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Wake-promoting agents with different mechanisms of action: comparison of effects of modafinil and amphetamine on food intake and cardiovascular activity

Angela P. Makris^{a,*}, Craig R. Rush^b, Robert C. Frederick^c, Thomas H. Kelly^b

^aWeight and Eating Disorders Program, Suite 3121, Department of Psychiatry, University of Pennsylvania, Philadelphia, PA 19104, USA

^bDepartment of Behavioral Science, University of Kentucky, Lexington, KY, USA

^cBristol-Myers Squibb Company, Princeton, NJ, USA

Abstract

Despite efforts to achieve a desirable weight, two-thirds of the population has an elevated body weight. Medications are useful in supporting weight loss, but produce adverse effects. This study compared the effects of amphetamine and modafinil on food intake and cardiovascular activity in healthy men and women. Participants ($n = 11$) completed 11 sessions. In random order, participants received placebo on five separate sessions and single oral doses of modafinil (1.75, 3.5, or 7.0 mg/kg) and amphetamine (0.035, 0.07, 0.14 mg/kg). Free time between hourly performance testing intervals gave participants the opportunity to eat. Like amphetamine, modafinil reduced the amount of food consumed and decreased energy intake, without altering the proportion of macronutrients consumed. Although both medications significantly increase heart rate and blood pressure at higher doses, the dose of modafinil that was efficacious in decreasing food intake did not significantly increase heart rate. Modafinil may be well suited for the treatment of obesity, although further studies with repeated dosing in overweight populations are warranted. Modafinil may have less adverse health consequences than some anorectic agents and greater treatment efficacy.

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Introduction

Despite efforts to achieve a desirable weight, two-thirds of the population has an elevated body weight (Flegal, Carroll, Ogen, & Johnson, 2002). The prevalence of obesity has been steadily rising over time across genders, ages, races, education levels, and geographical regions and has reached epidemic proportions (Wickelgren, 1998; Taubes, 1998; Mokdad et al., 2001). It has become increasingly apparent that safe and effective interventions are necessary to improve current conditions and promote lasting, healthy lifestyles. Medications have been successful in supporting weight loss but many of them have been withdrawn from the market or are not recommended for weight loss due to adverse effects such as hemorrhagic stroke (phenylpropanolamine), heart valve disease and pulmonary hypertension (fenfluramine, dexfenfluramine), and abuse liability (amphetamine).

Modafinil has recently been approved for use in the treatment of narcolepsy in the United States. Although its mechanism of action remains unclear, studies suggest that modafinil requires an intact adrenergic system to produce wakefulness (Duteil et al., 1990; Rambert, Pessonier, & Duteil, 1990; Hermant, Rambert, & Duteil, 1991). Other studies also suggest that modafinil produces arousal by indirectly decreasing γ -aminobutyric acid (GABA) levels via serotonergic, adrenergic, and/or glutamatergic systems (Tanganelli et al., 1995; Ferraro et al., 2000, 2001). These systems are also actively involved in the regulation of appetite (Leibowitz and Hoebel, 1986).

A limited number of studies have examined the effects of modafinil on food intake in nonhumans and humans. Nonhuman studies suggest that modafinil decreases appetite and food intake and reduces frequency of eating (Nicolaidis & Saint Hilaire, 1993; Shelton, Nishino, Vaught, Dement, & Mignot, 1995). Two human studies evaluating the efficacy of modafinil for the treatment of attention deficit hyperactivity disorder (ADHD) in adults reported reductions in energy intake or appetite suppression following acute

* Corresponding author.

E-mail address: makrisa@mail.med.upenn.edu (A.P. Makris).

administration of modafinil, while no changes in appetite were observed in another study evaluating the effects of modafinil in children with ADHD (Jasinski & Kovacevic-Ristanovic, 2000; Taylor & Russo, 2000; Rugino & Copley, 2001). Taken together, these findings suggest that modafinil might be effective for the management of food intake.

An examination of the profile of effects produced by modafinil supports its potential utility for appetite regulation and weight loss. Unlike most adrenergic agonists, modafinil displays a low incidence of sympathetic side effects (Lyons & French, 1991; Boivin, Montplaisir, Petit, Lambert, & Lubin, 1993; Billiard et al., 1994; Laffont, Mayer, & Minz, 1994; Wong, King, Laughton, McCormick, & Grebow, 1998). Modafinil is classified as a schedule IV medication. Studies suggest that modafinil has less abuse liability and produces fewer adverse behavioral effects than stimulant drugs (US Modafinil in Narcolepsy Multicenter Study Group, 2000; Warot, Corruble, Payan, Weil, & Duech, 1993; Gold & Balster, 1996; Jasinski & Kovacevic-Ristanovic, 2000; Rush, Kelly, Hays, Baker, & Wooten, 2002; Deroche-Gamonet et al., 2002). These characteristics may make modafinil a uniquely efficacious agent for the long-term treatment of obesity.

The overall aim of this study was to investigate the effects of the novel wake promoting compound, modafinil, on nutritional (i.e. energy and macronutrient intake) and physiological (i.e. cardiovascular activity) parameters in non-obese, healthy men and women. These effects were compared with those of *d*-amphetamine, an adrenergic anorectic with well-documented sympathetic side effects and abuse liability.

Method

Subjects

Eleven healthy, adult, nonsmoking males and females between the ages of 21 and 35 participated in the study. Participants were recruited by local and campus newspaper advertisements, posters, and word-of-mouth. Potential participants were informed that the purpose of the study was to determine the behavioral and subjective effects of medications and that a range of behaviors would be monitored and videotaped during the course of the study. Each volunteer completed a medical and psychological screen. One component of the screen was comprised of anthropometric measurements (i.e. height, weight), cardiovascular evaluations (i.e. blood pressure, heart rate), and a number of blood and urine tests (i.e. liver enzymes, glucose, lipids, drugs). The second component required the completion of questionnaires (i.e. Demographic Questionnaire, Health History Questionnaire, General Health Questionnaire, Eating Disorders Inventory (EDI), Three-Factor Eating Questionnaire (TFEQ), Psychiatric Screen, Beck

Depression Inventory (BDI)). Individuals reporting psychiatric problems, pre-existing health afflictions (i.e. any chronic diseases such as diabetes, hypertension, any type of cardiovascular disease, stroke, thyroid disease), recent weight loss, allergies, use of prescription medications, use of appetite modulators, heavy use of caffeine (> 350 mg/d), or regular alcohol, tobacco or other drug use were excluded from the study. In addition, individuals reporting eating disorders, dietary restraint, or a BMI below 19 or above 29 were excluded from the study. Because the effects of modafinil on food intake were evaluated in this study, individuals with atypical eating patterns (food restriction, restraint, or bingeing) or eating disorders (anorexia nervosa, bulimia nervosa, binge eating disorder) were excluded. Results of the medical screen were given to the study physician who reviewed the information, ordered additional tests, if necessary, and determined eligibility.

This study was reviewed and approved by the Medical Institutional Review Board of the University of Kentucky. Separate consent forms were signed prior to the medical evaluation, training, and study phase. All individuals were paid for participating in each stage of the study. At the end of the study, participants completed a debriefing session. During the debriefing session, participants were informed of the study drugs and doses and given the opportunity to comment and ask questions about the study.

Laboratory and equipment

The laboratory contained the following features: (1) a private work area; (2) bathroom; (3) a general-purpose area equipped with a computerized blood-pressure station (Macintosh IICI connected to a Sentry II blood pressure machine), television, sofa, three chairs and two tables, one for eating and another for playing games, and bookshelves stocked with compact discs and a compact disk player, magazines, board games, puzzles, and exercise equipment; (4) a kitchenette, containing shelves for non-refrigerated food items, basic cooking and eating utensils, sink, refrigerator, and two microwaves, and (5) a craft room for building models, making crafts, drawing, painting, or playing video games. The private work area, where assessment batteries were performed, contained a desk, chair, and computer. The laboratory allowed individuals to perform computerized assessment batteries while having free access to their choice of leisure activities and food in their spare time.

Each room, excluding the bathrooms, contained video cameras and microphones. Four additional video cameras were mounted specifically to monitor food preparation and consumption. The purpose of the video cameras was to provide continuous observation for maintaining subject safety and protocol integrity as well as to support the measurement of eating topography. All study sessions were videotaped.

Food

Prior to the start of the study, a minimum of one training session was required in order for volunteers to become familiar with the laboratory and learn the computer tasks that would be completed during the study. During the training session volunteers were oriented to the study area including the kitchen and the location of study foods. The use of kitchen equipment such as the microwave was explained during the break period of the training session. To diminish any novelty effects during the study and to ensure that all food items were palatable, volunteers were encouraged to sample any food items in which they were unfamiliar.

During the study, participants could choose any number or combination of food items and were allowed to use the sink, microwave, or any other piece of kitchen equipment to prepare their food. Participants were required to consume all food items on a table in the general-purpose area. In addition, participants were instructed to place all unconsumed portions, wrappers, and utensils on a tray, which was removed by a staff member each hour. All unconsumed portions were weighed and the amount was recorded in order to determine quantity of intake. No fewer than two servings of each food item were provided. Participants were not allowed to take any food or beverage items home at the end of the study day. A food inventory was taken immediately following the conclusion of each study day to verify consumption.

Prior to the study, a focus group of 14 participants recruited in the same manner as the study participants sampled 49 different food items, which they rated as 'highly acceptable,' 'acceptable,' and 'not acceptable.' Food and beverage items that were consumed on a daily and/or weekly basis, that were rated as 'acceptable' or 'highly acceptable' by the focus group, that had a relatively stable shelf life, and that were consistently available in local stores were used in the study. Food selection and intake is influenced, in part, by sensory factors such as taste, sight, smell, and texture (Rolls, 1985; Rolls, Rowe, & Rolls, 1982; Rolls, Hertherington, & Burley, 1988); therefore, the food items selected for the study varied in macronutrient content, flavor (e.g. sweet, salty, etc...), color, aroma, and texture (soft, crunchy, solid, fluid). In addition, food items ranged from fresh to processed and were varied in the amount of preparation required for consumption (i.e. ready to eat to requiring preparation). A variety of food items was provided to insure that all participants would have a choice of palatable food items. Table 1 presents a list of the food and beverage items available during the study. All food items were individually wrapped in single serving sizes.

Standard day and work tasks

Every participant completed 11 sessions, each separated by a minimum of 48 h. Sessions were conducted under

Table 1
Study foods and beverage items

Food and beverages	
Assorted hot and cold cereals	Assorted hard and soft cheeses ^a
Blueberry and banana nut muffins	Fruit flavored yogurt
Plain bagel	Klondike ice cream bar
Wheat and white bread	Popsicles
Popcorn	Assorted frozen meals ^a
Crackers-sandwich, club, saltines	Assorted soups
Assorted Nutri Grain bars	Chili
Animal crackers	Assorted cookies ^a
Potato chips	Chocolate bars ^a
Pretzels	Bottled water
Doritos	Orange and apple juices
Fresh, dried, and canned fruit	Milk ^a
Carrots, tomatoes, lettuce	Assorted decaffeinated cold soft drinks
Peanuts and peanut butter	Decaffeinated coffee and tea
Assorted sandwich meats—Turkey, Ham ^a , and Salami	Various condiments—mayonnaise ^a , mustard, salad dressings ^a , jelly

^a Both regular and low fat versions available.

isolated conditions in order to eliminate the influence of social factors on eating. Participants arrived at 8:00 a.m. after abstaining from food or calorie containing beverages for 10 h (i.e. since 10:00 p.m. the previous night) and alcohol for 12 h (i.e. since 8:00 p.m. the previous night). Each morning participants were weighed and urine and breath samples were tested for use of alcohol, nicotine, cocaine, benzodiazepines, amphetamine, opiates, THC, and barbiturates. Female urine samples were tested to ensure participants were not pregnant. Participants were also asked to complete a pre-session form consisting of a variety of questions regarding recent food and beverage consumption, drug and alcohol use, duration of sleep, and illness symptoms. One question on this form asked, 'Have you experienced any unusual feelings since the last session?' and another inquired, 'Has anything significant happened to you since your last session?' Participants reported perceived side effects under these questions and described them in further detail verbally.

A low fiber, low fat meal was served at 8:15 a.m., 45 min prior to oral drug administration. This meal provided 310 kcal (66% carbohydrate, 22% fat, and 12% protein) and 2.9 g of dietary fiber. A small meal after an overnight fast provided some energy and gastrointestinal standardization prior to drug administration but was not large enough to inhibit intake during the test day. Participants were given 15 min to consume breakfast in its entirety.

A brief (15 min) performance battery was presented 30 min prior to drug administration, and 0.5, 1, 2, 3, 4, and 5 h following drug administration. The computerized performance battery included subjective, psychomotor, and cognitive tests. Data from the subjective, psychomotor,

and cognitive tests will be presented elsewhere. A single heart rate and blood pressure measurement were taken immediately after each performance testing interval. Dose administration occurred at 9:00 a.m. After completing the 0.5 h session, the lights in the kitchenette were turned on indicating that participants were free to enter the kitchen and consume food and beverage from that time forward. Forty-five minutes of free time separated successive performance testing intervals. During this period, study participants were free to watch television, read, listen to music, or eat. Participants were paid and discharged after completing a post-session drug evaluation indicating the absence of residual behavioral effects of the drugs.

Medications

The appetite suppressing effects of amphetamine have been firmly established. For example, Foltin et al. demonstrated that 0.14 mg/kg produces appetite suppression in humans (Foltin, Kelly, & Fischman, 1990). This dose (0.14 mg/kg) has been used extensively in behavioral studies with humans and is well tolerated. Due to the absence of published literature relating to the effects of modafinil on food intake in humans at the time of study design, determining equivalence based on appetite effects was not possible. Several studies comparing the effects of modafinil and amphetamine on wakefulness have been published (Shelton et al., 1995; Lin et al., 1992; Rambert et al., 1990; Saletu et al., 1989; Touret, Sallanon-Moulin, & Jouvet, 1995), so potency equivalents were determined by comparing the effects of modafinil and amphetamine on wakefulness, rather than appetite. Based on these studies, the dose of modafinil that produced quantitatively similar effects on wakefulness to 0.14 mg/kg of amphetamine was determined (7.0 mg/kg modafinil). The dose of modafinil that produces the desired therapeutic effect with minimal adverse effect (i.e. the recommended daily dose) is 200 mg. The doses of modafinil used in this study have been used in other clinical studies, and no significant adverse effects associated with these doses have been reported.

Oral doses of placebo, modafinil (1.75, 3.5, 7.0 mg/kg), and *d*-amphetamine (0.035, 0.07, 0.14 mg/kg) were administered under double blind conditions. All doses were administered on a separate session and placebo sessions were interspersed between medication doses on five separate occasions, for a total of 11 sessions. The medications were administered in random order; however, on the first day, all study participants received placebo. Data from this session were recorded but not analyzed.

Food intake assessment and analysis

Medications can alter patterns of eating, modify food choice, vary energy intake, and impact subjective feelings of hunger (Rogers & Blundell, 1979). The topography of eating was evaluated by monitoring eating patterns such as

latency to eat, eating duration, number of mouthfuls, overall loading rate, frequency of intake, and number and length of pauses per eating occasion. Table 2 presents the definitions of eating measures examined in this study. These measures were evaluated using objective criteria through analysis of eating behavior on videotape by two different raters blind to drug conditions. Similar video-recording techniques and assessment strategies have been employed successfully in previous studies (Hill, Rogers, & Blundell, 1995; Martin & Bateson, 1993). Raters were trained through written and oral instruction to identify relevant measures and accurately record data prior to the study. Reliability was determined throughout the study by correlating measures of eating topography over time on randomly chosen videotaped sessions coded separately by independent observers. Correlation coefficients were never less than 0.8 throughout the study.

Table 2
Definitions of eating measures

Measure	Definition
Snack	A food item or eating occasion that does not require preparation
Meal	A food item or eating occasion that requires preparation of at least one food item
Eating occasion/episode	Any occurrence (snack or meal) in which a food item is consumed, separated by 10 min or longer
Mouthful	Occasion that food or beverage enters the mouth
Eating bout	Amount of time chewing each mouthful
Pause	Interval of time between eating bouts that is less than 10 min
Long pause	Pause greater than 30 s and less than 10 min
Latency to eat	Interval of time between the end of one eating occasion and the beginning of the next eating occasion
Eating occasion duration	Duration of time from the beginning of the first eating bout to the last eating bout
Time spent eating	Duration of eating occasion minus time not eating
Frequency of eating occasions	Total number of times an individual consumes a food item during the study session
Chews per mouthful	The number of times the jaw moves from a downward to upward position per mouthful
Overall loading rate	Mouthfuls/eating occasion duration
Local eating rate	Mouthfuls/time spent eating
Overall chewing rate	Chews/eating occasion duration
Local chewing rate	Chews/time spent eating
Time in kitchen	Amount of time spent in the kitchen selecting, preparing, or waiting for food to be ready
Time spent selecting food	Amount of time looking at food items or menus and selecting food items
Time spent preparing food	Amount of time spent combining ingredients and microwaving food items

The Nutritionist V Diet Analysis Program (First Data Bank) was used to analyze energy and macronutrient intake. This computer software program contains nutrient information on a wide variety of foods. Nutrient information that was not contained in the software program was obtained from food labels and added into the database. Based on known serving sizes and measurements of unconsumed food, the amount of food eaten, and its associated energy content and macronutrient composition, could be determined.

Statistical analysis

Statistical analysis was performed using the SAS V6.2 (Macintosh) program. Analysis of food data resulted in multiple outcome measures reflecting a single value for each session (e.g. total energy intake, macronutrient intake, measures of eating topography). These data were analyzed using repeated measures analysis of variance (ANOVA), with dose as a within-subject factor. Data from multiple placebo sessions (excluding session 1) were pooled to obtain a single placebo value. If results of the overall ANOVA were significant (i.e. $p < 0.05$), follow-up testing of the main effect of drug was conducted using the Tukey A procedure.

Cardiovascular outcome measures were obtained repeatedly at scheduled times during each session. These data were analyzed using repeated-measures ANOVA, with dose and time as within-subject factors. Significant main effects (i.e. $p < 0.05$) were analyzed using the Tukey A procedure. Significant interactions (i.e. dose by time interactions) were analyzed using a simple effects model. Heart rate and blood pressure were collected at two separate occasions prior to drug administration. These data were pooled to obtain a single baseline (i.e. pre-drug) measure.

Measures collected continuously over time (i.e. energy intake) were pooled into 1-hour bins and analyzed similarly to the above measures using a 2-way repeated measure ANOVA with dose and time as within-subject factors.

Results

Characteristics of participants

Five healthy adult nonsmoking males (one Caucasian, three Hispanic, one African-American) and six healthy adult nonsmoking females (three Caucasian, one Pacific Islander, one Asian/Native American, one Asian/Caucasian) between the ages of 21 and 35 (26.3 ± 1.4) recruited from the local community completed the study. All participants had completed a minimum of 14 years of education. Participants reported occasional alcohol (1.0 ± 0.3 occasions per month) and caffeine use (35 ± 10.6 , 8-oz servings of caffeinated beverages per month), but denied smoking cigarettes or the use of marijuana, cocaine, or amphetamine during the month prior to the study. Mean Body Mass Index

(BMI) was 26.2 ± 0.6 . All study participants remained within ± 2 kg of their baseline weight during the study, and no systematic changes in body weight were observed. Scores for dietary restraint and for each subscale of the Eating Disorders Inventory (i.e. Drive for Thinness, Body Dissatisfaction, Bulimia, Perfectionism, Interpersonal Distrust) were within normal limits for all participants.

Food and beverage intake

Both modafinil ($F(3, 30) = 4.49$, $p < 0.01$) and amphetamine ($F(3, 30) = 6.32$, $p < 0.002$) significantly reduced energy intake (Fig. 1). Intake at the moderate dose of modafinil was significantly lower than placebo ($p < 0.05$) and intake at the high dose of amphetamine was significantly less than placebo ($p < 0.05$). Compared to placebo, modafinil produced a 31% percent reduction in kilocalories and amphetamine decreased energy intake by 37% percent. Caloric intake was also analyzed as a function of time. A significant dose by time interaction was not observed.

Reductions in kilocalories following administration of modafinil and amphetamine primarily reflect decreases in intake of solid food items. Under placebo conditions, 87% of total energy intake was derived from solid food. Significant reductions in energy intake from solid food items were observed following both modafinil ($F(3, 30) = 3.54$, $p < 0.03$) and amphetamine ($F(3, 30) = 6.56$, $p < 0.002$) administration. Intake at the moderate dose of modafinil and the high dose of amphetamine was

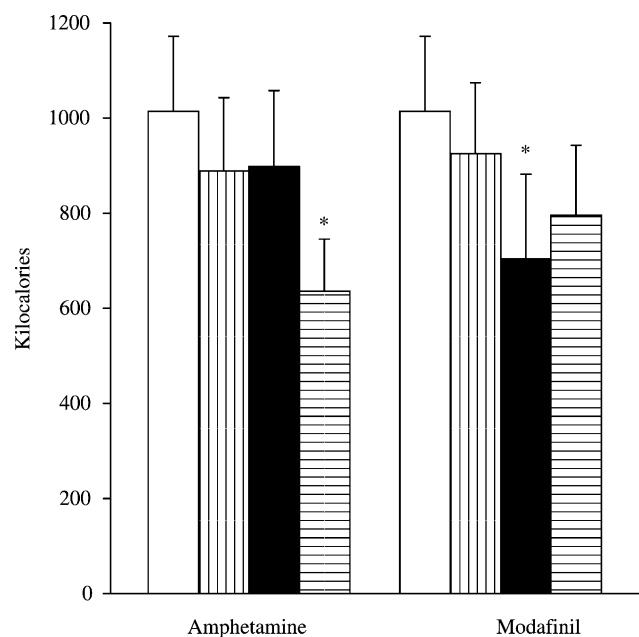


Fig. 1. Mean daily caloric intake from food and beverage items as a function of placebo (□) and low (▨), moderate (■) and high (▩) doses of amphetamine or modafinil. Values for placebo sessions are presented twice for ease of comparison. Error bars represent one SEM. Asterisks identify significant decreases relative to placebo.

significantly ($p < 0.05$) different from placebo. Although alterations in energy intake from beverages were observed, these changes were not statistically significant.

Modafinil significantly reduced intake of carbohydrate ($F(3, 30) = 5.26$, $p < 0.01$) (Fig. 2). Carbohydrate intake at the moderate dose of modafinil was significantly ($p < 0.05$) lower than at placebo. Although decreases in protein and fat were also observed following the moderate dose of modafinil, these effects were not significant. Similar to modafinil, decreases in macronutrient intake were observed following administration of amphetamine (Fig. 2). However, in contrast to modafinil, amphetamine significantly reduced intake of all three macronutrients (protein [$F(3, 27) = 3.79$, $p < 0.03$], carbohydrate [$F(3, 30) = 4.38$, $p < 0.02$], and fat [$F(3, 27) = 5.59$, $p < 0.005$]). Intake of each macronutrient following the high dose of amphetamine was significantly ($p < 0.05$) less than placebo. Although gram intake of macronutrients was reduced by both modafinil and amphetamine, the relative contribution of each macronutrient to total kilocalories (i.e. percent energy) was not significantly altered by either drug. Percent energy could not be calculated for one female participant who did not consume food, only water, following the moderate dose of modafinil and the moderate and high doses of amphetamine.

Both modafinil ($F(3, 30) = 4.89$, $p < 0.01$) and amphetamine ($F(3, 30) = 3.26$, $p < 0.05$) significantly reduced the weight of food consumed (Fig. 3). Intake at the moderate and high doses of modafinil was significantly ($p < 0.05$) lower than placebo. Intake at the high dose of amphetamine was significantly ($p < 0.05$) lower than intake at placebo.

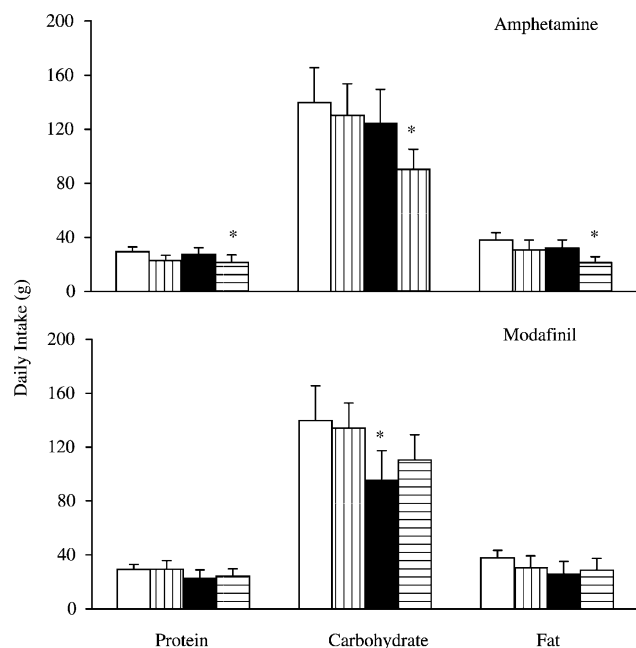


Fig. 2. Mean daily macronutrient intake from food and beverage items as a function of placebo (□), low (▨), moderate (■), and high dose (▩) of amphetamine and modafinil (as in Fig. 1). Error bars represent one SEM. Asterisks identify significant decreases compared to placebo.

Weight of beverage intake slightly decreased following administration of both medications; however, these effects were not statistically significant. Daily weight of food and beverage intake (grams) combined was not significantly altered following administration of modafinil and amphetamine.

Food waste was also examined. In general, participants consumed most of the food and beverage items that they selected (i.e., little food was discarded). On average, 66.1 ± 23.7 g of food and beverage were leftover per day under placebo conditions. Seventy percent of this weight was due to leftover beverage. Administration of modafinil or amphetamine did not significantly alter the amount of food and beverage that was left over each day.

Eating measures and behaviors

Compared to placebo, neither modafinil nor amphetamine significantly altered the frequency of eating occasions, latency to the first eating occasion, mean latency, eating occasion duration, time spent eating, time spent pausing, overall loading rate, local eating rate, overall chewing rate, or local chewing rate. In addition, neither medication significantly altered the time spent in the kitchen, time spent selecting food and beverage, or total preparation time; however, the reduction in the time spent in the kitchen following administration of modafinil approached significance ($p < 0.09$). Modafinil significantly reduced the number of mouthfuls ($F(3, 30) = 3.83$, $p < 0.03$) and the number of chews taken ($F(3, 30) = 5.39$, $p < 0.005$) and amphetamine significantly decreased the number of chews

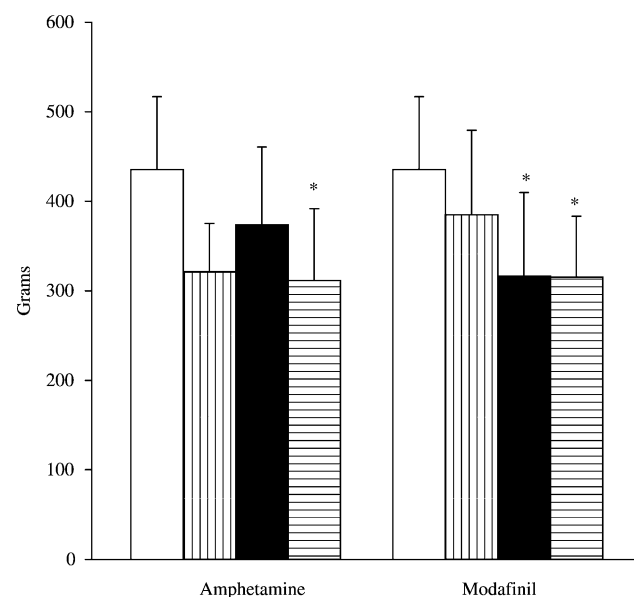


Fig. 3. Mean daily gram intake from food items as a function of placebo (□), low (▨), moderate (■), and high dose (▩) of amphetamine and modafinil (as in Fig. 1). Values for placebo sessions are presented twice for ease of comparison. Error bars represent one SEM; asterisks identify significant decreases compared to placebo.

taken ($F(3, 30) = 3.85, p < 0.02$). More specifically, the total number of mouthfuls following the high dose of modafinil was significantly ($p < 0.05$) lower than that of placebo. The number of mouthfuls taken per day was reduced following administration of amphetamine, but this effect only approached significance ($p < 0.08$). The total number of chews following the high doses of modafinil and amphetamine were significantly ($p < 0.05$) lower than the number of chews following placebo administration. The number of chews following the high dose of modafinil was also significantly ($p < 0.05$) lower than the number of chews following the low dose of modafinil.

Cardiovascular effects

Compared to placebo, both amphetamine and modafinil increased cardiovascular measures. Both amphetamine ($F(3, 30) = 5.89, p < 0.004$) and modafinil ($F(3, 30) = 14.9, p < 0.0001$) significantly increased heart rate (Fig. 4). Heart rate following the high dose of amphetamine was significantly ($p < 0.05$) higher than heart rate at placebo. Likewise, heart rate following the high dose of modafinil was significantly ($p < 0.05$) higher than heart rate at placebo. Drug effects on cardiovascular parameters were also analyzed as a function of time. A significant dose by time interaction was observed following administration of

amphetamine ($F(21, 210) = 2.44, p < 0.001$) and modafinil ($F(21, 210) = 3.05, p < 0.0001$). Simple effects analysis of the amphetamine by time interaction indicated significant dose effects 2, 3, 4, 5, and 6 h post-dose ($p < 0.05$) and significant time effects at all dose levels ($p < 0.05$). Significant modafinil dose effects were observed 0.5, 1, 2, 3, 4, 5, and 6 h post-dose ($p < 0.05$), and like amphetamine, significant time effects were observed at all dose levels ($p < 0.05$).

Both amphetamine ($F(3, 30) = 11.2, p < 0.0001$) and modafinil ($F(3, 30) = 19.1, p < 0.0001$) significantly increased systolic pressure. Systolic pressure following the high dose of amphetamine (133.6 ± 1.1 mm Hg) was significantly ($p < 0.05$) higher than systolic pressure at placebo (128.2 ± 1.0 mm Hg). Systolic pressure following the high dose of modafinil (136.7 ± 1.2 mm Hg) was significantly ($p < 0.05$) higher than systolic pressure at placebo (128.2 ± 1.0 mm Hg). A significant dose by time interaction was observed following administration of modafinil ($F(21, 210) = 2.90, p < 0.0001$) but not amphetamine. Simple effects analysis of the modafinil by time interaction indicated significant dose effects 0.5, 1, 2, 3, 4, 5, and 6 h post-dose ($p < 0.05$) and significant time effects at all dose levels ($p < 0.05$).

Both amphetamine ($F(3, 30) = 9.58, p < 0.0002$) and modafinil ($F(3, 30) = 19.5, p < 0.0001$) significantly increased diastolic pressure. Diastolic pressure at the high dose of amphetamine (75.3 ± 0.8 mm Hg) was significantly ($p < 0.05$) higher than diastolic pressure at placebo (71.4 ± 0.7 mm Hg). Similarly, diastolic pressure at the high dose of modafinil (77.2 ± 0.8 mm Hg) was significantly ($p < 0.05$) higher than diastolic pressure at placebo (71.4 ± 0.7 mm Hg). In addition, diastolic pressure at the moderate dose (73.5 ± 0.8 mm Hg) was significantly ($p < 0.05$) higher than diastolic pressure at placebo (71.4 ± 0.7 mm Hg) but significantly lower than that of the high dose (77.2 ± 0.8 mm Hg). Like systolic pressure, a dose by time interaction was observed following administration of modafinil ($F(21, 210) = 2.12, p < 0.005$) but not amphetamine. Simple effects analysis of the modafinil by time interaction indicated significant dose effects 0.5, 1, 2, 3, 4, 5, and 6 h post-dose ($p < 0.05$) and significant time effects at all dose levels ($p < 0.05$).

Profile of side effects

Only written responses to the questions on the pre-session form are described below since they were solicited systematically and were not influenced by staff comments or follow-up questions. Based on participant written statements, two males and three females reported side effects following administration of modafinil but not following administration of amphetamine. Unusual feelings or significant occurrences reported following administration of modafinil were 'head-ache,' 'hyped up/could run a marathon,' 'restless,' 'could not sleep,' 'extreme anxiety and sleeplessness,' and 'sick in my

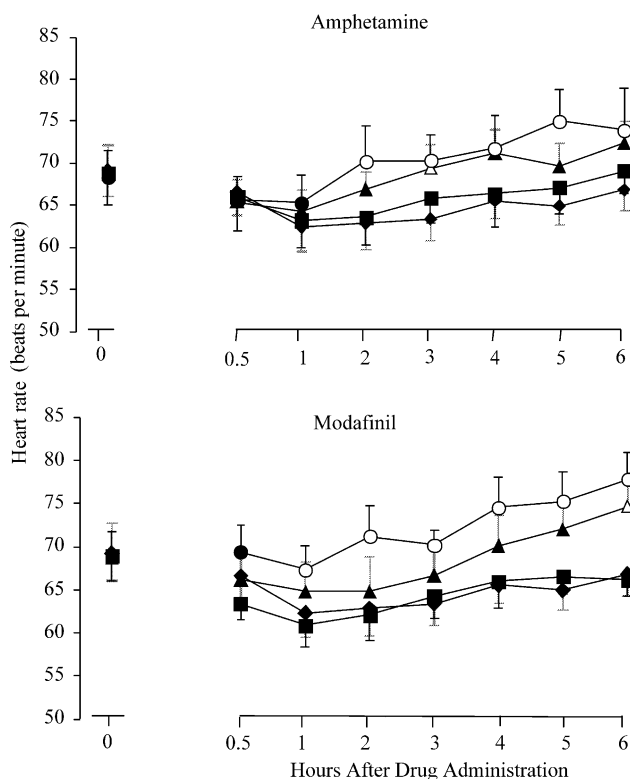


Fig. 4. Mean heart rate (beats per minute) as a function of placebo (◆), low (■), moderate (▲) and high (●) dose of amphetamine or modafinil. Error bars represent one SEM; open symbols identify significant changes compared to placebo.

stomach.' These effects occurred only after the high dose of modafinil and during the late afternoon and/or evening hours while participants were away from the laboratory. Although participants were advised during training to notify the staff if they had any concerns during the study sessions, no clear adverse events were spontaneously reported.

Discussion

Findings from this study suggest that modafinil, like amphetamine, reduces the amount of food consumed and decreases energy intake, without altering the proportion of macronutrients consumed. The findings also indicate that neither medication substantially alters the topography of eating behavior. Although both medications significantly increased heart rate and blood pressure at higher doses, the dose of modafinil that was efficacious in decreasing food intake did not significantly increase heart rate.

Participants in this study had free access to food across the day. They had the opportunity to select, prepare, and consume food and beverages between scheduled work sessions, which is similar to daily routines occurring in a free-living environment. In this setting, acute administration of the moderate dose (3.5 or 245.0 mg/70 kg) of modafinil produced significant decreases in total energy intake. Energy intake was decreased by approximately 31% or 311 kcal within a six-hour time frame. Only one other study has reported the effects of modafinil on energy intake; however, unlike the present study, this study measured energy intake during a single meal (Jasinski, 2000). Jasinski observed that morning (9:00 a.m.) administration of 200, 400, and 800 mg of modafinil decreased energy intake in humans at the noon meal, with the greatest decrease occurring after the highest dose of modafinil, which is two times the maximum therapeutic dose (Jasinski, 2000). The 200, 400, and 800 mg doses of modafinil decreased energy intake by approximately 10, 20, and 60%, respectively. The decrease in caloric intake at the 400 mg dose was similar to the decrease (i.e. 22% decrease) observed following the high dose (7.0 or 490 mg/70 kg) in the present study. Unlike the Jasinski study, a dose-dependent decrease in food intake was not observed in this study. The reason for the discrepancy between results is unclear. However, the effects on food intake in the present study are similar to those observed in an animal study evaluating the effects of modafinil on feeding (i.e. significant decreases in feeding at moderate doses and a non-significant decrease in feeding at the highest dose) (Nicolaidis & Saint Hilaire, 1993).

As expected, amphetamine reduced caloric intake. Acute administration of the high dose (0.14 mg/kg or 9.8 mg/70 kg) of amphetamine produced significant decreases in total caloric intake. Caloric intake was decreased by approximately 37% or 379 kcal within a six-hour time frame. These findings are similar to findings in other studies conducted on humans. Foltin et al. (1990)

observed a 30% decrease in 24-hour intake following administration of 10 mg/70 kg of amphetamine, bid (Foltin et al., 1990). Like the present study, participants had free access to food and beverage. In another study in which participants were presented with planned lunches, 24-hour caloric intake was decreased by a similar amount, 24–30%, following administration of 10–30 mg/70 kg of amphetamine (Foltin, Kelly, & Fischman, 1995).

Food and beverages contributed to total energy intake; however, food items supplied the majority of the calories consumed. Significant reductions in energy intake from food items were observed following the moderate dose of modafinil but not from beverages. As with modafinil, significant reductions in caloric intake from food items were observed following the high dose of amphetamine but not from beverages. One possible explanation is that these medications produce their effects by altering mechanisms that affect hunger rather than those that affect thirst. It is likely that the intake of soft drinks, fruit juice, and milk (i.e. beverages available in the present study) most likely occurred in response to thirst rather than hunger. Studies suggest that energy containing beverages produce weaker reductions in hunger than solid foods or viscous substances (Mattes & Rothacker, 2001; DiMeglio & Mattes, 2000). If so, a hunger-suppressing medication would likely have a greater effect on the intake of solid foods than beverages.

This is the first study to evaluate the effects of modafinil on macronutrient intake. A significant reduction in the amount of carbohydrate consumed from foods and beverages was observed; however, this decrease did not significantly alter the overall proportion of macronutrients consumed. Therefore, results from this study do not suggest that modafinil selectively alters macronutrient intake. A general trend toward an increase in the proportion of carbohydrate and protein and a decrease in the proportion of fat consumed following administration of modafinil was observed. This trend is similar to another observed in a study evaluating the effects of amphetamine on macronutrient intake in humans who self-selected lunch (Foltin et al., 1995). Similarly, these researchers observed an increase in the proportion of carbohydrate and a decrease in the proportion of fat to total caloric intake (percent energy) following administration of 30 mg/70 kg of amphetamine. However, unlike the present study, a decrease in the proportion of protein was also observed. In the same study, smaller doses (10 mg/70 kg and 20 mg/70 kg) of amphetamine administered failed to significantly alter selective macronutrient intake. Despite the decrease in intake of macronutrients from food and beverage, amphetamine did not significantly alter the overall proportion of macronutrients consumed in this study.

Nicolaidis & Saint Hilaire (1993) suggest that modafinil decreases food intake in rats by altering the frequency of eating, or more specifically, increasing meal-to-meal intervals, rather than by decreasing the size of meals (Nicolaidis & Saint Hilaire, 1993). Frequency of eating was

analyzed in this study by monitoring the number of eating occasions, snacks, and meals per day. Meal-to meal intervals were studied in terms of latency to the first eating occasion and average latency (i.e. the average interval of time between eating occasions) across the study day. Neither amphetamine nor modafinil significantly altered the frequency of eating, latency to the first eating occasion, or average latency. Frequency of eating occasions in the present study was reduced by 25% and latency to the first eating occasion was increased by 25% following the high dose of amphetamine; however, these findings were not statistically significant. Differences in findings between studies may be due to variance in study design (i.e. monitoring of food intake over a course of a few hours vs. 24 h intake). Increases in latency to the first meal and decreases in eating frequency following administration of adrenergic and serotonergic agents have been demonstrated in previous animals and human studies (Blundell et al., 1979; Blundell, Latham, Moniz, McArthur, & Rogers, 1987; Leibowitz et al., 1986; Wellman & Cockroft, 1989; Hill & Blundell, 1986).

The high doses of modafinil and amphetamine increased heart rate and blood pressure, but the magnitude of effects was relatively small. For example, compared to baseline measurements, heart rate increased by approximately 8 beat/min, reaching an apex of 78 beats/min, following the high dose of modafinil. A similar pattern was observed with blood pressure. The moderate dose of modafinil, which significantly reduced energy intake, increased cardiovascular measures to a lesser degree suggesting that it may have a safer profile of effects compared to amphetamine. These findings are comparable to the findings of previous studies, which report that modafinil produces fewer, if any, cardiovascular changes than stimulant drugs, is well tolerated, and produces a more desirable safety profile than stimulants. Significant increases in cardiovascular parameters generally occur following administration of doses greater than 400 mg (Jasinski & Kovacevic-Ristanovic, 2000; Rush et al., 2002; Caldwell, Caldwell, Smythe, & Hall, 2000; PDR, 2002). It should be noted that the moderate dose of modafinil (3.5 mg/kg) would be greater than 400 mg if administered to individuals weighing more than 115 kg.

The side effect profile of modafinil in this study was similar to those observed in previous studies, in which participants experienced headache, increased energy, insomnia, anxiety, and nausea (Billiard et al., 1994; Laffont et al., 1994; US Modafinil in Narcolepsy Multicenter Study Group, 1998, 2000). A low incidence of side effects at therapeutic doses have been reported, with higher doses (i.e. doses greater than 400 mg) producing more pronounced side effects (Lyons & French, 1991; Broughton et al., 1997; Buguet, Montmayeur, Pigeau, & Naitoh, 1995). Sensations of hyperactivity and insomnia were reported after the high dose of modafinil in this study. A reported benefit of modafinil over amphetamine is that doses between 100 and

300 mg (even bedtime doses) do not significantly alter the quality of sleep (Broughton et al., 1997; Arnulf, Homeyer, Garma, Whitelaw, & DerFenne 1997; Buguet, Moroz, & Radomski, 2003). Reports generated from this study suggest that this advantage does not persist when larger doses are administered as modafinil but not amphetamine yielded reports of insomnia. This study was not designed to carefully monitor side effects and these reports were generated from a small sample size; therefore, although they should not be ignored, these reports should be interpreted with caution.

Although this study was conducted in a controlled, laboratory environment and was designed to control confounding factors, limitations in study design emerged. Eleven individuals completed this study. Although adequately powered to evaluate the effects of these two medications on human food intake, a relatively small sample size was studied. Participants were varied in ethnic backgrounds, but most were recruited from university or college campuses. Furthermore, these medications were evaluated in healthy individuals, with normal or slightly elevated BMIs. Based on the findings of this study, the potential for modafinil to be used as a safe appetite suppressant is compelling; however, more studies need to be conducted using larger sample sizes, a more varied population, and with repeated exposure to modafinil in order to further examine its efficacy as a weight loss agent. Study participants had access to a variety of food and beverage items. Although individuals living in the United States are exposed to a variety of foods, they do not have free access to the wide range of food and beverage items in their homes or workplace. The novelty of the environment along with direct exposure to a large number of foods over several hours may have affected eating behavior. Although attempts were made to present participants with familiar foods and beverages, some foods and beverages may have been new to participants and in contrast, other typically consumed foods may not have been available. Finally, this study investigated the acute effects of modafinil on food intake and took place over the course of a few hours during the morning and afternoon. A more complete understanding of modafinil's effects on food consumption patterns and other behaviors would emerge if testing occurred over a longer duration of time. The effects of modafinil on food intake following chronic administration and steady state conditions would be an interesting area of future study.

The data generated from this study will expand the limited knowledge of the acute effects of modafinil on energy and macronutrient intake and topography of eating. These data may also contribute to the potential development of relatively safe and more effective weight loss agents that can be used in a number of clinical settings. Innovative interventions that address concerns about weight, minimize, or prevent weight gain play an important role in improving health conditions and halting the obesity epidemic.

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