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ORIGINAL INVESTIGATION

A pharmacological analysis of stimulant-induced increases in smoking

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Abstract
Rationale Stimulants increase tobacco smoking in healthy adults under controlled laboratory conditions. The mechanisms that mediate stimulant-induced increases in smoking are not known.
Objective The purpose of the present experiment was to characterize the pharmacological specificity of stimulant-induced increases in smoking. We tested the effects of methylphenidate and atomoxetine on smoking behavior. Atomoxetine is a norepinephrine transport inhibitor that does not increase dopamine levels in the nucleus accumbens or striatum. If stimulant-induced increases in smoking result from an additive or synergistic effect of these drugs and nicotine on dopamine levels in the nucleus accumbens or striatum, methylphenidate but not atomoxetine should increase smoking.
Materials and methods Doses of methylphenidate (10, 20, and 40 mg) and atomoxetine (20, 40, and 80 mg) were tested once while placebo was tested twice in 12 cigarette smokers. One hour after ingesting drug, participants smoked ad libitum for 4 h. Measures of smoking included total cigarettes, total puffs, and carbon monoxide levels. Snacks and decaffeinated drinks were available ad libitum, and food intake was calculated.
Results Methylphenidate but not atomoxetine dose-dependently increased the number of cigarettes, puffs, and carbon monoxide levels. Methylphenidate and atomoxetine decreased food intake.
Conclusions The results of this experiment are consistent with the notion that stimulant-induced increases in smoking may result from an additive or synergistic effect of these drugs and nicotine on dopamine levels in the nucleus accumbens or striatum. Additional research is needed to more fully understand the pharmacological mechanisms that mediate the relationship between stimulant use and smoking.

Keywords Methylphenidate · Atomoxetine · Smoking · ADHD · Subjective effects · Humans

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Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
ANOVA	Analysis of variance
THC	Tetrahydrocannibinol
DVD	Digital-video display
CO	Carbon monoxide

Tobacco smoking is a significant public health concern and is the leading cause of preventable death in the USA. In 2005, an estimated 60.5 million Americans, approximately

25% of the population age 12 or older, reported that they were current smokers (Substance Abuse and Mental Health Services Administration [SAMHSA] 2006). In addition, almost 11% of children between the ages of 12 and 17 reported smoking cigarettes (SAMHSA 2006). Currently, one in five deaths in the USA results from smoking-related illness. Thus, over 400,000 people die annually from smoking related causes. If current smoking trends remain the same, an estimated 64 million people currently under the age of 18 will die prematurely from smoking-related illnesses (Centers for Disease Control [CDC] 2003).

The results of human laboratory studies suggest that methylphenidate and *d*-amphetamine increase smoking (Chait and Griffiths 1983; Cousins et al. 2001; Henningfield and Griffiths 1981; Rush et al. 2005; Schuster et al. 1979; Sigmon et al. 2003; Tidey et al. 2000). In one laboratory study, the effects of *d*-amphetamine (5, 15, and 25 mg) and placebo on smoking behavior were examined in eight healthy adults (Henningfield and Griffiths 1981). Participants were administered medications 2 h before being allowed to smoke ad libitum for 90 min. Participants smoked an average of approximately three and five cigarettes after the administration of placebo and 25 mg *d*-amphetamine, respectively (Henningfield and Griffiths 1981). The effects of methylphenidate (0, 5, 10, 20, and 40 mg) were recently assessed on smoking in ten healthy adult cigarette smokers (Rush et al. 2005). Methylphenidate dose-dependently increased smoking as measured by number of cigarettes smoked, total puffs, and carbon monoxide (CO) levels during a 4-h ad libitum smoking session.

The mechanisms underlying stimulant-induced increases in cigarette smoking are not fully understood. From a behavioral perspective, stimulants may increase the reinforcing efficacy of cigarette smoking. Two laboratory studies have tested the effects of *d*-amphetamine on the reinforcing efficacy of smoking (Tidey et al. 2000; Sigmon et al. 2003). In the first study, the effects of *d*-amphetamine (0, 7.5, and 15 mg/70 kg) on choices between cigarette smoking and monetary reinforcement were examined (Tidey et al. 2000). Ninety minutes after medication administration, participants were given 20 choices between two puffs off of a cigarette or $0.25. *d*-Amphetamine dose-dependently increased the number of smoking choices relative to money choices. In the second study, the effects of *d*-amphetamine (0, 5, 10, and 15 mg/70 kg) on responding maintained by smoking and monetary reinforcement were examined (Sigmon et al. 2003). Ninety minutes after oral administration of *d*-amphetamine, participants were allowed to respond for money ($1.00 per ratio) or cigarette puffs (two puffs per ratio) using a progressive-ratio procedure. Of the 18 participants, ten showed higher breakpoint values for smoking reinforcement after pretreatment with *d*-amphetamine. This effect was not seen for monetary reinforcement.

The purpose of the present experiment was to characterize the pharmacological specificity of stimulant-induced increases in cigarette smoking in humans. To accomplish this aim, the effects of a range of doses of methylphenidate (10, 20, and 40 mg), atomoxetine (20, 40, and 80 mg), and placebo on cigarette smoking behavior were examined in 12 healthy adult participants. We chose to study methylphenidate because it is a prototypical stimulant that increases central dopamine levels (e.g., Gottlieb 2001; Mach et al. 1997; Volkow et al. 2005). We have shown previously that methylphenidate increases cigarette smoking (Rush et al. 2005). We chose to study atomoxetine because it is a potent norepinephrine transport inhibitor and, unlike methylphenidate, it does not increase extracellular dopamine levels in the striatum and nucleus accumbens, areas thought to be involved in drug reinforcement (e.g., Bymaster et al. 2002). We hypothesized that methylphenidate but not atomoxetine would dose-dependently increase smoking. To more fully characterize the effects of methylphenidate and atomoxetine, food intake after drug administration was also measured. Finally, drug effects were assessed using a battery of subject-rated drug-effect questionnaires and cardiovascular indices.

Materials and methods

Participants

Twelve healthy adult cigarette smokers (six men, six women) 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 10–20 cigarettes daily, (2) not attempting to quit smoking, (3) score less than 18 on an Attention Deficit Hyperactivity Disorder (ADHD) Rating Scale, (4) no significant medical or psychiatric disorders, other than nicotine dependence, (5) negative urine pregnancy test for women (Mainline confirms human chorionic gonadotropin), 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 completed questionnaires assessing drug use, medical, and psychiatric histories, and provided written informed consent before participating. Drug urine screens conducted during screening were negative for amphetamine, benzodiazepines, barbiturates, and cocaine (OnTrak Teststik, Lake Forest, CA).

General procedures

The Institutional Review Board of the University of Kentucky Medical Center approved this study and the informed consent document. Participants enrolled as out-

patients at the Laboratory of Human Behavioral Pharmacology (LHBP) at the University of Kentucky Medical Center. 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 regarding what they were "supposed" to do or what outcomes might be expected.

The experimental procedures used in the current experiment have been described in detail previously (Rush et al. 2005). Briefly, participants completed one practice session to familiarize them with the laboratory and daily procedures. Participants then reported to the LHBP for a total of eight experimental sessions. Participants arrived at the LHBP at approximately 08:00 hours and provided a urine sample before drug administration, which was screened for the presence of amphetamine, barbiturates, benzodiazepines, cocaine, opioids, and THC as well as an expired air specimen, which was assayed for the presence of alcohol using a hand-held breathalyzer (Intoximeters, Inc., St. Louis, MO). In order for an experimental session to commence, drug urine screens had to be negative for cocaine, amphetamine, benzodiazepines, barbiturates, and opioids, expired air specimens had to be negative for the presence of alcohol, and CO levels had to be less than or equal to 10 ppm.

Experimental medications were administered approximately 1 h after arrival. One hour after medication administration, participants were provided with a pack of their preferred brand of cigarettes and an assortment of snacks and decaffeinated drinks. Participants were then allowed to smoke, eat, and drink ad libitum for 4 h. Participants completed the self-reported drug-effect questionnaires 1, 2, 3, 4, and 5 h after drug administration. As a safety precaution, heart rate and blood pressure were recorded using an automated blood-pressure monitor (DINAMAP XL, Johnson and Johnson, Alexandria, TX) every 30 min for 3 h after medication administration and every hour for the remaining 2 h of the session. Carbon monoxide levels were recorded immediately before the participant completed the self-reported drug-effect questionnaires.

Outcome measures used to assess smoking included total cigarettes smoked, total puffs, and CO levels. Experimental sessions were digitally recorded, and smoking within each session was double-scored by a primary and secondary observer, both of whom were blind to the dose conditions. If the interobserver reliability was greater than or equal to 85%, data from the primary observer were used for data analysis. If the interobserver reliability was less than 85%, the session was rescored by both observers. Interobserver reliabilities exceeded 98%.

Food intake after drug administration was measured to further characterize the effects of methylphenidate and atomoxetine. 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 packages 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 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.

Subject-rated drug-effect questionnaires included a locally developed Drug-Effect Questionnaire and an Adjective-Rating Scale (Rush et al. 2005; Oliveto et al. 1992). As noted above, 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).

Drug administration

The drug conditions were methylphenidate (10, 20, and 40 mg), atomoxetine (20, 40, and 80 mg), and placebo. Each active dose of methylphenidate and atomoxetine was tested once, while placebo was tested twice. Doses were administered in mixed order with the exception that the highest dose of either medication was never administered during the first experimental session. All dose conditions were administered in a double-blind fashion. The commercially available drug (10 mg methylphenidate, CelTech, Rochester, NY or 20 mg atomoxetine, Eli Lilly, Indianapolis, IN) was over-encapsulated 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. 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 $p \leq 0.05$. Preliminary analyses indicated no significant differences between the two placebo sessions on number of cigarettes, CO levels, or number of puffs. For all subsequent analyses, data were averaged across the two placebo sessions.

For all measures, data were analyzed by one-factor repeated measures analysis of variance (ANOVA) with Dose (10, 20, and 40 mg methylphenidate, 20, 40, and 80 mg atomoxetine, and placebo) as the factor (StatView, SAS Institute, Cary, NC). If the effect of Dose attained statistical significance, planned pairwise comparisons were conducted to compare each of the active dose conditions to placebo. If corresponding doses of both methylphenidate and atomoxetine (e.g., 40 mg methylphenidate versus 80 mg atomoxetine) differed significantly from placebo, planned comparisons were conducted to determine whether these means differed significantly from each other. Carbon monoxide levels were analyzed as peak effect (i.e., maximum level observed during the 4-h smoking period). For the Adjective-Rating Scale, Drug Effect Questionnaire, and cardiovascular measures, data after the first hour was considered uninterpretable because participants determined the amount they smoked (i.e., they smoked varying numbers of cigarettes with different nicotine contents). For this reason, only data from the first hour were used in the analyses for these measures.

Results

Demographics

Participants ranged in age from 19 to 30 years (mean = 21), and body mass indices ranged from 19 to 30 (mean = 23.6). Participants reported smoking 10–19 cigarettes/day (mean = 14) and consuming between 0 and 480 mg caffeine/day (mean = 202). Participants had completed 12–16 years of education (mean = 14).

Smoking

The one-way ANOVA that included the seven experimental conditions revealed a significant effect of Dose on the number of cigarettes smoked ($F_{6, 66}=4.6$, $p<0.001$), number of puffs ($F_{6, 66}=5.2$, $p<0.001$), and CO levels ($F_{6, 66}=4.8$, $p<0.001$). Planned pairwise comparisons revealed that 20 and 40 mg methylphenidate but none of the atomoxetine doses increased the number of cigarettes smoked, the number of puffs, and CO levels significantly above values observed with placebo (Fig. 1).

Cigarette rating scale

The one-way ANOVA that included the seven experimental conditions revealed a significant effect of Dose on ratings of Crave ($F_{6, 66}=2.6$, $p<0.05$), Enjoy ($F_{6, 66}=3.5$, $p<0.01$), and Pleasure ($F_{6, 66}=2.8$, $p<0.02$) from the Cigarette Rating Scale (Fig. 2). Planned pairwise comparisons revealed that methylphenidate (20 and 40 mg) increased ratings of Enjoy and Pleasure significantly above placebo levels, while only the highest dose of methylphenidate, 40 mg, increased ratings of Crave. There were no significant effects of atomoxetine on any item of the Cigarette Rating Scale.

Food intake

The one-way ANOVA that included the seven experimental conditions revealed a significant effect of Dose on the number of items ($F_{6, 66}=6.6$, $p<0.001$) and calories consumed ($F_{6, 66}=9.0$, $p<0.001$). Planned pairwise comparisons revealed that all active doses of methylphenidate and atomoxetine decreased the number of items and calories

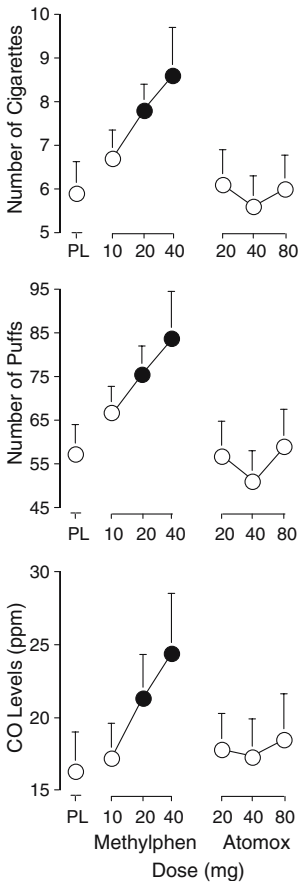

Fig. 1 Dose–response functions for number of cigarettes (*top panel*), number of puffs (*middle panel*), and CO levels (*bottom panel*). x-*Axes*: methylphenidate (*Methylphen*) and atomoxetine (*Atomox*) dose in milligrams; data points above PL designate placebo values. Data points show means of 12 participants; 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 test)

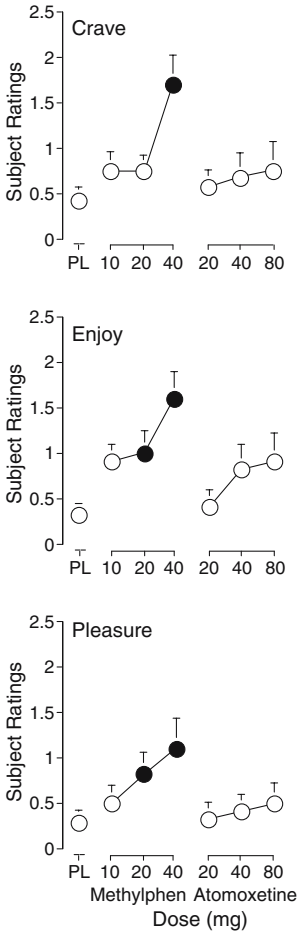

Fig. 2 Dose–response functions for Ratings of Crave (*top panel*), Enjoy (*middle panel*), and Pleasure (*bottom panel*) from the Cigarette Rating Scale. x-*Axes*: methylphenidate (*Methylphen*) and atomoxetine (*Atomox*) dose in milligrams; data points above PL designate placebo values. Data points show means of 12 participants; 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 test)

consumed significantly below placebo levels (Fig. 3). Planned pairwise comparisons also revealed that 40 mg methylphenidate reduced caloric intake to a significantly greater extent than 80 mg atomoxetine.

Food rating scale

The one-way ANOVA that included the seven experimental conditions revealed a significant effect of Dose on ratings of Crave ($F_{6,\ 66}=2.3$, $p<0.05$) from the Food Rating Scale. Planned pairwise comparisons revealed that 10 and 40 mg methylphenidate as well as 20, 40, and 80 mg atomoxetine decreased ratings of Crave significantly below placebo levels (data not shown). There were no significant differences between corresponding doses of methylphenidate and atomoxetine. There were no significant effects of methylphenidate or atomoxetine on any other item from the Food Rating Scale.

Subject-rated drug-effect questionnaires

The one-way ANOVA conducted on first-hour data that included the seven experimental conditions revealed a significant effect of Dose on ratings of High and Shaky from the Drug-Effect Questionnaire (data not shown). Planned pairwise comparisons revealed that 20 mg methylphenidate increased ratings of High significantly above placebo levels. Atomoxetine (40 mg) increased ratings of Shaky significantly above placebo levels. There were no significant effects of methylphenidate or atomoxetine on any other item from the Drug-Effect Questionnaire. The one-way ANOVA conducted on first-hour data (i.e., 1 h post-medication) that included the seven experimental conditions did not reveal a significant effect of Dose on the Stimulant or Sedative scales of the Adjective-Rating Scale.

Heart rate and blood pressure

The one-way ANOVA conducted on first-hour data that included the seven experimental conditions revealed a significant effect of Dose on systolic ($F_{6,\ 66}=4.6$, $p<0.001$) and diastolic pressure ($F_{6,\ 66}=2.5$, $p<0.05$; data not shown). Planned pairwise comparisons revealed that methylphenidate (40 mg) and atomoxetine (40 and 80 mg) increased systolic pressure significantly above placebo levels. Planned pairwise comparisons also revealed that 40 mg atomoxetine increased systolic pressure to a significantly greater extent than 20 mg methylphenidate. Atomoxetine (80 mg) increased diastolic pressure significantly above placebo levels. There were no significant effects of methylphenidate or atomoxetine on heart rate ($p>0.05$).

Discussion

Methylphenidate dose-dependently increased the total number of cigarettes smoked, number of puffs, and CO levels, which is consistent with results from a previous study (Rush et al. 2005). Atomoxetine did not affect smoking behavior under the current experimental conditions. Both

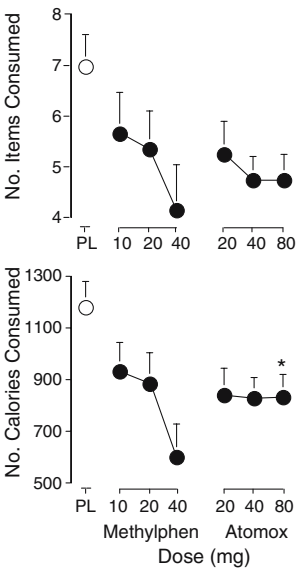

Fig. 3 Dose–response functions for number of food items (*top panel*) and number of calories (*bottom panel*) consumed. x-*Axes*: methylphenidate (*Methylphen*) and atomoxetine (*Atomox*) dose in milligrams; data points above PL designate placebo values. Data points show means of 12 participants; brackets 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 test). An *asterisk* above an atomoxetine dose indicates that dose is significantly different from the corresponding methylphenidate dose ($p \leq 0.05$, Fisher's Protected Least Significant Difference test)

methylphenidate and atomoxetine decreased the number of food items consumed and caloric intake. Before participants were allowed to smoke (i.e., one hour after drug administration), methylphenidate and atomoxetine increased some subject ratings as well as blood pressure.

The results of the current experiment systematically replicate the results of a previous study conducted in our laboratory in which the effects of methylphenidate (5, 10, 20, and 40 mg) on smoking were assessed (Rush et al. 2005). In our previous study, methylphenidate (10, 20, and 40 mg) increased the number of cigarettes, puffs, and CO levels significantly above placebo. In the current study, methylphenidate (20 and 40 mg) increased the number of cigarettes, puffs, and CO levels significantly above placebo. Worth noting is that the magnitude of the effect is similar for both studies. For example, in our previous study, methylphenidate (10, 20 and 40 mg) increased the number of puffs by 13, 14, and 21, respectively, relative to levels observed with placebo. In the current study, methylphenidate (10, 20, and 40 mg) increased the number of puffs by 9, 18, and 27, respectively, relative to levels observed with placebo.

Atomoxetine did not increase smoking under the current experimental conditions. The most parsimonious explanation for the absence of effect is that we did not test sufficient doses. However, the atomoxetine doses administered in the present experiment correspond to doses that we have administered in previous studies. We have previously demonstrated that atomoxetine (60 and 90 mg) significantly increases scores on the Stimulant-sensitive Adjective-Rating Scale, while the 60-mg dose increases heart rate significantly above placebo (Lile et al. 2006). In addition, all doses of atomoxetine administered in the current experiment reduced caloric intake. Thus, the atomoxetine doses tested in the current experiment are behaviorally and physiologically active when administered acutely under laboratory conditions. A second potential explanation for the lack of effect of atomoxetine on smoking in the current study is the acute dosing regimen. Atomoxetine may not reach maximal clinical efficacy for several weeks (e.g., Wilens et al. 2006). Whether atomoxetine would have differential effects on smoking behavior when administered chronically is unknown but should be explored.

The finding that atomoxetine did not increase smoking supports the notion that stimulant-induced increases in smoking may have a pharmacological basis. Atomoxetine is a potent norepinephrine transport inhibitor that also has a lower affinity for various other transporters and receptors and does not increase extracellular dopamine in the nucleus accumbens and striatum, brain areas thought to mediate drug reinforcement (Bymaster et al. 2002; Christman et al. 2004; Gehlert et al. 1995; Michelson et al. 2002, 2003). Methylphenidate, like other stimulants, increases extracellular dopamine levels in the striatum and nucleus accumbens (e.g., Gottlieb 2001; Mach et al. 1997; Volkow et al. 2005). Nicotine increases extracellular dopamine levels in these areas indirectly via activation of nicotinic acetylcholine receptors located at presynaptic dopaminergic terminals in the ventral tegmental area (Hamada et al. 2004). An additive or synergistic increase in mesocorticolimbic dopamine levels might explain the methylphenidate-induced increases in smoking observed in the present as well as the previous experiment (Gerasimov et al. 2000; Huston-Lyons et al. 1993; Rush et al. 2005). Consistent with this notion, the results of one study demonstrated that methylphenidate augments the reinforcing, discriminative-stimulus, and locomotor-activating effects of nicotine in rats (Wooters et al. 2007). Worth noting, under the current experimental conditions, we did not directly assess the role of dopamine in stimulant-induced increases in smoking. Future studies should more fully characterize the role of dopamine in stimulant-induced increases in smoking by determining whether pretreatment with dopamine antagonists attenuates stimulant-induced increases in smoking.

The finding that methylphenidate increased positive subject ratings of cigarettes (i.e., Enjoy and Pleasure) partially supports the idea that stimulants may increase the reinforcing effects of smoking or nicotine. Positive subject-rated drug effects are considered to be an indirect measure of the reinforcing effects of drugs (Henningfield et al. 1986). Future studies should directly examine the effects of methylphenidate on the reinforcing effects of smoking.

Methylphenidate increased ratings of High while atomoxetine increased ratings of Shaky from the Drug-Effect Questionnaire. Methylphenidate and atomoxetine also increased blood pressure. The subject-rated and cardiovascular effects of methylphenidate and atomoxetine in the present study were not as robust as those we have observed previously (Lile et al. 2006; Rush et al. 2001; Stoops et al. 2005a, b). In the current experiment, subject-rated and cardiovascular effects were analyzed 1 h after medication administration, perhaps before the effects of methylphenidate or atomoxetine peaked. In our previous studies, these measures were analyzed as peak effect or area under the time–action curve for 5 h post-medication. Only first-hour data in this study were analyzed because after this time, volunteers controlled the amount that they smoked. Separating the combined effects of methylphenidate or atomoxetine and nicotine on these measures was, therefore, impossible. Once volunteers were allowed to smoke, the subject-rated and cardiovascular effects of methylphenidate and atomoxetine were more pronounced. To more fully characterize the potential interaction of methylphenidate or atomoxetine with nicotine, future studies should examine the subject-rated and cardiovascular effects of fixed doses of these drugs and nicotine alone and in combination in the same group of volunteers.

Although the effects of methylphenidate and atomoxetine on smoking behavior were distinct, the effects of these medications on eating behavior overlapped. All doses of methylphenidate and atomoxetine reduced the number of items and calories consumed significantly below placebo levels. Methylphenidate and atomoxetine also reduced ratings of Crave from the Food Rating Scale. The current findings emphasize the importance of using multiple outcome measures when characterizing the effects of drugs. While all doses of methylphenidate and atomoxetine reduced caloric intake, their effects on eating behavior were somewhat distinct. The effects of methylphenidate on caloric intake were dose related, whereas the effects of atomoxetine were not. This finding may demonstrate that dopaminergic and noradrenergic mediation of energy intake is distinguishable (Berridge 1996; Leddy et al. 2004; Nisoli and Carruba 2000). Perhaps methylphenidate reduced caloric intake via a direct pharmacological mechanism while atomoxetine may have reduced caloric intake via nonspecific peripheral actions (i.e., nausea). Considering that stimulant medications have a significant abuse potential in humans, including obese patients (e.g., Bray 1993; Weigle 2003), future studies should be conducted to determine if atomoxetine might have clinical utility as an appetite suppressant (Gadde et al. 2006).

The results of the current experiment may be important clinically because stimulant medications are prescribed for a variety of disorders including the treatment of ADHD, narcolepsy, and excessive daytime sleepiness, obesity, and to augment antidepressant therapy (Feinberg 2004; Reeves and Schweitzer 2004; Schwartz 2004; Spencer et al. 2004; Weigle 2003). Persons that suffer from conditions in which stimulant medications are prescribed as well as persons that are stimulant dependent tend to smoke at greater rates compared to the general population (e.g., Budney et al. 1993; Lasser et al. 2000). The pharmacological and behavioral profiles of atomoxetine are distinct from commonly prescribed stimulant medications (e.g., Bymaster et al. 2002; Heil et al. 2002; Lile et al. 2006; Wee and Woolverton 2004), although it is prescribed for similar purposes (e.g., Carpenter et al. 2005; Gadde et al. 2006; Mignot and Nishino 2005; Simpson and Plosker 2004). Perhaps clinicians, when determining treatment plans for patients that may require prescription stimulants, should consider alternative medications when the patient smokes or is at risk to smoke.

While the results of this study are important in understanding the pharmacological specificity of stimulant-induced increases in smoking, there are a few caveats that warrant discussion. First, the volunteers that participated in the current experiment consisted of healthy, nondrug-dependent, adult smokers. Whether methylphenidate or other stimulant medications would increase smoking in a clinically relevant population is unknown. Persons with ADHD, for example, may or may not increase smoking after stimulant pretreatment. The clinical and epidemiological literature on this topic is mixed regarding whether or not stimulant medications increase the risk of tobacco smoking in ADHD-diagnosed individuals (Biederman et al. 1999; Lambert 2002; Lambert and Hartsough 1998; Loney et al. 2002). Second, the acute effects of immediate-release methylphenidate were tested in the current experiment, whereas in a treatment setting, sustained-release formulations are commonly prescribed (e.g., Lage and Hwang 2004). Rate-of-onset has been shown to modulate the behavioral effects of stimulant drugs including methylphenidate and cocaine (Abreu et al. 2001; Kollins et al. 1998). Future studies should determine whether immediate- and sustained-release methylphenidate produce quantitatively different effects on smoking. Finally, in a treatment setting, methylphenidate is prescribed chronically. Future studies should also determine whether differential effects on smoking behavior would be observed after the chronic administration of methylphenidate. Bupropion, for example, increases cigarette smoking when administered acutely (i.e., Cousins et al. 2001) but reduces smoking when administered chronically (for a review, see Henningfield et al. 2005).

In conclusion, methylphenidate but not atomoxetine increased cigarette smoking under the current experimental conditions. This finding is consistent with the notion that stimulant-induced increases in smoking result from an additive or synergistic effect of these drugs and nicotine on extracellular dopamine levels in the nucleus accumbens or striatum. Future studies should be designed to further characterize the pharmacological mechanisms underlying stimulant-induced increases in smoking in clinical populations. Identifying these mechanisms may help to elucidate the complex relationship between stimulant use and cigarette smoking. This knowledge could lead to improved treatment options for persons that smoke and use stimulants either therapeutically or recreationally.

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