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ORIGINAL INVESTIGATION

Craig R. Rush · Stephen T. Higgins · Andrea R. Vansickel · William W. Stoops · Joshua A. Lile · Paul E. A. Glaser

Methylphenidate increases cigarette smoking

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Abstract *Rationale:* Methylphenidate (Ritalin) and *d*-amphetamine (Dexedrine), stimulants commonly prescribed for behavioral problems associated with atttention deficit hyperactivity disorder (ADHD), produce a similar constellation of behavioral effects. The results of previous studies suggest that *d*-amphetamine increases rates of smoking and the reinforcing effects of smoking. The effects of methylphenidate on smoking have not been assessed although it is the most commonly prescribed pharmacotherapy for ADHD and individuals with ADHD are at increased risk for smoking. *Objective:* In this experiment the acute effects of a range of doses of methylphenidate (5, 10, 20, and 40 mg) and placebo were assessed in ten cigarette smokers who were not attempting to quit and were without ADHD or other Axis I psychiatric disorders. *Methods:* Each dose of methylphenidate was tested once, whereas placebo was tested twice. One hour after ingesting drug, participants were allowed to smoke ad libitum for 4 h. Measures of smoking included total cigarettes smoked, total puffs, latency to the first cigarette, and carbon monoxide levels. Snacks and decaffeinated drinks were available ad libitum, and caloric intake during the 4-h smoking session was calculated. *Results:* Methylphenidate dose dependently increased the total number of cigarettes smoked, number of puffs, and carbon monoxide levels. As expected, methylphenidate dose dependently decreased the number of food items consumed and caloric intake. *Conclusions:* The results of this experiment suggest that methylphenidate, like *d*-amphetamine, increases rates of cigarette smoking.

Keywords Methylphenidate · Smoking · ADHD · Subjective effects · Humans

Abbreviations ADHD: Attention Deficit Hyperactivity Disorder · ANOVA: analysis of variance · THC: Tetrahydrocannibinol · DVD: digital video disc · CO: carbon monoxide

C. R. Rush (✉) · A. R. Vansickel · W. W. Stoops · J. A. Lile
Department of Behavioral Science, College of Medicine,
University of Kentucky,
Lexington, KY, 40536, USA
e-mail: crush2@uky.edu

C. R. Rush · P. E. A. Glaser
Department of Psychiatry, College of Medicine,
University of Kentucky,
Lexington, KY, 40536, USA

C. R. Rush · A. R. Vansickel · W. W. Stoops
Department of Psychology, College of Arts and Science,
University of Kentucky,
Lexington, KY, 40536, USA

S. T. Higgins
Departments of Psychiatry and Psychology,
College of Medicine, University of Vermont,
Burlington, VT, 05401, USA

P. E. A. Glaser
Department of Anatomy and Neurobiology,
College of Medicine, University of Kentucky,
Lexington, KY, 40536, USA

P. E. A. Glaser
Department of Pediatrics, College of Medicine,
University of Kentucky,
Lexington, KY, 40536, USA

Introduction

Cigarette smoking is a significant public health concern and continues to be the leading cause of preventable death in the United States. In 2002, for example, more than 61 million or 26% of American adults (i.e., 12 years and older) reported recent (i.e., past month) use of tobacco cigarettes (National Survey on Drug Use and Health [NSDUH] 2002). Of the 61 million Americans that reported current cigarette use, nearly 39 million (i.e., 64%) reported daily smoking in the past month.

The societal costs of cigarette smoking are staggering. Cigarette smoking is associated with increases in a number of life-threatening diseases including cancer (e.g., bladder, cervix, esophagus, kidney, lung, oral cavity, pancreas, pharynx, and trachea), ischemic heart disease, and chronic

obstructive pulmonary disease (Center for Disease Control [CDC] 2003). Between 1995 and 1999, smoking resulted in approximately 440,000 premature deaths annually. Over 38,000 premature deaths from lung cancer and heart disease were attributed to exposure to second-hand smoke. Smoking during pregnancy resulted in the death of nearly 2,000 infants. On average, adult smokers lost nearly 14 years of life expectancy. Decreasing smoking would obviously result in a significant reduction in the loss of life and productivity.

Both biological (e.g., genetic) and psychosocial (e.g., socioeconomic status and population density) risk factors for smoking have been identified (e.g., Batra et al. 2003; Li 2003; Lu et al. 2001; Stellman and Resnicow 1997; Tyas and Pederson 1998; Tyndale 2003; Yoshimasu and Kiyohara 2003). Current or past psychiatric illness significantly increases the risk of smoking. Among respondents with no history of mental illness, a lifetime history, or a past-month history, current smoking rates were approximately 22, 35, and 41%, respectively (Lasser et al. 2000). Worth noting is that in this survey nearly every psychiatric diagnosis was associated with increased smoking rates.

Attention deficit hyperactivity disorder (ADHD) is the most commonly diagnosed childhood psychiatric disorder, occurring in 3–18% of school-age children (e.g., Rowland et al. 2002; Leung and Lemay 2003; Scahill and Schwab-Stone 2000; Szatmari 1992). ADHD, like other psychiatric disorders, is associated with increased rates of smoking (e.g., Lambert and Hartsough 1998; Milberger et al. 1997a,b; Pomerleau et al. 1995; Tercyak et al. 2002). In one survey, data were obtained from 218 ADHD and 182 non-ADHD adults (i.e., Lambert and Hartsough 1998). By 17 years of age, 46% of the ADHD adults reported smoking daily compared to 24% of the non-ADHD controls.

Stimulant medications (e.g., *d*-amphetamine and methylphenidate) are the most commonly prescribed pharmacotherapies for the treatment of ADHD (Reeves and Schweitzer 2004; Spencer et al. 2004). The results of at least three studies suggest that stimulant-treated ADHD patients may be at increased risk to smoke relative to their untreated counterparts (Biederman et al. 1999; Lambert 2002; Lambert and Hartsough 1998). In one study, for example, the effects of stimulant pharmacotherapy on substance use were examined in stimulant-treated (n=131) and untreated (n=268) ADHD patients that had been part of a 22-year longitudinal study (i.e., 6 to 28 years of age) (Lambert 2002). A significantly greater percentage of stimulant-treated patients reported regular smoking relative to untreated controls. Worth noting is that the results of a much smaller study suggest that medicated ADHD patients (n=11) smoked less than their untreated counterparts (n=16) (Whalen et al. 2003).

Results of laboratory studies examining the effects of stimulants on cigarette smoking demonstrate that these drugs increase smoking (Chait and Griffiths 1983; Cousins et al. 2001; Henningfield and Griffiths 1981; Schuster et al. 1979; Tidey et al. 2000). In the most recently published study, for example, the effects of *d*-amphetamine (0, 10 and 20 mg) were assessed on smoking (Cousins et al. 2001). *d*-Amphetamine dose dependently increased smoking as measured by number of cigarettes smoked during a 3-h ad libitum smoking session.

Even though methylphenidate is the most commonly prescribed stimulant for the treatment of ADHD (Drug Enforcement Administration [DEA] 2004), we are unaware of any published studies examining its acute effects on cigarette smoking. The purpose of the present experiment was to assess the effects of a range of doses of methylphenidate on smoking. Because methylphenidate and *d*-amphetamine produce a similar constellation of behavioral effects (e.g., Hoffman 2001; Rush et al. 1998, 2001; Stoops et al. 2004, 2005b), we hypothesized that methylphenidate, like *d*-amphetamine, would dose dependently increase smoking. The effects of methylphenidate on food and beverage intake after drug administration were also measured. Finally, drug effects were assessed using a battery of subject-rated drug-effect questionnaires and physiological indices.

Methods

Participants

Ten healthy adult cigarette smokers (five males, five females) were recruited via newspaper ads, flyers, and word of mouth to participate in this experiment. Potential participants had to meet the following inclusion criteria: (1) report smoking cigarettes daily, (2) not attempting to quit smoking, (3) score between 3 and 6 on the Fagerstrom Test for Nicotine Dependence (FTND) (Heatherton et al. 1991), (4) score <18 on the ADHD Rating Scale, (5) no significant medical or psychiatric disorders, other than nicotine dependence, (6) negative urine pregnancy test for females (Mainline Confirms human chorionic gonadotropin [HCG]), and (7) no medical contraindications to stimulant drugs. Participants were excluded if they had a history of ADHD or other Axis I psychiatric disorders. Participants were paid $40 per session to participate in this experiment and received an additional \$40 per session if they completed the experiment.

Participants completed questionnaires assessing drug use and medical and psychiatric histories, and provided written informed consent before participating. All participants were in good health with no contraindications to stimulant medications. Drug urine screens conducted during screening were negative for amphetamine, benzodiazepines, barbiturates, and cocaine (OnTrak Teststik, Lake Forest, CA, USA). Drug urine screens conducted during screening were positive for tetrahydrocannibinol (THC) for three participants, and one was positive for opioids for another participant before the conduct of the "practice" session. Participants were not allowed to begin the experiment proper until a drug-free specimen was obtained.

Participants ranged in age from 18 to 27 years (mean 22), and in weight from 57 to 95 kg (mean 75). These participants reported smoking 8 to 20 cigarettes per day (mean 14) and consuming 0 to 432 mg caffeine per day

(mean 106). Participants had completed 12 to 16 years of education (mean 14).

General procedures

The Institutional Review Board of the University of Kentucky Medical Center approved this study and the informed consent document. Participants enrolled as outpatients at the Laboratory of Human Behavioral Pharmacology at the University of Kentucky Medical Center Monday through Friday for six experimental sessions. Participants were informed that during their participation they would receive various drugs and these could include placebo and medications indicated for ADHD. Participants were told that the purpose of the study was to see how these drugs affect mood and behavior. Other than receiving this general information participants were blind to the type of drug administered and were given no instructions rearding what they were "supposed" to do or what outcomes might be expected.

Before initiating medication testing, participants completed one "practice" session, which was used to familiarize them with the drug-effect questionnaires and daily laboratory routine. No medications were administered on these days.

Participants were requested to refrain from using all illicit psychoactive drugs throughout the study, caffeine and solid food for 4 h before a scheduled experimental session, and alcohol for 12 h before a scheduled experimental session. On each experimental-session day, participants arrived at the laboratory and provided a urine sample before drug administration, which was screened for the presence of amphetamine, barbiturates, benzodiazepines, cocaine, opioids, and THC. Participants also provided an expired air specimen, which was assayed for the presence of alcohol using a hand-held breathalyzer (Intoximeters, Inc., St. Louis, MO). All expired air and urine specimens were negative.

Participants generally arrived at the Laboratory of Human Behavioral Pharmacology at approximately 0800 hours. Participants were instructed to abstain from smoking for 4 h before arriving at the laboratory. Immediately after arriving, participants provided an expired breath sample that was used to determine their carbon monoxide (CO) level. Carbon monoxide levels had to be <10 ppm for a volunteer to participate that day. If an acceptable carbon monoxide level could not be obtained within 1 h of arrival, the experimental session was cancelled and rescheduled. Between 0815 and 0830 hours, volunteers were allowed to smoke one cigarette of their preferred brand in order to reduce the possibility of testing the effects of methylphenidate during acute nicotine withdrawal. Between 0830 and 0845 hours, volunteers were provided a standard low-fat breakfast. At approximately 0845 hours, volunteers completed the drug-effect questionnaires. Between 0830 and 1000 hours, volunteers were alone in the experimental testing room, but they were not allowed to smoke. During this time, volunteers were allowed to engage in sedentary recreational activities (e.g., read, watch television), but they could not sleep.

Experimental medications were administered at 0900. At 1000, volunteers were provided with a pack of their preferred brand of cigarettes and an assortment of snacks and decaffeinated drinks. Subjects completed the self-reported drug-effect questionnaires 1, 2, 3, 4, and 5 h after drug administration. Heart rate, blood pressure, and carbon monoxide levels were recorded immediately before the participant completed the self-reported drug-effect questionnaires.

Smoking procedures

Participants were tested individually in a 3×3-m room that contained a lounge chair for the volunteer, a television and digital video disc player (DVD), a computer (iBook, Apple Computer, Inc., Cupertino, CA, USA) for completing the subject-rated drug-effect questionnaires, and an assortment of reading material. During each session, volunteers remained seated in the lounge chair. One hour after ingesting drug, participants were allowed to smoke ad libitum for 4 h.

Outcome measures used to assess smoking included total cigarettes smoked, total puffs, and latency to the first cigarette. All experimental sessions were digitally recorded. All smoking within each session was double scored from the digital recording by a primary and secondary observer, both of whom were blind to the dose conditions. Dividing the number of agreements between observers by the number of possible agreements and multiplying by 100 determined the interobserver reliability (Interobserver Reliability 2004). If the interobserver reliability was ≥85%, data from the primary observer were used for data analysis. If the interobserver reliability was <85%, the session was rescored by both observers. Interobserver reliabilities exceeded 98%.

Carbon monoxide levels were assayed from an expired breath sample using a handheld piCO meter (Smokerlyzer, Bedfont Scientific Ltd., Medford, NJ, USA). Carbon monoxide levels were recorded immediately when participants arrived at the Laboratory of Human Behavioral Pharmacology and 1, 2, 3, 4, and 5 h after drug administration. Carbon monoxide levels were recorded immediately before participants completed the subject-rated drug-effect questionnaires.

Food intake

Food and beverage intake after drug administration were measured to further characterize the behavioral effects of methylphenidate. An assortment of food items and decaffeinated beverages were available ad libitum during each experimental session. The available food items and beverages remained constant across all experimental sessions for each participant. Both the number of items consumed and the total caloric intake were determined. The number of items consumed was calculated at the end of each experimental session by counting the number of food pack-

ages and beverage containers opened by the volunteer. To calculate caloric intake, the available food items and beverages were weighed before being served. At the end of the session, if a food item or beverage was not completely consumed, it was reweighed and the proportion consumed was multiplied by the caloric content of the entire food item. If a food or beverage item was completely consumed, the caloric content for the entire item was recorded. The number of calories consumed for each food item and beverage was then summed to calculate the total caloric intake for the experimental session.

Subject-rated drug-effect questionnaires

Self-reported drug-effect questionnaires were administered on a computer. The self-reported drug-effect questionnaires were completed in fixed order. Unless otherwise noted, these questionnaires were completed approximately 30 min before drug administration and 1, 2, 3, 4, and 5 h after drug administration.

Cigarette rating scale Approximately 5 h after drug administration, volunteers completed a five-item cigarette rating scale. The items rated were the following: (1) Did you "ENJOY" your cigarettes more than usual during today's session? (2) Did you "CRAVE" cigarettes more than usual during today's session? (3) Did your cigarettes "TASTE" better than usual during today's session? (4) Did you "LIKE" your cigarettes more than usual during today's session? and 5) Did you get more "PLEASURE" from your cigarettes during today's session? Participants responded either yes or no to each of these questions (scored numerically as 1 or 0, respectively). Responses to individual items were then summed to produce a composite score.

Adjective-Rating Scale The Adjective-Rating Scale consisted of 32 items and contained two subscales: Sedative and Stimulant (Oliveto et al. 1992). Each subscale consisted of 16 adjectives. Volunteers responded to each item using the computer mouse to point to and select among one of five response options: not at all, a little bit, moderately, quite a bit, and extremely (scored numerically from 0 to 4, respectively). Responses to individual items were summed to produce a composite score for each subscale. The maximum possible score on each subscale was 64.

Drug-Effect Questionnaire A 20-item Drug-Effect Questionnaire that has been described previously was used in this experiment (Rush et al. 2003). Items were presented on a computer, one at a time. Participants rated each of the items using a 5-point scale similar to the one described above.

Physiological measures

Heart rate and blood pressure were recorded using an automated blood pressure monitor (DINAMAP XL, Johnson and Johnson, Alexandria, TX, USA). Heart rate and blood pressure were monitored for approximately 30 min before drug administration and 0.5, 1, 1.5, 2, 2.5, 3, 4, and 5 h after drug administration. Heart rate and blood pressure were recorded immediately before participants completed the subject-rated drug-effect questionnaires.

Drug administration

The drug conditions were placebo, 5, 10, 20, and 40 mg methylphenidate. Each active dose of methylphenidate was tested once, whereas placebo was tested twice. Doses were administered in mixed order with the exception that the highest dose was never administered during the first experimental session. All dose conditions were administered in a double-blind fashion. Commercially available drug (5 or 10 mg, methylphenidate, CelTech, Rochester, NY, USA) was overencapsulated in a size 0 capsule to prepare the doses. Cornstarch was used to fill the remainder of these capsules. Placebo capsules were prepared by filling a 0 capsule with cornstarch.

During each experimental session participants ingested four capsules. Administering the appropriate number of active and placebo capsules varied dose. Capsules were taken orally with approximately 150 ml of water. Drug administration procedures were designed to ensure that participants swallowed the capsules. To accomplish this, the research assistant (1) watched the participants to ensure that they swallowed the capsules and did not remove them from their mouths, (2) conducted a brief oral examination to ensure that the participants were not hiding the capsules under their tongues, and (3) spoke with the participants to determine if they had anything in their mouths. Drug doses were administered in mixed order, and at least 24 h separated all drug administrations.

Data analysis

Data were analyzed statistically as raw scores for all measures. Effects were considered significant for $p \leq 0.05$. For the placebo condition, data were averaged across the two sessions.

For measures of smoking and scores on the cigarette rating scale, data were analyzed by one-factor repeated measures ANOVA with dose (0, 5, 10, 20, and 40 mg methylphenidate) as the factor (StatView, SAS Institute Inc., Cary, NC, USA). If the effect of dose attained statistical significance, the mean square error term was used to conduct Fisher's protected least significance difference post hoc test to compare each of the active dose conditions to placebo. For carbon monoxide levels, peak effect (i.e., maximum level observed during the 4-h smok-

ing period) was calculated for each participant and analyzed in a similar fashion.

For the Adjective-Rating Scale, Drug-Effect Questionnaire, heart rate, and blood pressure, data were analyzed by two-factor, repeated measures ANOVA with dose (placebo and the four methylphenidate conditions) and time (predrug, 1, 2, 3, 4, and 5 h postdrug for the Adjective-Rating Scale and Drug-Effect Questionnaire; predrug, 0.5, 1, 1.5, 2, 2.5, 3, 4, and 5 h postdrug for heart rate and blood pressure) as factors. If the interaction of dose and time attained statistical significance, the mean square error term was used to conduct Fisher's protected least significance difference post hoc test comparing placebo with each of the drug conditions at each postdrug time point.

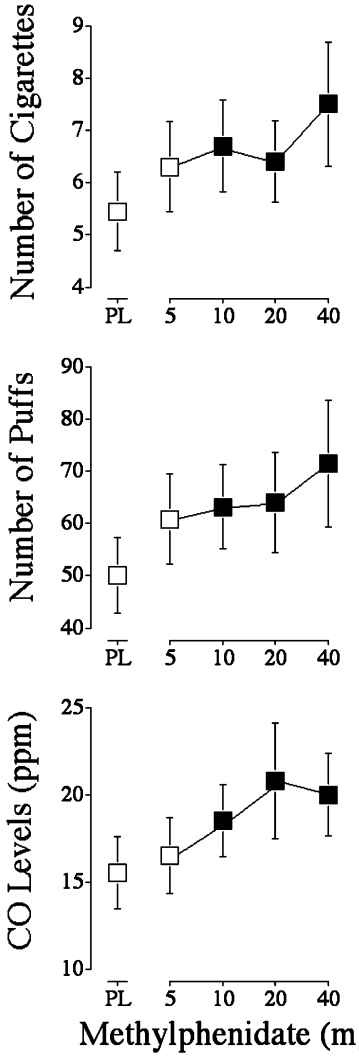

Fig. 1 Dose–response functions for number of cigarettes, number of puffs, and carbon monoxide (CO) levels. *x-axes*, methylphenidate dose in milligrams; *data points above PL* designate placebo values. *Data points* show means of ten subjects; *brackets* show ±1 SEM. *Filled symbols* indicate those values that are significantly different from the placebo value ($p \leq 0.05$, Fisher's protected least significant difference post hoc test)

Results

Smoking Methylphenidate increased the number of cigarettes smoked ($F_{4,36}=3.3$, $p<0.03$), number of puffs ($F_{4,36}=2.9$, $p<0.04$), and carbon monoxide levels ($F_{4,36}=3.3$, $p<0.03$) as an orderly function of dose. Post hoc analyses revealed that 10, 20, and 40 mg methylphenidate increased the number of cigarettes smoked, the number of puffs, and carbon monoxide levels significantly above placebo levels. Methylphenidate did not significantly alter the latency to the first cigarette. Figure 1 shows the dose-related effects of methylphenidate for number of cigarettes smoked, number of puffs, and carbon monoxide levels.

Food intake Methylphenidate decreased the number of items ($F_{4,36}=6.6$, $p<0.001$) and calories consumed ($F_{4,36}=8.2$, $p<0.001$) as an orderly function of dose (Fig. 2). Post hoc analyses revealed that all active doses of methylphenidate decreased the number of items consumed significantly below placebo levels, whereas 10, 20, and 40 mg methylphenidate significantly decreased the number of calories consumed.

Cigarette Rating Scale Methylphenidate dose dependently increased scores on the Cigarette Rating Scale ($F_{4,36}=10.5$, $p<0.001$; Fig. 3). Post hoc analyses revealed that only the highest dose of methylphenidate tested, 40 mg, increased these scores significantly above placebo levels.

Adjective-Rating Scale The interaction of dose and time failed to attain statistical significance on the Stimulant and

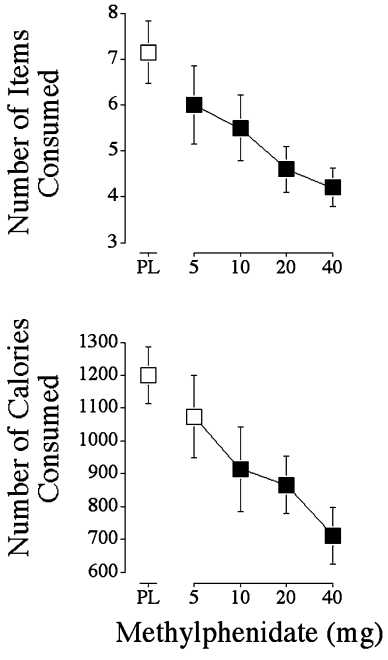

Fig. 2 Dose–response functions for number of items and calories consumed. *x-axes*, methylphenidate dose in milligrams; *data points above PL* designate placebo values. *Data points* show means of ten subjects; *brackets* show ±1 SEM. *Filled symbols* indicate those values that are significantly different from the placebo value ($p \leq 0.05$, Fisher's protected least significant difference post hoc test)

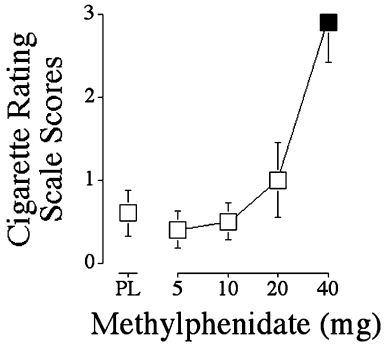

Fig. 3 Dose–response functions for scores on the Cigarette Rating Scale. *x-axes*, methylphenidate dose in milligrams; *data points above PL* designate placebo values. *Data points* show means of ten subjects; *brackets* show ±1 SEM. *Filled symbols* indicate those values that are significantly different from the placebo value ($p \leq 0.05$, Fisher's protected least significant difference post hoc test)

Sedative scales of the Adjective-Rating Scale. The main effect of dose attained statistical significance on the Stimulant scale ($F_{4,36}$=5.6, p<0.05).

Drug-Effect Questionnaire A significant interaction of Dose and Time was detected on eight items from the Drug-Effect Questionnaire: any effect, active/alert/energetic, bad effects, like drug, impairing performance, shaky/jittery, stimulated, and talkative/friendly ($F_{20,180}$ values >1.6, p<0.05). Figure 4 shows dose–response and time-action function for methylphenidate for subject ratings of Stimulated. This figure shows that methylphenidate increased these ratings as an orderly function of dose and time. The 10-, 20-, and 40-mg doses of methylphenidate generally increased these ratings significantly above placebo levels throughout the experimental session. The main effect of dose attained statistical significance on subject ratings of good effects, high, and improving performance ($F_{4,36}$ values >3.0, p<0.03).

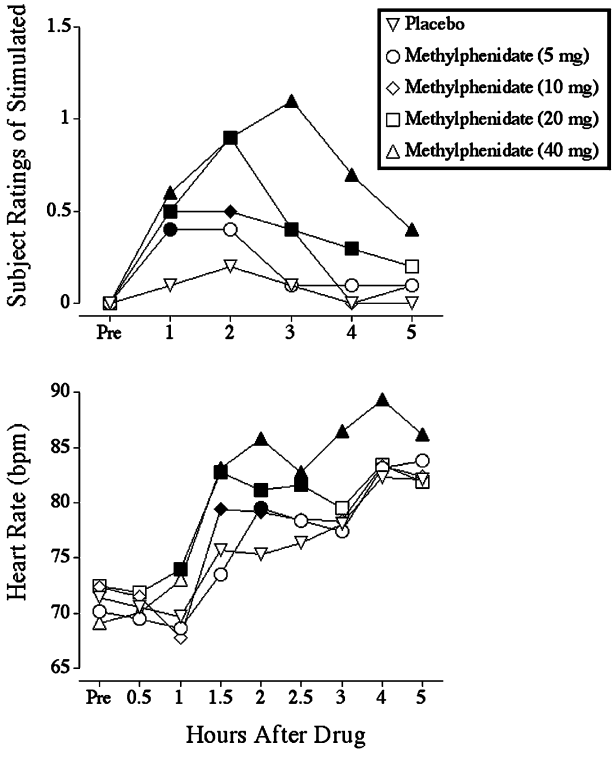

Fig. 4 Time course functions and dose effects for methylphenidate for subject ratings of Stimulated from the Drug-Effect Questionnaire and heart rate. *x-axes*, time after drug administration in hours. *Pre* indicates predrug. *Data points* show means of ten subjects. *Filled symbols* indicate those values that are significantly different from the corresponding placebo value at the same time point ($p \leq 0.05$, Fisher's protected least significant difference post hoc test). Standard error bars are omitted for clarity

Heart rate and blood pressure A significant interaction of dose and time was detected on heart rate, systolic pressure, and mean arterial pressure ($F_{32,288}$ values >1.5, p<0.05). Figure 4 shows dose–response and time-action functions for the effects of methylphenidate on heart rate. This figure shows that methylphenidate increased heart rate as an orderly function of dose and time. The 10, 20, and 40 mg doses of methylphenidate generally increased heart rate significantly above placebo levels throughout most of the experimental session. The main effect of dose attained statistical significance for diastolic pressure ($F_{4,36}$=5.7, p<0.002), whereas the interaction of dose and time approached statistical significance ($F_{32,288}$=1.4, p<0.07).

Discussion

In this experiment the acute effects of a range of doses of methylphenidate (5–40 mg) and placebo on smoking were examined in ten cigarette smokers who were not attempting to quit. To our knowledge, the acute effects of methylphenidate on smoking have not been reported. Methylphenidate dose dependently increased the total number of cigarettes smoked, number of puffs, and carbon monoxide levels. Methylphenidate also dose dependently decreased the number of food items consumed and caloric intake. Before volunteers were allowed to smoke (i.e., 1 h after drug administration), methylphenidate produced prototypical, stimulant-like, subject-rated drug effects (e.g., increased ratings of Stimulated on a Drug-Effect Questionnaire) and increased heart rate and blood pressure.

The finding that methylphenidate increased smoking is concordant with the results of previous laboratory studies in which the acute effects of *d*-amphetamine were assessed on smoking (e.g., Chait and Griffiths 1983; Cousins et al. 2001; Henningfield and Griffiths 1981; Schuster et al. 1979; Tidey et al. 2000). In the most recent study, the effects of *d*-amphetamine (0, 10, and 20 mg) were assessed on smoking (Cousins et al. 2001). *d*-Amphetamine dose dependently increased smoking as measured by number of cigarettes smoked during a 3-h ad libitum smoking session. The results of the present experiment extend the findings of these previous experiments by demonstrating that methylphenidate, the most commonly prescribed stimulant for ADHD, like *d*-amphetamine, increases smoking.

Future studies should directly compare the effects of a range of doses of methylphenidate and *d*-amphetamine

on smoking to determine the relative potency relationship. Previous research conducted in our laboratory has consistently demonstrated that across different behavioral arrangements (i.e., drug discrimination, drug self-administration, and subject-rated drug effects), *d*-amphetamine is approximately twice as potent as methylphenidate (Rush et al. 1998, 2001; Stoops et al. 2004, 2005b). Worth noting is that relative to placebo, 20 mg methylphenidate increased smoking by approximately 28% in the present experiment, whereas 20 mg *d*-amphetamine produced a 30% increase in a previous study (Cousins et al. 2001). This observation suggests that methylphenidate and *d*-amphetamine are approximately equipotent. Thus, potency relationship differences may exist between smoking and other behavioral measures for methylphenidate and *d*-amphetamine. More definitive conclusions regarding the relative potency relationship of methylphenidate and *d*-amphetamine on smoking would be possible if these drugs were compared in the same group of participants.

Neither the behavioral nor pharmacological mechanisms that mediate methylphenidate-induced increases in smoking can be gleaned from the present experiment. From a behavioral perspective, perhaps methylphenidate increased the reinforcing effects of smoking. The results of two previously published experiments suggest that *d*-amphetamine increases the reinforcing effects of smoking (Sigmon et al. 2003; Tidey et al. 2000). In the earlier study, *d*-amphetamine (0, 7.5, and 15 mg/70 kg) dose dependently increased choice of smoking (i.e., two puffs per choice) over money (i.e., \$0.25 per choice) (Tidey et al. 2000). In the more recent study, *d*-amphetamine (0, 7.5, and 15 mg/70 kg) increased the reinforcing efficacy of smoking, but not money, under a progressive-ratio procedure (Sigmon et al. 2003). Whether similar effects would be observed with methylphenidate is unknown.

From a pharmacological perspective, perhaps methylphenidate increased the reinforcing effects of nicotine. To the best of our knowledge, there are no published studies in which the reinforcing effects of nicotine were explicitly examined after stimulant pretreatment even though there is a large scientific literature supporting the role of nicotine reinforcement in smoking (e.g., Benowitz 1992, 1999; Henningfield 1984; National Institute on Drug Abuse [NIDA] 2002; Perkins 1999). Nicotine increases dopamine levels and this mechanism may in part mediate the reinforcing effects of smoking (Huston-Lyons et al. 1993). Methylphenidate also increases dopamine levels and this is likely the mechanism by which it exerts its behavioral and clinical effects (e.g., Gottlieb 2001; Kuczenski and Segal 1997; Volkow et al. 2001). Increases in smoking or the reinforcing effects of smoking or nicotine after stimulant pretreatment may be due to an additive or supra-additive effect of these drugs and nicotine on dopamine levels (Gerasimov et al. 2000).

Methylphenidate dose dependently decreased the number of food items consumed and caloric intake. The present findings are concordant with those from previous studies that assessed the effects of methylphenidate on caloric intake (e.g., Jasinski 2000; Leddy et al. 2004; Martin et al. 1971). In one study, methylphenidate (45 and 90 mg) dose dependently decreased caloric intake (Jasinski 2000). Relative to placebo, 45 mg methylphenidate decreased caloric intake by approximately 46%. In the present experiment, the highest methylphenidate dose tested, 40 mg, produced a comparable effect (i.e., decreased caloric intake by 41%). The results of the present experiment are consistent with the notion that dopaminergic mechanisms mediate energy intake and eating behavior (Berridge 1996; Leddy et al. 2004).

Methylphenidate produced prototypical stimulant-like subject-rated (e.g., increased ratings of Active–Alert–Energetic and Stimulated on a Drug-Effect Questionnaire) and physiological effects (i.e., increased heart rate and blood pressure). These findings are concordant with the results of several studies conducted in our laboratory that assessed the effects of similar doses of oral methylphenidate (e.g., Kollins et al. 1998; Rush and Baker 2001; Rush et al. 1998, 2001; Stoops et al. 2004, 2005a,b). The dose-related effects of methylphenidate were evident 1 h after drug administration when volunteers had not yet been allowed to smoke. Once volunteers were allowed to smoke, the subject-rated and physiological effects of methylphenidate were more pronounced. Because volunteers smoked varying amounts of different cigarettes, separating the combined effects of methylphenidate and nicotine on these measures is not possible. The time-action curves of methylphenidate on the physiological measures were reported to demonstrate that administering a stimulant and then allowing volunteers to smoke ad libitum did not result in a clinically significant increase in heart rate or blood pressure (e.g., heart rate did not exceed 90 bpm). These findings are concordant with the results of previous studies that demonstrated that ad libitum smoking is safe to study after the administration of stimulants (Cousins et al. 2001; Schuster et al. 1979).

The present finding that methylphenidate increases smoking may be important clinically because, as noted above, ADHD is associated with increased rates of smoking and methylphenidate is the most commonly prescribed pharmacotherapy for this disorder (Drug Enforcement Administration [DEA] 2004; Lambert and Hartsough 1998; Milberger et al. 1997a,b; Pomerleau et al. 1995; Tercyak et al. 2002). One caveat of the present study is that the acute effects of immediate-release methylphenidate were tested. Sustained-release formulations of methylphenidate are commonly used to manage the symptoms of ADHD, and, of course, it is administered chronically (e.g., Lage and Hwang 2004). The results of a previous study conducted in our laboratory suggest that the behavioral effects of immediate-release and sustained-release methylphenidate (20 and 40 mg) differ quantitatively (Kollins et al. 1998). Future studies should determine whether immediate- and sustained-release methylphenidate produce quantitatively different effects on measures of smoking and whether the increase observed in the present experiment also occurs under chronic dosing conditions.

Future studies should also determine whether novel compounds used to manage the symptoms of ADHD increase

smoking. Atomoxetine, bupropion, and modafinil are effective in the treatment of ADHD in children and adults (e.g., Michelson et al. 2002, 2003; Rugino and Copley 2001; Rugino and Samsock 2003; Simpson and Plosker 2004; Spencer et al. 2002; Taylor and Russo 2000). Bupropion is pharmacologically similar to *d*-amphetamine and methylphenidate, and increases smoking (Cousins et al. 2001; Heikkila and Manzino 1984; Javitch et al. 1984). Atomoxetine and modafinil are pharmacologically distinct from methylphenidate (e.g., Bymaster et al. 2002; Gehlert et al. 1995; Gottlieb 2001; Mignot et al. 1994). We are unaware of any published reports in which the effects of atomoxetine or modafinil on cigarette smoking were assessed. Determining whether other formulations of methylphenidate or novel compounds increase smoking could have important clinical implications for the safer treatment of patients with ADHD.

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