allergy to MPH; no history of ADHD or current diagnosis of an axis 1 psychiatric disorder (eg, depressive or anxiety disorders) as measured by the Wender-Utah Rating Scale (35–37) and Structured Clinical Interview for DSM-IV (38); no current use of thyroid medication or any medication or dietary supplement that could affect appetite; normal blood pressure (BP); no history of cardiac problems or symptoms suggestive of any cardiac condition; no history of diabetes or insulin resistance; no excessive use of alcohol (>21 drinks/wk) or alcoholism or current addictions to opiates, cocaine, or stimulants; no history of glaucoma; no personal or family history of seizure disorders; not currently taking monoamine oxidase inhibitors, pressor agents, Coumadin, anticonvulsants, phenylbutazone, or tricyclic antidepressants; no history of thyroid disease; no personal or family history of motor tics or Tourette syndrome; and the ability and willingness to comply with the scheduled appointments and experimental protocol. Descriptive characteristics of the sample are presented in Table 1. This study received approval from the Research Ethics Boards at the University of Ottawa and Health Canada.

Design and experimental procedures

We used a randomized, double-blind, placebo-controlled, crossover laboratory study to test the effects of MPH (0.5 mg/kg) on energy intake and the relative reinforcing value of food over the course of a mixed meal buffet lunch in young men and women. Participants visited our laboratory for 1 screening session and 2 testing sessions under drug or placebo, with the order in which participants received medication (MPH or placebo) counterbalanced. We implemented a period of 1 wk between administration of MPH and placebo conditions to ensure that the medications were washed out of the body.

The study was conducted between May 2005 and April 2006 at the University of Ottawa. MPH used in this study was manufactured by Novartis Pharmaceuticals Inc (Montreal, Canada).

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>23.7 ± 4.8</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170.0 ± 6.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72.4 ± 13.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.0 ± 4.0</td>
</tr>
<tr>
<td>Obese with BMI &gt;30 (%)</td>
<td>21.4</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>85.0 ± 10.9</td>
</tr>
<tr>
<td>Percentage of body fat (%)</td>
<td>24.2 ± 10.5</td>
</tr>
<tr>
<td>Dietary restraint³</td>
<td>17.8 ± 9.3</td>
</tr>
<tr>
<td>Depression²</td>
<td>2.5 ± 3.5</td>
</tr>
<tr>
<td>ADHD symptoms⁴</td>
<td>13.1 ± 9.3</td>
</tr>
</tbody>
</table>

¹ All values are x ± SD; n = 14.
² Measured with the Three-Factor Eating Questionnaire.
³ Measured with the Beck Depression Inventory II.
⁴ ADHD, attention-deficit hyperactivity disorder. Measured with the Wender-Utah Rating Scale.

Potential participants were screened by telephone to determine whether they met basic inclusion criteria, and eligible participants were invited to the laboratory for a more thorough screening. During the initial laboratory visit in which participants heard more about the purpose and requirement of the study, written informed consent was obtained from all subjects interested in volunteering for the study, followed by additional screening. Eligible and interested participants underwent a complete demographic, medical, psychological, and nutritional history assessment completed by clinical interview; physical (medical) examination; and questionnaires to fully assess inclusion criteria. Subjects were screened for current symptoms of ADHD with the Wender-Utah Rating Scale (37), depression with the Beck Depression Inventory II (39), and restrained eating with the Three-Factor Eating Questionnaire (40). Eligible participants then rated all of the foods that were used in the standardized ad libitum buffet eating portion of the experiment (Appendix A) with the use of a 5-point scale (41). Those who rated 50% of foods below moderate liking (≤3) on the 5-point scale would have been excluded, but no participant met this exclusion criterion. Participants were then given, in single blind fashion, a dose of MPH (0.5 mg/kg) to assess tolerability before undergoing the experimental test sessions. A drug effects and side effects checklist and vital signs (BP and heart rate) were completed before and 1 h after administration of the test dose. Those who reported severe side effects (eg, extreme nervousness), systolic BP exceeding baseline reading by 20 mm Hg, diastolic BP exceeding the baseline reading by 10 mm Hg, BP > 160/100, or resting heart rate increased by > 20 beats/min from the baseline reading were excluded from the study. However, no participant was excluded for these reasons. Subjective side effects were measured for 19 potential adverse consequences (eg, headache, nausea, nervousness, etc) by having participants rate the intensity of their symptoms with the use of the following scale: 1) none, 2) mild, 3) moderate, and 4) severe. No participants were excluded because of adverse drug effects. Although subjects were informed about the potential side effects of the medication, they were not told about any potential actions of the medications. Eligible participants were then scheduled for 2 half-day experimental (test) sessions scheduled 1 wk apart; 1 day each for evaluating energy intake under drug or placebo conditions. Women were always...
tested during days 1–5 of the follicular phase of the menstrual cycle to control for monthly hormonal effects on appetite and energy intake.

On testing days, subjects arrived at the laboratory at 0930. On arrival, they completed a visual analog scale (VAS) to assess hunger and a 24-h food intake recall (42) to ensure adherence to a 12-h overnight fast, as instructed, including abstinence from alcohol and caffeine. Subjects were also told to abstain from vigorous physical activity 24 h preceding testing and were required to self-report this information on visiting the laboratory. All participants adhered to these preexperimental conditions except for 3 participants who required rescheduling because of excessive exercise within 24 h of testing and 2 subjects exhibited symptoms of the common cold. Subjects who had upper respiratory ailments were rescheduled because these conditions hinder gustatory and olfactory sensations and may interfere with food hedonics or food intake (43).

At 0945 subjects were then evaluated for height, weight, waist circumference, and body composition with the use of dual-energy X-ray absorptiometry (DXA), followed by rest in a supine position. At 1010 subjects then completed an assessment of hunger with the use of a VAS and completion of side effects checklist and vital signs. This was immediately followed by administration of MPH (0.5 mg/kg) or placebo in a double-blind fashion, counterbalanced by order, followed by 60 min of leisure time activities and evaluation of hunger with the use of VAS, side effect checklist and vital signs at 1110, as well as the reinforcing value of high-fat dessert food with the use of a questionnaire developed and validated by Goldfield et al (44). We chose a therapeutic dose of 0.5 mg MPH/kg based on previous research showing that 7 of 9 obese subjects responded to this dose, with no greater reductions in energy intake associated with an increased dose of 1.0 mg/kg (34), indicating that this dose was the minimal effective dose. At 1115, approximately 1 h after administration of drug or placebo, total food intake, macronutrient preference, and satiation were assessed by evaluating energy intake from a standardized mixed meal buffet-style eating method (45), with hunger reevaluated every 30 min for 3 h after completion of the meal to assess satiety. We chose a lag period between drug administration and meal initiation of 60 min because oral MPH takes this long to reach peak brain concentration in adults (28). Subjects were told they were free to eat as much as they wanted in a 30-min period. Ad libitum cooled water consumption was measured during the buffet-eating sessions. At the end of the final session, subjects completed a treatment completion questionnaire (see below) and were phoned at home 4 h after completing the protocol to reassess side effects to ensure they did not need medical assistance because of any delayed drug effects.

Measurements

Anthropometric measurements

DXA (Lunar Prodigy; GE Medical Systems, Madison, WI) was used to measure body composition. Briefly, participants lay on an examination table, fully clothed, while a low-intensity X-ray scanned their entire body. The measurement took 15 min. Height (HR-100 Height Rod; Tanita Corporation of America Inc, Arlington Heights, IL) and body weight (BWB-800AS Digital Scale; Tanita Corporation of America Inc) were measured. Waist circumference was measured with the use of the measuring tape by placing the measuring tape horizontally midway between the bottom of the rib cage and the iliac crest and recording the measurement at the end of a normal expiration (46). CVs and correlation for percentage of fat measured with DXA in 12 subjects tested in our laboratory were 1.8% and r = 0.99, respectively, when compared with underwater weighing. On the basis of height and weight data, BMI was calculated according to the following formula: BMI = kg/m².

Vital signs

BP was measured by a physician with a standard mercury sphygmomanometer and a large-sized cuff. Resting heart rate was measured by a heart rate monitor (Polar CIC, Port Washington, NY).

Food record

Twenty-four hour food records were administered to participants to calculate energy intake the day before testing.

Energy intake

Regarding the buffet-style meal, food intake was measured during an ad libitum meal offered to subjects at lunchtime. The reproducibility of this measurement was reported (45). Briefly, this meal consisted of a variety of foods of differing macronutrient composition. These foods were offered in large amounts, and the subject was instructed to eat until satiation was achieved. More food was made available to the subjects in the event that they consumed all that was laid out at the beginning of the measurement. The subject was given 30 min for this meal, and it was performed in a controlled environment. All foods were weighed to the nearest 0.1 g before and after ingestion. Subjects were blinded to this procedure. Energy and macronutrient contents were assessed with the use of FOOD PROCESSOR SQL from ESHA Research Inc (Salem, OR). Participants were asked to rate all of the foods that were used in the ad libitum buffet eating with the use of a 1–5 rating scale (Appendix 1) to ensure that foods consumed were liked and foods not consumed were not because of taste aversions.

Hunger VAS

Desire to eat, hunger, fullness, and prospective food consumption were rated immediately before (after a 12-h overnight fast) and after drug or placebo administration, and at 30, 60, 90, 120, 150, and 180 min after completion of the standardized test meal with the use of a 150-mm VAS, anchored by “not at all” to “very much.” This VAS was adapted from Hill and Blundell (41). The VAS measurements were always performed in the same environment, using the same table with the same lighting in the same room which was kept free of odors and sounds as well as other factors that might contaminate this measurement (visual stimuli, persons in the room, etc). Under these conditions, VAS measurements in our laboratory (47) and others (48) have been shown to be reliable before in response to meals.

Eating behavior

To assess attitude toward food and dietary restraint, the Three-Factor Eating Questionnaire was used (40). This 54-item inventory measures cognitive aspects of dietary restraint, disinhibition, and hunger. Thus, subscale of interest in this study was dietary restraint. Item responses include true and false, frequency of symptoms reported (rarely to always), and Likert-type scale.
responses of “not like me” to “describes me perfectly.” The psychometric properties of this instrument are well established in adults and adolescents (49, 50).

Wender-Utah Rating Scale

This is a 61-item self-report scale designed to screen for retrospective childhood-onset ADHD. It was shown to be a sensitive and valid tool in identifying ADHD in adults (35–37). Research has shown that scores > 46 on this rating scale are indicative of ADHD; thus, subjects who scored above this clinical cutoff were excluded from the study (35).

Beck Depression Inventory-II

This is a widely used and validated 21-item inventory that assesses cognitive, behavioral, and vegetative symptoms of depression (39). Subjects scoring ≥30, indicative of severe clinical depression, were excluded from the study.

Side effects checklist

Nineteen subjective responses of potential side effects (headache, nausea, anxiety, etc) were measured by having subjects rate the intensity of their symptoms according to the following scale: 1) none, 2) mild, 3) moderate, 4) severe. The checklist was based on the most common side effects listed in the Compendium of Pharmaceuticals and Specialties reference guide, as well as one used by Leddy et al (34) to compare side effects profiles of MPH between studies.

Treatment completion questionnaire

Participants were asked to identify the substance they received at each session (MPH or placebo) and rate how much they liked its effects with the use of a 100-mm VAS anchored by “not at all” to “very much.”

Analytic plan

The distributional properties of outcome measures were examined to evaluate the assumption that they were normally distributed. As expected, some distributions were not normally distributed (eg, relative reinforcing value of food) and log transformations failed to normalize them. Thus, both parametric and nonparametric tests were conducted and the pattern of results that emerged was identical, so only results of the parametric tests are presented here to aid in the interpretation of data.

The degree to which MPH influenced overall food intake, macronutrient consumption, food reinforcement, drug effects, and vital signs were assessed by a repeated measures analysis of variance (ANOVA) with drug (MPH compared with placebo) as the repeated subjects variable. The effects of drug on premeal hunger and satiety response were evaluated with the use of separate 2-factor repeated measures ANOVAs. For premeal hunger, drug (MPH compared with placebo) and time (before or after administration) represented the within (repeated) subject factors. To assess satiety, drug (MPH compared with placebo) and time (0, 30, 60, 90, 120, 150, 180 min after meal hunger ratings) represented the within-subjects repeated measures variables. Corrections for violations of sphericity that typically occur with > 3 repeated measures with ANOVA were handled by adjusting the P values based on the Huyn-Feldt tests. Significant findings on repeated measures were followed by linear contrasts to determine the time points in which hunger ratings differed between groups, using α set at 0.05.

To explore the extent to which reduced hunger is a mechanism that links MPH with reduced energy intake was first evaluated by a repeated measures ANOVA with group (MPH compared with placebo) and time (baseline compared with after administration) as repeated measure factors. Then, Pearson correlations between after MPH or placebo administration on premeal hunger and overall energy intake were examined in both MPH and placebo conditions. Similarly, the extent to which the relative reinforcing value of high-fat snack food is a mechanism linking MPH and reduced energy intake or intake from dietary fat, a within-subjects ANOVA was first conducted, with group (drug compared with placebo) as the within subjects factor and relative reinforcing value of high-fat snack foods (ie, button presses for snacks) as the dependent measure. Then, Pearson correlations between after MPH or placebo administration on the relative reinforcing value of high-fat snack food and overall energy intake and intake from dietary fat was examined in both MPH and placebo conditions.

Chi-square analyses were conducted to evaluate the accuracy in which participants identified drug or placebo conditions, as well as the frequency of reported side effects in each drug condition. Two-tailed α set at 0.05 was used to evaluate statistical significance for all tests. Statistical analyses were conducted with the use of SPSS software, version 13.0 (SPSS Inc, Chicago, IL).

RESULTS

As shown in Figure 1, ANOVA showed that MPH produced significant reductions relative to placebo in overall kilocalories consumed (P = 0.023) as well as intake (in g) from fat (P = 0.003) (see Figure 2), but no differences for intake of carbohydrates (P = 0.17) or protein (P = 0.11) were found between MPH and placebo, respectively.

Repeated measures ANOVA showed a significant main effect of time on before and after administration changes in premeal hunger, whereby hunger increased significantly in both MPH (P < 0.001) and placebo (P < 0.001) conditions. However, a drug × time interaction was significant (P = 0.05), whereby MPH (baseline: 49.8 ± 28.7; after administration: 83.5 ± 28.4) attenuated the increase in premeal hunger compared with placebo (Baseline:

FIGURE 1. Mean (±SEM) effects of methylphenidate (MPH) and placebo on energy intake. Data were analyzed by repeated-measures ANOVA, with 2-tailed α set at P < 0.05. *Significantly different from MPH. MPH significantly reduced overall energy intake.
Hunger rating between MPH and placebo after administration and before the buffet did not differ significantly. As shown in Table 2, a nonsignificant trend favoring MPH over placebo was observed in the reduction of the relative reinforcing value of snack food. No differences between drug conditions emerged on potential confounds such as water intake during buffet meal, liking or satisfaction of buffet meal, or liking the feel of the drug. The 2-factor repeated measures ANOVA indicated that neither the drug nor the drug × time interaction was significant on hunger ratings over 3 h after the buffet lunch. However, a main effect of time on hunger was significant (P < 0.001), indicating that hunger increased (satiety decreased) over time for all participants. Pearson correlations showed that the relative reinforcing value of high-fat snack food was not significantly correlated with reduced fat intake in the overall sample or in the MPH or placebo conditions. Similarly, changes in hunger before and after administration of MPH or placebo did not significantly correlate with energy intake in the overall sample or in the MPH or placebo conditions.

### Drug effects and vital signs

ANOVA showed no significant effects involving differences between MPH and placebo in vital signs such as systolic or diastolic BP or heart rate in beat per minute. Similarly, chi-square tests indicated no differences between MPH and placebo on the drug (side) effects during the screening or test dose. All drug effects reported for both MPH and placebo were in the mild-to-moderate range, with no symptoms reported for the severe range. Moreover, there were no significant differences in drug liking between MPH and placebo. Sixty-four percent of participants correctly identified that they received placebo, which chi-square tests showed not significantly different from chance (ie, 50%). Similarly, 50% of participants correctly identified that they received MPH, a rate that also did not differ significantly from that expected by chance.

### DISCUSSION

Based on a randomized, double-blind, placebo-controlled crossover design, which yields the highest quality of evidence in human laboratory studies, our data show that MPH, a drug that increases brain dopamine by blocking dopamine transporter occupancy (28, 51), significantly reduced overall food intake from a mixed-meal buffet style lunch relative to placebo. Interestingly, MPH selectively reduced consumption of high-fat foods but had no significant effects on carbohydrate or protein intake. Moreover, no differences in side effects or vital signs between MPH and placebo were reported, suggesting MPH is well tolerated during acute administration, which is often a period when people experience the most severe side effects from psychotropic medications.

Our data indicate that MPH produced an 11% reduction in energy intake from a single meal relative to placebo, which although statistically significant, is below the 23% reduction shown by Leddy et al (34) using the same 0.5 mg/kg dose. Several differences in methods between our study and that of Leddy et al (34) may help explain, in part, the discrepancies in drug effects on energy intake. Although differences in characteristics of the samples may contribute to the differences in treatment response, these differences are unlikely to explain much of the variance because these variables were included in the ANOVA models as covariates and identical results were obtained. Perhaps a more important difference in methods between studies relates to the eating paradigms used to assess energy intake. Our study used an all-you-can-eat mixed-meal buffet style eating paradigm, whereas Leddy et al (34) used a single-food all-you-can-eat (pizza) model. Given the well-documented support for sensory-specific satiety (52–54), a phenomenon whereby persons tend to become sated on one food but continue eating when they are presented with another food with different sensory characteristics (ie, taste, smell, mouth feel), these differences in eating paradigms may partially explain differences in caloric reduction observed with MPH. The 20% higher energy intake during placebo and MPH conditions observed in our study compared with Leddy et al (34), despite our sample having lower mean BMI values, supports this interpretation that sensory-specific characteristics may partially explain the differences in drug response. Alternatively, there is wide variability within and between persons in serum concentrations of weight-standardized doses of...
Methylphenidate and energy intake, and food and drug hedonics

TABLE 2
Effects of methylphenidate (MPH) or placebo on food reinforcement, water intake, and food and drug hedonics

<table>
<thead>
<tr>
<th>Variable</th>
<th>MPH (n = 14)</th>
<th>Placebo (n = 14)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water intake (g)</td>
<td>199.2 ± 290.8</td>
<td>128.3 ± 203.9</td>
<td>0.302</td>
</tr>
<tr>
<td>Food reinforcement (button presses)</td>
<td>95.7 ± 58.8</td>
<td>134.3 ± 82.4</td>
<td>0.100</td>
</tr>
<tr>
<td>Liking of buffet meal (VAS mm)</td>
<td>117.6 ± 27.7</td>
<td>124.5 ± 19.2</td>
<td>0.453</td>
</tr>
<tr>
<td>Drug liking (VAS mm)</td>
<td>70.7 ± 20.2</td>
<td>65.6 ± 19.2</td>
<td>0.381</td>
</tr>
</tbody>
</table>

⁎ All values are ± SD. VAS, visual analog scale. Effects of drug on each outcome measure were analyzed by repeated measures ANOVA. All tests were conducted by using 2-tailed α set at 0.05.

MPH, and these unmeasured differences could explain the different treatment effects. Of course, it is quite possible that the obese sample studied by Leddy et al (34) are simply more responsive to MPH than our predominantly lean sample. This interpretation is consistent with the reward deficiency syndrome of obesity, which states that low concentrations of dopamine may motivate one to overeat (and become obese) as a means of compensating for a dysregulated reward circuitry (10, 18, 20, 55, 56). Thus, increasing brain dopamine should theoretically result in a greater reduction in the reinforcing value of food, motivation to eat, and reduced intake in obese compared with lean persons (15–17, 19–22).

Because MPH acts on brain dopamine and dopamine mediates the reinforcing value of appetitive behaviors such as eating (1, 13), and because animal and human models show stronger craving and reward value for snack foods high in fat and simple carbohydrate (23), we hypothesized that MPH could have selective effects on fat or carbohydrate intake or both. Our data show that MPH did in fact selectively reduce, relative to placebo, intake of dietary fat by 17% but had no significant effects on carbohydrate or protein intake during the buffet lunch. Interestingly, MPH also produced a corresponding reduction in the reinforcing value of high-fat snack food by 29%, which, although only a nonsignificant trend rather than significant difference, may be clinically significant given food reinforcement was shown to be a determinant of food intake in previous research (57). To our knowledge, this is the first study to document that MPH has an impact on macronutrient preference. Although the role that dietary fat intake plays in the cause and nutritional intervention of obesity has come under scrutiny with the proliferation of low-carbohydrate diets (58), nutritional guidelines from the American Dietetic Association, derived from evidence-based systematic reviews with the use of meta-analysis (59), recommend a low-fat (<30%) diet for the treatment and prevention of obesity and its comorbidities. Moreover, low-fat diets were shown to reverse heart disease processes (60), providing evidence that adherence to low-fat diets is critical to attenuate obesity-related comorbidities. It is important to note that the current findings were obtained in samples predominantly comprising nonobese adults, and future research is needed to determine whether MPH selectively reduces fat intake in obese persons.

As secondary objectives, we explored the degree to which the hypophagic effects of MPH were due to mechanisms of reduced hunger, reduced food reinforcement, or both. Hunger increased significantly after administration of both MPH and placebo, which is not surprising because the length of time from the previous meal increased in both conditions. Although MPH attenuated the increase in hunger relative to placebo, no differences between drug conditions emerged after administration and before the buffet meal, yet subjects in the MPH group ate less than those in the placebo group. This finding, combined with a nonsignificant correlation between hunger and energy intake, indicates that changes in hunger did not mediate the hypophagic response to MPH in the sample obtained. In exploring reduced food reinforcement as a potential mechanism linking MPH with reduced energy intake, we found that MPH showed a nonsignificant trend toward reduced food reinforcement relative to placebo, and snack food reinforcement was only moderately, and not significantly, correlated with fat and energy intake. However, the current study was statistically powered to detect differences between MPH and placebo on energy intake rather than determining mechanisms of action. On the basis of the current effects of MPH on snack food reinforcement, power analysis calculations indicate we would have required ≈29 subjects (twice the sample size) to detect significant differences and perhaps even more subjects to detect a significant correlation between reduced snack food reinforcement and reduced energy intake or macronutrient preference. This suggests that future research using larger samples that measures food intake during a 24- or 48-h period are needed to adequately examine the extent to which changes in hunger or food reinforcement mediate reduction in energy intake and macronutrient preference resulting from MPH. Although not significant in this study, future research should also investigate the relative importance of satiety and between-meal snacking as potential mechanisms of action of the hypophagic effects of MPH.

In summary, our data show that administering a single dose of short-acting MPH at 0.5 mg/kg produced a significant reduction in energy intake, with selective reduction in macronutrient preference for high-fat foods. The current study did not support the hypothesis that reductions in hunger or food reinforcement mediate the reductions in energy intake and macronutrient consumption resulting from MPH administration, possibly because the study was not primarily designed to detect these potential mechanisms of action. Although the anorexic effects of MPH are well documented, it is of theoretical importance that future research using larger samples investigate altered food reinforcement as a potential mechanism of action of MPH given that MPH increases brain dopamine, food is a primary reinforcer, and dopamine transport and synthesis mediate the reinforcing value of food (1, 13). Our main findings of reduced energy intake and dietary fat consumption from MPH are consistent with the neurobiological “reward deficiency” hypothesis that the dopaminergic system plays an important role in regulating the consumption of appetitive behaviors such as eating and smoking. Consistent with the reward deficiency model of obesity (20, 55, 56), our data suggest that increasing brain dopamine results in reduced energy
intake, whereas other studies indicate that decreasing brain dopamine through administration of antipsychotic medications results in overeating and weight gain (61). As such, our data along with previous laboratory data of MPH on eating in obese men (34) suggest that MPH and possibly other agents that increase brain dopamine by blocking its reuptake and synthesis warrant further study as methods of inhibiting eating behavior. With regard to future research on MPH, identifying optimal dose and timing of dose on energy intake, as well as examining the safety, tolerability, and possible abuse potential of sustained use of MPH, in obese men and women is needed before it can be considered for testing as a pharmacologic agent in the treatment of obesity.

We thank the Montfort Hospital for providing methylphenidate and placebo and for maintaining the double blind conditions.

The author’s responsibilities were as follows—GSG and ED: conceived the study; CL and ED: conducted the experiment; GSG, ED, and CL: analyzed and interpreted the data; GSG: wrote the paper. None of the authors had a financial conflict of interest in relation to this paper.

REFERENCES

APPENDIX A

Food item selection and quantity of food offered in buffet lunch:

<table>
<thead>
<tr>
<th>Foods</th>
<th>Weight before</th>
<th>Weight after</th>
<th>Total weight consumed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turkey breast slices</td>
<td></td>
<td>130</td>
<td></td>
</tr>
<tr>
<td>Liver pâté</td>
<td></td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Brie cheese double cream</td>
<td></td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Mozzarella cheese</td>
<td></td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Cottage cheese</td>
<td></td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Butter</td>
<td></td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Mayonnaise</td>
<td></td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Italian dressing</td>
<td></td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Ranch dressing</td>
<td></td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Mustard</td>
<td></td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Ketchup</td>
<td></td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>White bread</td>
<td></td>
<td>150</td>
<td></td>
</tr>
<tr>
<td>Whole-wheat bread</td>
<td></td>
<td>150</td>
<td></td>
</tr>
<tr>
<td>Soda crackers</td>
<td></td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Lettuce</td>
<td></td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Tomatoes</td>
<td></td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Baby carrots</td>
<td></td>
<td>150</td>
<td></td>
</tr>
<tr>
<td>Apple quarters</td>
<td></td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Chocolate chip cookies</td>
<td></td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Chocolate cake</td>
<td></td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>Fruit yogurt</td>
<td></td>
<td>250</td>
<td></td>
</tr>
<tr>
<td>Skimmed milk (0%)</td>
<td></td>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>Partly skimmed milk (2%)</td>
<td></td>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>Whole-fat milk (2%)</td>
<td></td>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>Orange juice</td>
<td></td>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>Coca-Cola</td>
<td></td>
<td>355</td>
<td></td>
</tr>
<tr>
<td>7UP</td>
<td></td>
<td>355</td>
<td></td>
</tr>
<tr>
<td>Regular chips</td>
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<td>60</td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td></td>
<td>1000</td>
<td></td>
</tr>
</tbody>
</table>

1 Total weight (in g) of foods consumed was calculated by subtracting weight of each food remaining after eating from the weight of each food as presented before eating. All subjects reported moderate liking or higher for foods.
2 Low fat and low sucrose (12 items).
3 High fat, high sucrose, or both (11 items).
4 Medium fat, medium sucrose, or both (6 items).
5 Kraft Foods Inc, Northfield, IL.
6 Coca-Cola Company, Atlanta, GA.
7 Dr Pepper/Seven Up Inc, Plano, TX.