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Stimulant-induced changes in smoking and caloric intake: Influence of rate of onset

Andrea R. Vansickel [a,c], Megan M. Poole [c], William W. Stoops [a], Karolyn E. Hays [a], Margaret B. Upchurch [e], Paul E.A. Glaser [b,d], Craig R. Rush [a,b,c,*]

[a] Department of Behavioral Science, College of Medicine, University of Kentucky, Lexington, KY 40536, United States
[b] Department of Psychiatry, College of Medicine, University of Kentucky, Lexington, KY 40536, United States
[c] Department of Psychology, College of Arts and Science, University of Kentucky, Lexington, KY 40536, United States
[d] Department of Anatomy and Neurobiology, College of Medicine, University of Kentucky, Lexington, KY 40536, United States
[e] Department of Psychology, Transylvania University, Lexington, KY 40508, United States

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ABSTRACT

Rate-of-onset modulates the subject-rated effects of stimulants. Results of two studies from our laboratory demonstrate that immediate-release methylphenidate increases smoking and decreases caloric intake. Whether rate-of-onset influences the effects of methylphenidate on smoking and eating is unknown. The present experiment examined the influence of a range of doses of immediate- (7.5–30 mg) and sustained-release (18–72 mg) methylphenidate as well as placebo on smoking and eating. Eight cigarette smokers participated. A double-dummy drug administration procedure was used to maintain the double blind because immediate-release methylphenidate produces peak plasma concentrations 1.5–2 h and the sustained-release formulation produces peak plasma concentrations 6–8 h after oral administration. Smoking and eating were assessed for 4 h across the predicted peak effects of both methylphenidate formulations. Measures of smoking included total cigarettes, puffs, and carbon monoxide levels. Snacks and decaffeinated beverages were available *ad libitum* and caloric intake was monitored during the four-hour smoking session. Immediate- and sustained-release methylphenidate increased smoking and decreased caloric intake. The effects of methylphenidate generally did not vary as a function of formulation. The results of this study may have important implications for the treatment of disorders that require stimulant medications. Smoking should be monitored in patients that are prescribed stimulant medications, regardless of the formulation type.

1. Introduction

Rate-of-onset has been shown to modulate the behavioral effects of stimulants including methylphenidate and cocaine (Abreu et al., 2001; Kollins et al., 1998; Woolverton and Wang, 2004). In general, preparations that allow for drug effects to onset more slowly may have lower abuse potential than immediate-release formulations (Abreu et al., 2001; Jasinski and Krishnan, 2008; Kollins et al., 1998; Spencer et al., 2006; Woolverton and Wang, 2004). In one study, for example, 10 healthy adult participants were administered sustained-release (20 and 40 mg) and immediate-release (20 and 40 mg) methylphenidate on separate occasions (Kollins et al., 1998). Participants completed a battery of subject-rated drug-effect questionnaires and performance measures periodically for 6 h following medication administration. Immediate- but not sustained-release methylphenidate produced prototypical stimulant-like subject-rated effects. Both formulations increased heart rate and blood pressure.

Stimulants such as methylphenidate, amphetamine and cocaine increase cigarette smoking under controlled laboratory conditions (e.g. Chait and Griffiths, 1983; Cousins et al., 2001; Henningfield and Griffiths, 1981; Rush et al., 2005; Schuster et al., 1979; Tidey et al., 2000; Vansickel et al., 2007) and in the natural environment (Roll et al., 1997). Cigarette smoking is associated with significant morbidity and mortality and it is estimated that nearly 62 million people in the United States are current cigarette smokers and of those people, approximately 2.7 million smoke cigarettes and abuse stimulants (SAMHSA, 2007). The extent of smoking-related morbidity and mortality is directly related to the amount and duration of cigarette smoking (Streppel et al., 2007). Therefore, stimulant-induced increases in smoking could be a significant health risk for persons prescribed stimulants and for those who use stimulants recreationally.

Obesity is also a significant health problem in the United States. In 2006, approximately 34% of the US population age 20 or older was considered obese (defined as a Body Mass Index [BMI] >30) (Centers for Disease Control [CDC], 2007a). Obesity is associated with increased

* Corresponding author. Department of Behavioral Science, University of Kentucky, Medical Behavioral Science Building, Lexington, KY 40536-0086, United States. Tel.: +1 859 323 6130; fax: +1 859 257 7684.
E-mail address: crush2@email.uky.edu (C.R. Rush).

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risk of numerous health complications including cardiovascular disease, type II diabetes, liver disease and certain forms of cancer (Aronne and Isoldi, 2007; CDC, 2007b). The recommended intervention for overweight/obese individuals is diet and lifestyle change. However, in cases where diet and lifestyle changes do not lead to significant weight reduction, pharmacological interventions may be indicated (Aronne and Isoldi, 2007). Several stimulant medications have been used for the treatment of obesity because of their anorectic effects (reviewed in Weigle, 2003). Immediate-release formulations of methylphenidate, for example, decrease caloric intake when administered acutely (Jasinski, 2000; Leddy et al., 2004; Rush et al., 2005; Vansickel et al., 2007). Whether sustained-release formulations of methylphenidate would decrease caloric intake to the same extent as immediate-release preparations is unknown.

The purpose of the current experiment was to determine the effects of a range of doses of immediate-release (7.5, 15, and 30 mg) and sustained-release (18, 36, and 72 mg) methylphenidate as well as placebo on smoking and caloric intake. Eight cigarette smokers who were otherwise healthy participated. The doses of immediate- and sustained-release methylphenidate were chosen based on relative peak plasma concentrations (Modi et al., 2000). Outcome measures included cigarette smoking, caloric intake, cardiovascular indices, and subject-rated drug-effect questionnaires. We hypothesized that both immediate- and sustained-release methylphenidate would increase smoking and decrease caloric intake.

2. Methods

2.1. Participants

Eight healthy adult smokers (3 men, 5 women) completed this study. Potential participants had to meet the following inclusion criteria: 1) report smoking 10–20 cigarettes daily; 2) not attempting to quit smoking; 3) score <18 on an ADHD Rating Scale; 4) no significant medical or psychiatric disorders, other than nicotine dependence; 5) negative urine pregnancy test for females (Mainline Confirms Human Chorionic Gonadotropin [HCG]); and 6) no medical contraindications to stimulant drugs. Participants were excluded if they had a history of ADHD or other Axis I psychiatric disorders. Participants were compensated for their participation.

Participants were in good physical and psychiatric health and ranged in age from 19 to 33 years (mean = 22), body mass indices ranged from 19 to 31 (mean = 24) and participants had completed 13 to 16 years of education (mean = 14). One participant had a BMI of 31, however, the nurse and physician on this study considered this clinically insignificant because of her body build. Participants smoked 10 to 19 cigarettes/day (mean = 13). Cigarette nicotine contents of their preferred brands ranged from 0.7 to 1.2 mg (mean = 0.85 mg), expired carbon monoxide levels at screening ranged from 4 to 18 parts per million (ppm) (mean = 11 ppm) and scores on the Fagerstrom Test for Nicotine Dependence (FTND) ranged from 0 to 6 (mean = 2.75).

2.2. General procedures

The Institutional Review Board of the University of Kentucky Medical Center approved the conduct of this study and all volunteers gave their sober, written informed consent prior to enrolling. Participants enrolled as outpatients at the Laboratory of Human Behavioral Pharmacology at the University of Kentucky Medical Center and visited the lab Monday through Friday for eight experimental sessions. Participants completed one "practice" session to familiarize them with the drug-effect questionnaires and daily laboratory routine. Participants were required to abstain from illicit drug use throughout their participation, alcohol at least 12 h prior to participation and caffeine and cigarette smoking for at least 4 h prior to participation. In order to participate in an experimental session, participants had to provide an expired breath sample that was negative for alcohol, have a carbon monoxide reading of ≤10 ppm, provide a urine sample that was negative for amphetamine, benzodiazepines, barbiturates, cocaine and opiates and pass a field sobriety test.

With the exception of a double-dummy dosing procedure and extended session length, general procedures for this experiment were identical to those described previously (Rush et al., 2005; Vansickel et al., 2007). The session length was extended to 11 h in order to assess the effects of sustained- and immediate-release methylphenidate on smoking during their peak effects and the double-dummy dosing procedure was used to maintain the double blind (see Table 1 for the timeline of experimental sessions).

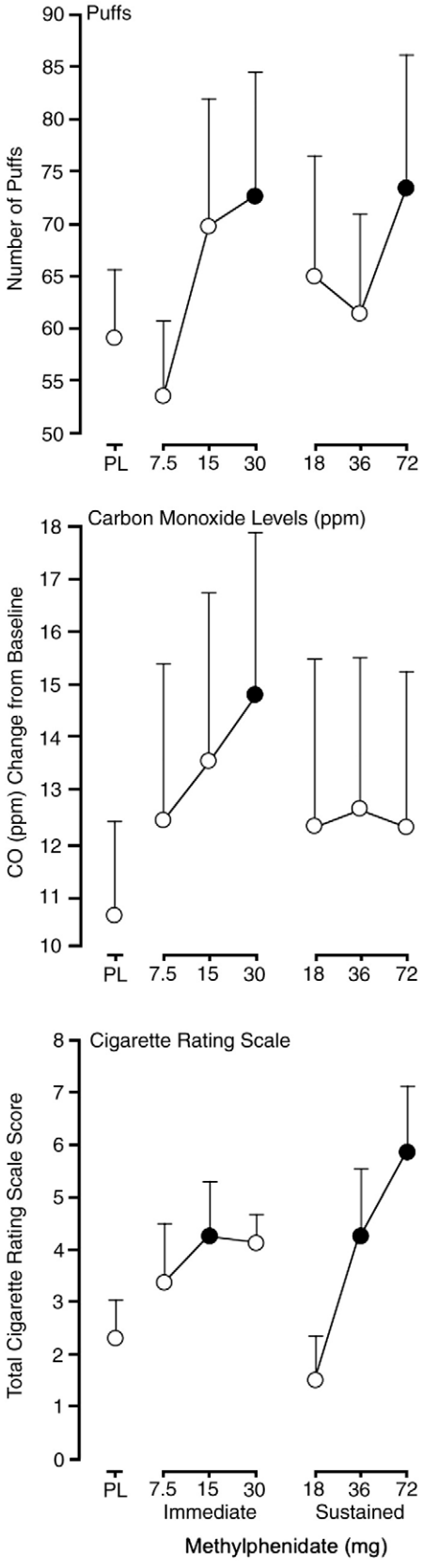
2.3. Outcome measures

Participants were allowed to smoke their preferred brand of cigarettes *ad libitum* for four hours one hour following the second medication administration. The four-hour smoking period was digitally recorded to be scored for various smoking behaviors by two observers (Rush et al., 2005; Vansickel et al., 2007). Outcome measures for smoking included carbon monoxide levels, number of cigarettes and number of puffs. Subject-rated drug-effect questionnaires included a locally developed Drug-Effect Questionnaire and an Adjective-Rating Scale (Rush et al., 2003; Oliveto et al., 1992). These questionnaires were completed approximately 30 min before drug administration, and 1, 2, 3, 4, and 5 h after drug administration. Approximately 5 h after drug administration, participants completed a five-item Cigarette Rating Scale as well as a five-item Food Rating Scale. Other than the words "cigarettes" and "food", these scales were identical in wording. The items rated were: 1) Did you "ENJOY" your cigarettes/food more than usual during today's session?; 2) Did you "CRAVE" cigarettes/food more than usual during today's session?; 3) Did your cigarettes/food "TASTE" better than usual during today's session?; 4) Did you "LIKE" your cigarettes/food more than usual during today's session?; and 5) Did you get more "PLEASURE" from your cigarettes/food during today's session? Participants responded to these questions using five options: Not At All, A Little Bit, Moderately, Quite A Bit and Extremely (scored numerically from 0 to 4). Cardiovascular measures included heart rate and blood pressure.

Table 1
Timeline for experimental sessions.

Time	Procedures
0800–0845	Vitals (3 checks), urine screen, sobriety test, CO level, pre-session subject-rated drug-effect measures, standard low-fat breakfast, 1 cigarette (outside)
0900	Vitals check, verification of pre-session measures, *drug administration (sustained-release methylphenidate or placebo)*
1000	Vitals check, subject-rated drug-effect measures, CO level
1100	Vitals check, subject-rated drug-effect measures, CO level, 1 cigarette (outside)
1200	Vitals check, subject-rated drug-effect measures, CO level, standard low-fat lunch provided
1300	Vitals check, subject-rated drug-effect measures, CO level, 1 cigarette (outside)
1400	Vitals check, verification of pre-session measures, *drug administration (immediate-release methylphenidate or placebo)*
1430	Vitals check, volunteer escorted to smoking room
1500	Recording of session initiated, vitals check, subject-rated drug-effect measures, CO level *Snacks, decaffeinated beverages and cigarettes available ad-libitum until end of session.*
1530	Vitals check
1600	Vitals check, subject-rated drug-effect measures, CO level
1630	Vitals check
1700	Vitals check, subject-rated drug-effect measures, CO level, standard dinner provided
1800	Vitals check, subject-rated drug-effect measures, CO level
1900	Vitals check, subject-rated drug-effect measures, CO level, Cigarette and Food Rating Scales

Caloric intake during the four-hour smoking period was also recorded. Available food items remained constant across sessions. Both the number of items consumed and the total caloric intake during the four-hour smoking period were determined. The number of items consumed was calculated at the end of each experimental session by counting the number of food packages and beverage containers opened by the volunteer. To calculate caloric intake, the available food items and beverages were weighed prior to being served. At the end of the session, if a food item or beverage was only partially 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.



2.4. Medication administration

The drug conditions were placebo, immediate-release methylphenidate (7.5, 15, and 30 mg) and sustained-release methylphenidate (18, 36, and 72 mg). Each active dose of immediate-release and sustained-release methylphenidate was tested once, while placebo was tested twice. Doses were administered in mixed order with the exception that the highest dose of either formulation was never administered during the first experimental session. Dose conditions were administered in a double blind, double-dummy fashion such that, participants received placebo during at least one of the medication administrations within a session. Placebo capsules were prepared by filling a 0 capsule with cornstarch.

2.5. Data analysis

Data were analyzed statistically as raw scores for all measures. Effects were considered significant for $p \leq 0.05$. Planned comparisons were used to compare each of the active dose conditions to placebo and to compare corresponding doses of immediate- and sustained-release methylphenidate. Carbon monoxide levels were analyzed as the change from baseline (i.e. the first reading of the day) to peak (i.e. maximum reading). For the Adjective-Rating Scale, Drug-Effect Questionnaire, and cardiovascular measures, only data from the first hour following the second drug administration (i.e. 1400 to 1500) were used in the analyses. Data collected after that time were considered uninterpretable because participants determined the amount they smoked (i.e. they smoked varying numbers of cigarettes with different nicotine contents).

3. Results

3.1. Smoking measures

Immediate- (30 mg) and sustained-release (72 mg) methylphenidate increased the number of puffs significantly above placebo (Fig. 1, Top Panel). Both formulations also generally increased the number of cigarettes smoked although this effect was not significant. Immediate- and sustained-release methylphenidate did not differ from each other.

Average carbon monoxide levels increased significantly following administration of immediate- release (30 mg) methylphenidate, consistent with the observed increase in number of puffs (Fig. 1, Middle Panel). Carbon monoxide levels were higher following administration of immediate-release methylphenidate than sustained-release methylphenidate.

Fig. 1. Dose-response functions for number of puffs, carbon monoxide levels (represented as change from baseline to peak) and Cigarette Rating Scale Total score. *X*-Axes: Placebo (PL) and doses of immediate- (7.5, 15 or 30 mg) and sustained-release (18, 36 or 72 mg) methylphenidate. *Y*-Axes: Number of puffs taken during the four-hour smoking period (Top Panel), change in carbon monoxide levels from baseline (i.e. first reading of the day) to peak (i.e. maximum reading) (Middle Panel) and Total score from the Cigarette Rating Scale (Bottom Panel). Data were averaged across participants. Filled symbols indicate that the data point is significantly different from placebo. Unidirectional error bars represent one standard error of the mean.

Immediate- (15 mg) and sustained-release (36 and 72 mg) methylphenidate significantly increased the Total score from the Cigarette Rating Scale (Fig. 1, Bottom Panel). Immediate- and sustained-release methylphenidate did not differ from each other.

3.2. Caloric intake

Immediate- (15 and 30 mg) and sustained-release (36 and 72 mg) methylphenidate significantly reduced the number of calories consumed during the four-hour experimental period (Fig. 2). Immediate- and sustained-release methylphenidate did not differ from each other. No effect of immediate- or sustained-release methylphenidate was found on items from the Food Rating Scale.

3.3. Subject-rated drug-effect questionnaires

Immediate- (15 mg) and sustained-release (72 mg) methylphenidate increased ratings of Restless from the Drug-Effect Questionnaire relative to placebo. Sustained-release methylphenidate (72 mg) increased the Stimulant score from the Adjective-Rating Scale. Sustained-release methylphenidate (36 mg) increased ratings of Stimulated, sustained-release methylphenidate (72 mg) increased ratings of Any Effect and sustained-release methylphenidate (36 and 72 mg) increased ratings of Stimulated and Restless from the Drug-Effect Questionnaire significantly above corresponding doses of immediate-release methylphenidate (15 and 30 mg). Sustained-release methylphenidate (72 mg) increased ratings of Any Effect from the Drug-Effect Questionnaire as well as the Stimulant score from the Adjective-Rating Scale significantly above the corresponding dose of immediate-release methylphenidate (30 mg).

3.4. Heart rate and blood pressure

Immediate- (15 mg) and sustained-release (72 mg) methylphenidate increased heart rate significantly compared to placebo. Immediate- (15 mg) and sustained-release (36 and 72 mg) methylphenidate increased systolic pressure. Sustained-release (72 mg) methylphenidate increased diastolic pressure relative to placebo. Sustained-release methylphenidate (72 mg) increased systolic pressure and heart rate significantly above the corresponding dose of immediate-release methylphenidate (30 mg).

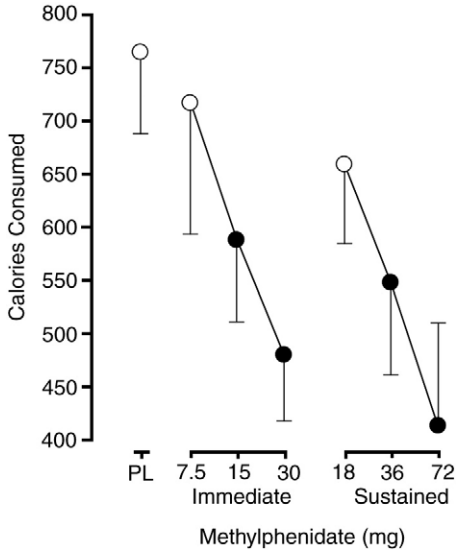


Fig. 2. Dose-response function for number of calories consumed. *X*-Axis: Placebo (PL) and doses of immediate- (7.5, 15 or 30 mg) and sustained-release (18, 36 or 72 mg) methylphenidate. *Y*-Axis: Number of calories consumed during the four-hour smoking period. Data were averaged across participants. Filled symbols indicate that the data point is significantly different from placebo. Unidirectional error bars represent one standard error of the mean.

4. Discussion

To the best of our knowledge, this was the first study to examine the effects of immediate- and sustained-release methylphenidate on cigarette smoking and eating in healthy, non-ADHD, adult cigarette smokers. Results of the current investigation suggest that both immediate- and sustained-release methylphenidate increase smoking and decrease caloric intake when administered acutely. The two preparations only differed in terms of their effects on smoke inhalation as evidenced by greater expired carbon monoxide values following the administration of the high dose of immediate-release methylphenidate.

The main objective of the current study was to determine whether rate-of-onset would influence the effects of methylphenidate on cigarette smoking. Doses of immediate- and sustained-release methylphenidate were chosen to produce similar peak plasma concentrations (Modi et al., 2000). Acute administration of immediate- and sustained-release methylphenidate increased cigarette smoking relative to placebo. The magnitude of the effect of immediate- and sustained-release methylphenidate on these measures was comparable. Immediate- and sustained-release methylphenidate did, however, differ with regard to carbon monoxide levels. Increases in carbon monoxide levels were greater following administration of the high dose of immediate-release methylphenidate relative to the corresponding dose of sustained-release methylphenidate. Because carbon monoxide levels are a biological measure of smoke inhalation, this finding may be important clinically. When it is necessary to prescribe methylphenidate, perhaps a sustained-release preparation would be a better option when there is concern regarding the smoking of patients.

The results of this study add to current knowledge regarding the interaction of stimulant drugs and nicotine and/or cigarette smoking. Stimulant-induced increases in smoking may be due to an additive or synergistic effect of methylphenidate and nicotine on mesocorticolimbic dopamine levels (Gerasimov et al., 2000; Rush et al., 2005; Vansickel et al., 2007). While we did not measure methylphenidate blood plasma concentrations, the doses chosen for this study should produce comparable peak plasma concentrations (Modi et al., 2000). Maximal dopamine transporter receptor occupancy is highly correlated with plasma concentration of methylphenidate (Spencer et al., 2006). The main difference between the immediate- and sustained-release formulations of methylphenidate is the rapidity with which maximal dopamine transporter receptor occupancy is achieved; this dissimilarity is thought to account for differences in the abuse-related effects of the two formulations (Spencer et al., 2006; Swanson and Volkow, 2003). The results of the current study suggest that stimulant-induced increases in cigarette smoking are dependent on drug concentration rather than rate-of-onset of drug action.

Whether stimulant-induced increases in smoking are due to pharmacological or behavioral mechanisms remains unclear. For example, nicotine functions as a reinforcer in cigarette smokers (e.g. Le Foll and Goldberg, 2006). Whether stimulants increase the reinforcing efficacy of nicotine is unknown. There is also evidence to suggest that the stimuli associated with smoking can function as reinforcers (Rose et al., 2000; Shahan et al., 1999). Nicotinized and de-nicotinized cigarettes elicit similar levels of responding on a progressive-ratio schedule of reinforcement, suggesting that the cues associated with smoking function as reinforcers (Shahan et al., 1999). Whether stimulants increase the saliency of cues associated with smoking is also unknown. Elucidating the mechanisms underlying stimulant-induced increases in smoking could lead to the discovery of improved treatment options for cigarette smokers that use stimulants either therapeutically or recreationally.

Methylphenidate decreased caloric intake. The results of both the present and previous studies are consistent with the notion that dopaminergic mechanisms mediate energy intake and eating (e.g. Berridge, 1996; Leddy et al., 2004). To our knowledge, this was the first study to compare the effects of sustained- and immediate-release methylphenidate on caloric intake. The number of calories consumed during the four-hour *ad-libitum* smoking and eating period was reduced by 37% and 47% relative to placebo under the high doses of immediate- and sustained-release methylphenidate, respectively. The present findings are concordant with those from previous studies that assessed the effects of immediate-release methylphenidate on caloric intake (Jasinski, 2000; Leddy et al., 2004; Rush et al., 2005; Vansickel et al., 2007). Results of the present study suggest that the anorectic effects of methylphenidate are dependent on the concentration of drug at the dopamine transporter and are not dependent on rate-of-onset. As noted above, stimulants are often prescribed for the treatment of obesity. Prescription stimulants are associated with problems of abuse and dependence (Weigle, 2003). The abuse potential of sustained-release preparations is lower than with immediate-release stimulant formulations and may therefore be a safer pharmacological treatment for obesity.

Worth noting, the effects of methylphenidate on caloric intake cannot be disentangled from the potential effects of nicotine on caloric intake in the current study. Participants controlled the amount that they smoked during the four-hour *ad-libitum* period. Nicotine decreases eating via increased dopaminergic and serotonergic transmission in the lateral hypothalamic area (Miyata et al., 1999). Methylphenidate increased smoking and, consequently, nicotine intake in the current study. The effect of nicotine and methylphenidate on appetitive behavior may, therefore have been additive. Future studies should assess the effects of sustained-release methylphenidate on caloric intake in the absence of nicotine.

The subject-rated and cardiovascular effects of immediate- and sustained-release methylphenidate differed from one another in the current study. Sustained-release methylphenidate generally increased subject ratings and cardiovascular indices to a greater extent than immediate-release methylphenidate. This finding is counter to findings from previous studies that examined the effects of different drug formulations or preparations on subject-rated and cardiovascular measures (Abreu et al., 2001; Jasinski and Krishnan, 2008; Kollins et al., 1998; Spencer et al., 2006). In those studies, slower onset of drug effects was associated with lower subject ratings and smaller effects on cardiovascular indices.

The reason for the discordant findings in the current study is unknown. The most parsimonious explanation may be that the doses of sustained-release methylphenidate administered in the current study are functionally higher than those of immediate-release methylphenidate. Dose selection in the current study was, however, based on published data and the magnitude of the effects of both formulations on smoking and eating was similar. One caveat of the current study is that blood plasma concentrations of methylphenidate were not collected. This would have ensured that the doses of immediate and sustained-release methylphenidate reached similar peak blood plasma concentrations.

An alternative explanation for the discordant findings of the present experiment may be that a different data analytic strategy was used. Data collected after the first hour post-second drug administration was considered uninterpretable because after that time participants controlled the amount that they smoked. The effects of methylphenidate, therefore, cannot be dissociated from the potential effects of nicotine following the first hour. Immediate-release methylphenidate reaches peak plasma concentration 1 to 2 h after oral administration whereas sustained-release methylphenidate reaches peak plasma concentration approximately 6 to 8 h following oral administration. First-hour data used in the analysis were taken one-hour after administration of immediate-release methylphenidate and 6 h following administration of sustained-release methylphenidate. The effects of immediate-release methylphenidate, therefore, may have peaked after the first hour.

A few caveats of the current study warrant mention. First, immediate- and sustained-release methylphenidate were administered acutely under a limited set of conditions. Methylphenidate is taken chronically and, of course, in the natural environment when prescribed for a medical condition. Whether the effects of methylphenidate on smoking and eating would vary based on the chronicity of treatment or the circumstances under which it is administered is unknown. Future studies should determine the effects of chronic methylphenidate administration on smoking and eating. Second, participants in the current study were generally free of clinical disorders. Methylphenidate may have different effects on smoking and eating in a clinical population. Future studies should assess the effects of methylphenidate on smoking and eating in a clinical population. Finally, the results of the current study suggest that immediate- and sustained-release methylphenidate had different effects on smoke inhalation (demonstrated by differences in expired carbon monoxide) but not on smoking. Smoking topography was not directly assessed in the current study; therefore, we cannot conclusively say that formulation type altered the effects of methylphenidate on smoke inhalation. Future studies should investigate directly the effect various formulations of methylphenidate have on smoking topography.

In conclusion, both immediate- and sustained-release methylphenidate increased smoking and decreased caloric intake under the current experimental conditions. Differences between the immediate-release and sustained-release methylphenidate formulations were minimal. This finding suggests that stimulant-induced increases in cigarette smoking and decreases in caloric consumption may depend on the concentration of drug at the dopamine transporter and not the rate at which dopamine transporter receptors are occupied. Characterization of the pharmacological and behavioral mechanisms underlying stimulant-induced increases in smoking and decreases in caloric intake could lead to the development of improved treatment options for persons that smoke and use stimulants as well as for obese individuals that do not respond to standard interventions.

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