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Nicotine alters some of cocaine's subjective effects in the absence of physiological or pharmacokinetic changes☆

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Abstract

Tobacco smoking and cocaine use often co-occurs and the frequency of smoking has been positively correlated with the likelihood of cocaine use. In addition, nicotine pretreatment has been shown to increase the rate of cocaine self-administration in rats and to enhance cue-induced cocaine craving in humans. The present study was conducted to investigate whether nicotine pretreatment via a transdermal patch alters the behavioral, physiological, and pharmacokinetic effects of an acute dose of cocaine in nondependent human volunteers. Seven male tobacco smokers who used cocaine occasionally provided informed consent and participated in this placebo-controlled, four-visit study. Following pretreatment with a transdermal nicotine patch (placebo, 14 mg), subjects were challenged with an acute dose of intranasal cocaine (placebo, 0.9 mg/kg). Nicotine pretreatment attenuated cocaine-induced increases in reports of "high" and "stimulated" and increased the latency to detect cocaine effects and cocaine-induced euphoria. Nicotine did not alter cocaine's effects on heart rate, skin temperature, and blood pressure or plasma cocaine, benzoylecgonine (BE), or ecgonine methylester (EME) concentrations. Our findings indicate that nicotine pretreatment alters some of the positive subjective effects of cocaine in humans without affecting cocaine's effects on physiologic responses or pharmacokinetic profiles.

Keywords: Cocaine; Nicotine transdermal patch; Subjective effects; Plasma levels; Physiologic responses; Human subjects

1. Introduction

Cocaine and nicotine are two of the most widely used stimulant drugs in the United States and are often used in combination (Monitoring the Future Study, 1999). Epidemiological studies have shown that the frequency of tobacco smoking is positively correlated with the likelihood of cocaine use and that the heavier the tobacco smoking, the heavier the use of cocaine and other drugs of abuse (Henningfield et al., 1990; Konings et al., 1995; Schorling et al., 1994). Similarly, cocaine users have been found to smoke tobacco cigarettes more often than nonusers (Budney et al., 1993; Roll et al., 1997; Sees and Clark, 1991) and smoke more when under the influence of cocaine than when sober (Roll et al., 1996). In addition, cocaine-dependent tobacco smokers report an earlier age onset and more frequent use of cocaine than cocaine-dependent nonsmokers (Budney et al., 1993) and cocaine use has been shown to increase the frequency of cigarette smoking in laboratory settings (Higgins et al., 1994; Nemeth-Coslett et al., 1986). Pharmacologically, cocaine and nicotine produce similar physiological and subjective effects, including increases in heart rate and stimulant-like mood effects (Foltin and Fischman, 1991; Henningfield and Griffiths, 1981; Higgins et al., 1990; Jones et al., 1999; Lukas et al., 1990).

Data from animal studies have demonstrated that nicotine pretreatment increases the rate of cocaine self-administration in rats (Horger et al., 1992) and that both nicotine and cocaine increase dopaminergic activity by inhibiting reuptake (Bergman et al., 1989; Di Chiara and Imperato, 1988;

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Izenwasser et al., 1991; Nisell et al., 1997), supporting the idea that these drugs share common neural substrates. Moreover, nicotine and cocaine have been shown to stimulate dopamine release in the nucleus accumbens in an additive manner (Zerning et al., 1997), suggesting that nicotine may enhance the reinforcing effects of cocaine.

Further support for the notion that the combination of nicotine and cocaine may produce cumulative and/or synergistic effects comes from anecdotal reports of cocaine-dependent individuals. For instance, when interviewed about their cocaine and tobacco use, patients reported that smoking mentholated cigarettes prolonged the cocaine high and postponed the post-cocaine "crash" (Sees and Clark, 1993; Wiseman and McMillan, 1998). Similarly, in another interview study, 15% of patients with histories of combined cocaine and tobacco use reported that using cocaine and nicotine together produced an increased cocaine effect and 22% indicated that the drug combination produced an increased nicotine effect (Wiseman and McMillan, 1996). Moreover, cue-induced increases in cocaine craving are strongly enhanced by nicotine pretreatment via a transdermal nicotine patch (Reid et al., 1998) and behavioral routines typically associated with tobacco smoking have been shown to serve as cues that trigger cocaine craving in crack users (Sees and Clark, 1993).

In spite of the substantial epidemiological, clinical, and preclinical data suggesting that the simultaneous use of nicotine and cocaine may result in additive reinforcing effects, to our knowledge, there are no published studies investigating the interactive effects of this drug combination in humans. The present study was designed to assess whether nicotine pretreatment via a transdermal patch alters the behavioral, physiological, and pharmacokinetic effects of an acute dose of cocaine in nondependent human volunteers.

2. Methods

2.1. Subjects

Seven healthy male volunteers between the ages of 21 and 35 were recruited from the Boston metropolitan area via newspaper advertisements. To be included in the study subjects had to: (1) smoke tobacco cigarettes regularly (10–20 cigarettes/day), (2) report using cocaine no less than three times per year but no more than two times per month, (3) have normal physical and psychiatric status examinations, (4) have normal hemogram and blood chemistry analyses, (5) have no history of neurological disease, a chronic medical illness, or a history of mental health problems, (6) have no history of drug or alcohol dependence, and (7) be able to sign informed consent. None of the subjects had previous experience with the nicotine transdermal patch. The subjects' demographic characteristics and drug use history are depicted in Table 1.

Subjects meeting initial study criteria were told that the study was designed to investigate the interaction between nicotine and cocaine on behavior and physiologic responses. Subjects were also told that they could receive any combination of active or placebo cocaine and active or placebo nicotine on each of the study visits. The protocol was reviewed and approved by the McLean Hospital Institutional Review Board. Subjects signed informed consent and were paid for their participation in the study.

2.2. Experimental design

This was a placebo-controlled study investigating the effects of nicotine pretreatment on cocaine's behavioral [subjective reports of intoxication, Addiction Research Center Inventory (ARCI), visual analog scales (VAS)], physiological (heart rate, blood pressure, skin temperature), and pharmacokinetic [plasma levels of cocaine, benzoylecgonine (BE), and ecgonine methylester (EME)] effects. Subjects came to the laboratory on four separate occasions separated by at least 1 week; each visit consisted of a nicotine pretreatment (placebo or 14 mg) followed by an acute intranasal challenge of either cocaine (0.9 mg/kg) or placebo. All treatments were presented in a randomized fashion. Each study visit lasted for 3.5 h in the laboratory: 30 min of baseline monitoring followed by cocaine (or placebo) administration and a 3-h post-administration monitoring period. Subjects were allowed to have a light breakfast on the morning of each study but were required to

Table 1
Demographic characteristics of study subjects

$N=7$	Average (mean ± S.D.)	Range
Age (years)	24.0 ± 3.5	22–30
Height (cm)	184.3 ± 6.0	175–190
Weight (kg)	79.5 ± 11.6	61–91
Body mass index	23.0 ± 2.6	20–26
Education (years)	14.3 ± 1.7	12–16
Tobacco smoking (number of cigarettes per day)	16.4 ± 4.8	10–20
Cocaine use (number of times per month)	1.7 ± 0.5	1–2
Cocaine use (years)	3.9 ± 2.5	1–7
Ethanol use (drinks per week)	13.0 ± 6.2	7–19

abstain from over-the-counter drugs, caffeine, nicotine, milk, and egg products from midnight before the study visit.

On the morning of the study, subjects were screened for drug use with a urine screen kit (Triage, Biosite Diagnostics, San Diego, CA) and urine specimens had to be negative for PCP, benzodiazepines, cocaine, amphetamines, THC, opiates, and barbiturates. Any subject with a positive urine screen for any drug on the morning of the study was rescheduled. In addition, subjects' breath was tested for the presence of ethanol using an AlcoSensor (Intoximeter, St. Louis, MO) and only subjects with a zero breath ethanol level were allowed to participate in the study.

2.3. Nicotine pretreatment

2.3.1. Active nicotine patches

On the afternoon before each scheduled study visit, subjects came to the laboratory and were given a nicotine patch (14 mg Nicoderm CQ, SmithKline Beecham). Subjects were instructed to apply the patch on their upper arm at 11:00 p.m. that night, to call the laboratory at that time, and to leave a message stating they had applied the patch. Subjects were not allowed to participate in the study the next morning if they did not call the laboratory at 11:00 p.m. the night before.

2.3.2. Placebo nicotine patches

Placebo patches consisted of an active 14-mg patch without the adhesive back plastic cover removed. In order to maintain the blind, placebo patches were applied by a research assistant at 5:00 p.m. before the scheduled study day. Subjects were told that as part of the study protocol, some patches had to be applied by a member of the research team and some by the subjects themselves.

Subjects were instructed to abstain from smoking tobacco cigarettes from the time the patch was applied until the study was over. On the morning of the study, subjects arrived at the laboratory between 8:30 and 9:00 a.m. and smoking abstinence was verified via a carbon monoxide breath monitor. Since subjects were required to remain abstinent from tobacco for approximately 6 h longer during the placebo nicotine condition than the active nicotine condition (and did not receive nicotine replacement), special attention was paid to the physiologic and behavioral measures during the pre-cocaine baseline period to determine whether subjects were experiencing significant nicotine withdrawal during the placebo condition. Changes from baseline values were used in the statistical analyses for all measures that were found to be different at baseline as a function of nicotine pretreatment.

2.4. Acute cocaine challenge

During the conduct of each 3.5-h laboratory study, subjects sat in a sound- and light-attenuated double-walled chamber (IAC, Bronx, NY) equipped with a wired intercom and a closed-circuit video camera to provide auditory and visual contact with the subjects. Verbal instructions during the experiment were given to the subjects via the intercom. Subjects sat in a reclinable chair and were instructed to relax but to remain awake. Cocaine (or placebo) was administered after a 30-min baseline and data collection continued for 3 h after cocaine (or placebo) administration. At the end of the study, subjects were provided with a light lunch and were kept in a waiting room until all overt signs of intoxication and physiological responses had waned. All subjects were transported to and from the laboratory by taxicab.

Cocaine hydrochloride USP (Mallinkrodt, St. Louis, MO) was administered intranasally at a dose of 0.9 mg/kg. A small amount of lactose powder was added to each dose to bring the total weight of powder delivered to 100 mg. The placebo preparation consisted of 5 mg of cocaine to which 95 mg of lactose powder was added. Both the cocaine and placebo were self-administered intranasally using a modified snort-stick device (Kouri et al., 2000; Lukas et al., 1994). Subjects were instructed to snort one-half of the dose in one nostril and the second half in the other nostril, the cocaine administration procedure lasted 30–60 s.

2.5. Subjective measures

Subjects reported cocaine's subjective effects on a continuous basis via an instrumental joystick device (Lukas et al., 1986, 1996) available during the entire study. Subjects were instructed to press a button on the joystick panel labeled "detect" whenever they felt the effects of cocaine, a button labeled "euphoria" whenever they experienced feelings of intense well-being, good effects, or intense pleasure, and to press a button labeled "dysphoria" if they experienced an intense bad feeling, or intense displeasure. Movement of the joystick was time-coded and recorded directly by a customized computer program. Joystick responses were displayed on a computer screen in the experimental chamber during the entire study; this feature provided subjects with a continuous report of their behavior that was being recorded.

At various times during the study, subjects were asked to respond to a set of nine computerized Visual Analog Scale (VAS) by moving a cursor on a 100-mm line with the words "none" or "extremely" at either end that represented their answer to the following questions: "how *good* do you feel right now?," "how *happy* do you feel right now?," "how *high* do you feel right now?," "how *stimulated* do you feel right now?," "how *anxious* do you feel right now?," "how *bad* do you feel right now?," "how strong is your *desire to use* cocaine right now?," "how *intoxicated* do you feel right now?," and "how strong is your *desire to not use* cocaine right now?" In addition, subjects completed the 49-item ARCI (Martin et al., 1971). The VAS and the ARCI were presented on eight occasions during the study: 15 min

before the cocaine/placebo challenge, and 20, 40, 60, 90, 120, 150, and 180 min after administration.

2.6. Physiologic variables

A continuous record of electrocardiogram (EKG) activity was collected during the study using standard electrodes placed on the subjects' arms, legs, and chest (Lead IV montage). Skin temperature also was collected during the entire study using a thermistor attached to the subjects' middle finger (Hewlett Packard 78352A). Subjects were fitted with an automatic blood pressure cuff and readings were taken 17 min before and at 17, 37, 57, 87, 117, 147, and 177 min after drug administration, using a Marshall 94 Digital Blood Pressure Monitor (Omron Healthcare, Vernon Hills, IL). Subjects were not permitted to leave the laboratory until their heart rate and blood pressure readings returned to baseline levels.

2.7. Blood sampling procedures/plasma analyses

An intravenous catheter was inserted in an antecubital vein immediately prior to the study for blood withdrawal. The distal end of the tubing was attached to a 10-ml syringe mounted on a withdrawal syringe pump situated outside the experimental chamber. The blood withdrawal pump was set to withdraw blood at a continuous rate of 1 ml/min. Syringes were changed every 2.5 min into vacutainer tubes containing sodium fluoride (to prevent cocaine hydrolysis), immediately centrifuged and the plasma removed, and frozen at $-70°C$ for subsequent quantitative analyses. A solid phase extraction procedure was used to separate the analytes from the plasma; the extracts were subsequently analyzed by gas chromatography/mass spectrometry (GC/MS) as described by Cone et al. (1994). Cocaine and two of its metabolites, BE and EME, were simultaneously detected and quantified against reference standards of known concentrations. Deuterated analogs of the drugs were used as internal standards. The sensitivity limit was established at 5 ng/ml for each analyte (see Kouri et al., 2000; Lukas et al., 1996).

2.8. Data analysis

All behavioral (ARCI, VAS, joystick) and physiologic (heart rate, skin temperature, blood pressure) data were analyzed using 2 (Nicotine Pretreatment) $\times$ 2 (Cocaine Dose) repeated measures analyses of variance (ANOVAs) with time as the repeated factor. When baseline differences were found, the data were analyzed as change from baseline instead of raw scores. Post hoc *t* tests were performed when significant main effects were uncovered in order to identify the specific time points that were significantly different. A secondary analysis comparing peak subjective and physiologic responses was performed using two-factor ANOVAs. For all statistical analyses, differences were considered to be statistically significant at the $P \leq .05$ level.

3. Results

3.1. Physiologic responses

3.1.1. Heart rate

Analysis of the 30-min pre-cocaine baseline revealed no significant differences in heart rate as a function of nicotine dose. Administration of cocaine significantly increased heart rate compared to placebo [$F(1,12) = 5.5$, $P = .028$], with time points 15 through 60 being significantly higher following the active cocaine dose compared to placebo. Analysis of the heart rate data during the 60-min post-cocaine administration yielded a significant main effect of nicotine dose [$F(1) = 5.1$, $P = .044$] and a significant main effect of time [$F(12) = 4.9$, $P < .0001$]. Subjects achieved an average post-cocaine peak heart rate of 83.8 ± 2.1 (bpm $\pm$ S.E.M.) during the active nicotine pretreatment condition vs. 75.0 ± 2.3 during the placebo nicotine condition (Fig. 1).

Even though baseline heart rate levels were not statistically different as a function of nicotine pretreatment, visual inspection of the data revealed that heart rates during nicotine pretreatment were slightly higher compared to placebo pretreatment. The average heart rate during the 30-min pre-cocaine baseline for the two active nicotine conditions combined was 69.2 ± 1.3 compared to an average of 61.8 ± 2.1 bpm during placebo nicotine conditions combined. Therefore, a secondary analysis of the heart rate data was performed using change from baseline values instead of raw values. This secondary analysis revealed no significant changes in cocaine-induced heart rate responses as a function of nicotine dose.

3.1.2. Skin temperature

Analysis of the 30-min pre-cocaine baseline showed no significant effect of nicotine pretreatment on skin temperature. Following cocaine administration, there was a significant cocaine dose by time interaction [$F(1,12) = 4.5$, $P = .018$]. Post hoc analyses revealed that cocaine significantly decreased skin temperature at time points 25 to 55 min post-cocaine administration. The peak decrease in skin temperature occurred at time 25 min post-cocaine, with an average decrease of 2.2°C from baseline. There were no significant effects of nicotine pretreatment on cocaine-induced decreases in skin temperature.

3.1.3. Blood pressure

There were no significant changes in systolic/diastolic blood pressure as a function of nicotine or cocaine treatment. Subjects achieved peak systolic/diastolic blood pressure readings of 129.33 ± 5.87 and 73.33 ± 5.37, respectively, during the active nicotine condition and 126.00 ± 4.03/70.83 ± 3.87 during the placebo nicotine condition.

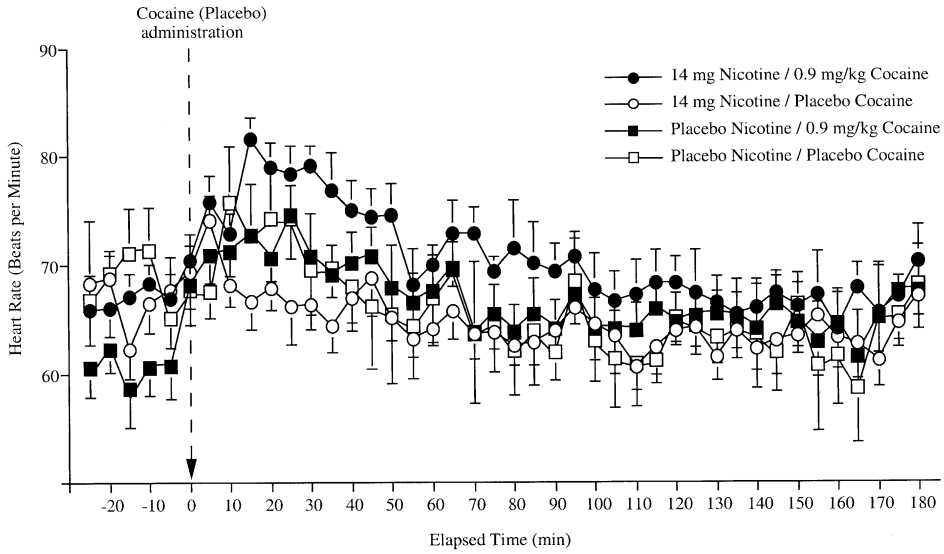

Fig. 1. Mean (±S.E.M.) heart rate (bpm) following 0.9 mg/kg intranasal cocaine (filled symbols) or placebo (open symbols) administration during active nicotine (circle symbols) and placebo nicotine (square symbols) pretreatment conditions. Heart rates were calculated from continuous recordings and averaged over consecutive 5-min time intervals. Cocaine (or placebo) was administered at time 0 (arrow).

3.2. Subjective effects

3.2.1. Visual analog scales

Analysis of baseline scores revealed no significant differences in VAS ratings as a function of nicotine pretreatment. Analysis of the VAS scores during the 60 minutes post-cocaine revealed that cocaine significantly increased ratings of "high" [$F(1,3)=11.3$, $P<.0001$], "stimulated" [$F(1,3)=4.6$, $P=.006$], and desire to use cocaine [$F(1,3)=4.0$, $P=.01$] over time and decreased ratings of desire not to use cocaine [$F(1,3)=2.8$, $P=.04$] over time compared to placebo. There was a trend toward a significant main effect of nicotine dose for the VAS scale "stimulated" [$F(1)=4.1$, $P=.06$] (Fig. 2). A secondary analysis of peak

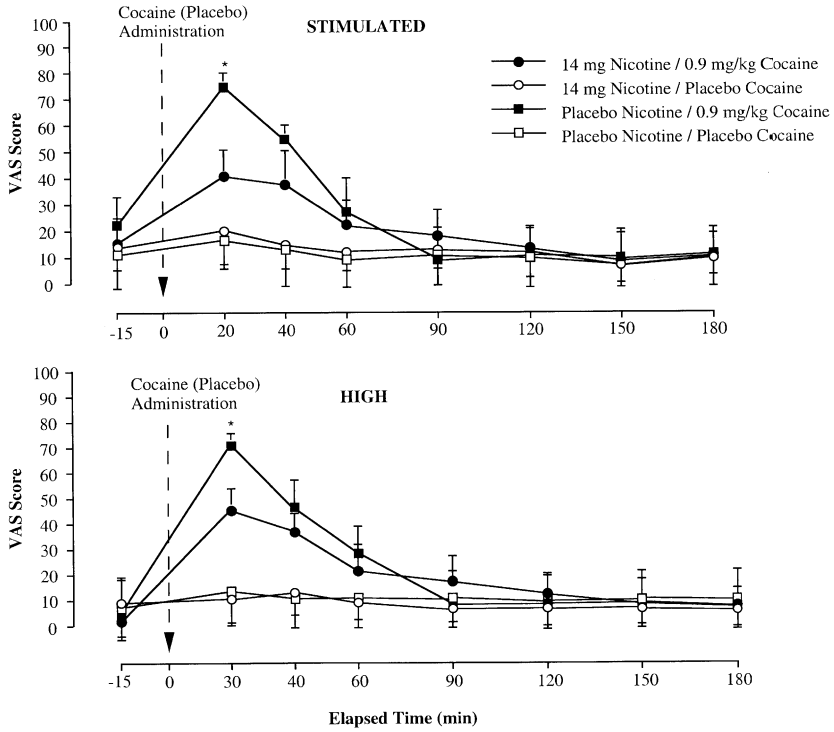

Fig. 2. Mean (±S.E.M.) subjective reports of "stimulated" and "high" via VAS following 0.9 mg/kg intranasal cocaine (filled symbols) or placebo (open symbols) during active nicotine (circle symbols) and placebo nicotine (square symbols) pretreatment conditions. Cocaine (or placebo) was administered at time 0 (arrow). * Statistically significant differences between peak ratings during the two nicotine pretreatment conditions at $P<.05$.

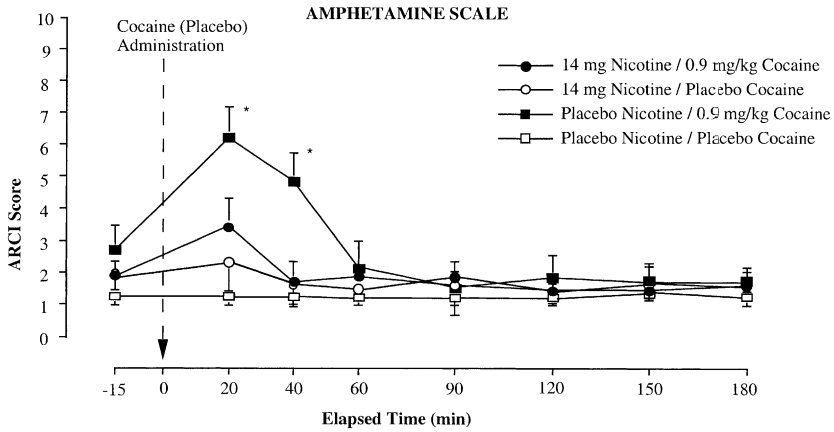

Fig. 3. Mean (±S.E.M.) scores of the amphetamine ARCI scale following 0.9 mg/kg intranasal cocaine (filled symbols) or placebo (open symbols) during active nicotine (circle symbols) and placebo nicotine (square symbols) pretreatment conditions. Cocaine (or placebo) was administered at time 0 (arrow). * Statistically significant differences between the two nicotine pretreatment conditions at $P<.05$.

VAS scores revealed a significant nicotine pretreatment by cocaine dose interaction on peak ratings of "high" [$F(1,1)=4.3$, $P=.05$] and peak ratings of "stimulated" [$F(1,1)=4.9$, $P=.04$].

3.2.2. Addiction Research Center Inventory

There were no significant differences in the baseline scores of any ARCI subscale as a function of nicotine pretreatment. Analysis of ARCI scores during the 60 minutes post-cocaine revealed that cocaine significantly increased the scores for the morphine Benzedrine group [$F(1,3)=4.0$, $P=.01$] and the amphetamine [$F(1,3)=4.2$, $P=.009$] subscales and decreased LSD scores [$F(1,3)=3.9$, $P=.01$] compared to placebo. There was a significant main effect of nicotine dose for the amphetamine scale [$F(1)=5.0$, $P=.04$], a main effect of time [$F(3)=10.6$, $P=.0001$], and a trend toward a significant nicotine dose by time interaction [$F(1,3)=2.6$, $P=.07$]. Analysis of peak ARCI scores showed a significant nicotine pretreatment by cocaine dose interaction on scores in the amphetamine subscale [$F(1,1)=5.1$, $P=.03$] (Fig. 3).

3.2.3. Joystick

None of the subjects reported detecting the effects of cocaine when the placebo dose was snorted. Two subjects failed to report detecting the effects of cocaine with the joystick device during the active cocaine/14 mg nicotine condition. One subject failed to report cocaine effects with the joystick during the active cocaine/placebo nicotine condition. Analysis of the data from the remaining subjects yielded a significant main effect of nicotine dose on latency to detect cocaine's effects [$F(1)=5.9$, $P=.04$]. Subjects took significantly longer to detect cocaine effects during the active nicotine condition (10.3 ± 1.9 min) than the placebo nicotine condition (5.1 ± 0.8 min) Similarly, there was a significant main effect of nicotine dose on latency to

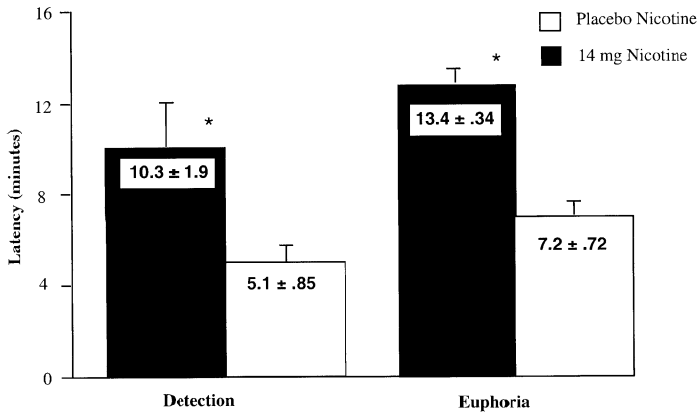

Fig. 4. Mean (±S.E.M.) latency to report detection of cocaine's effects (left panel) and cocaine-induced euphoria (right panel) following acute administration of an intranasal dose of cocaine (0.9 mg/kg). Data were collected via an instrumental joystick device available to subjects on a continuous basis. Filled columns depict the active nicotine (14 mg) condition and open columns depict the placebo nicotine condition. * Statistically significant differences between the two nicotine pretreatment conditions at $P<.05$.

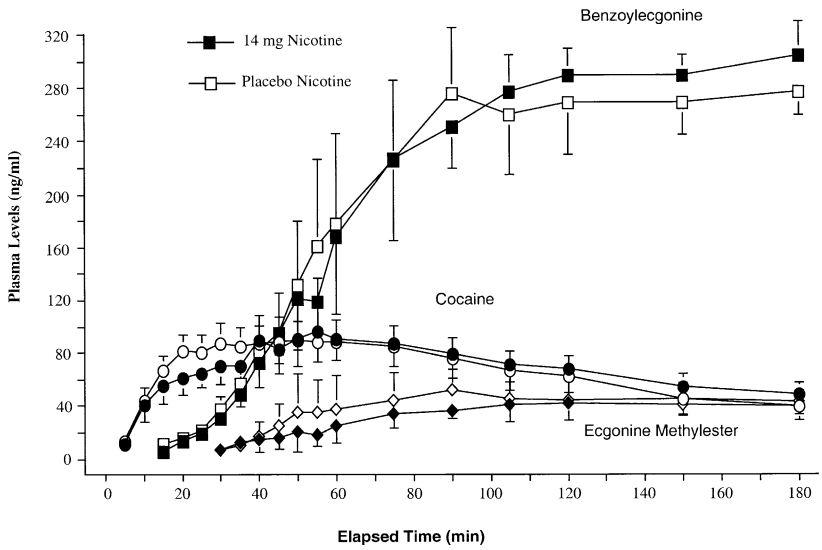

Fig. 5. Mean (±S.E.M.) plasma cocaine, BE, and EME levels after acute cocaine (0.9 mg/kg in) during active nicotine (14 mg) or placebo nicotine patch conditions.

report euphoria [$F(1)=31.8$, $P=.005$]. During the active nicotine condition subjects took longer to report cocaine-induced euphoria (13.4±0.3 min) than during the placebo nicotine condition (7.2±0.7 min) (Fig. 4). The overall duration of cocaine effects, duration of euphoria and dysphoria were not different between the two active cocaine conditions (data not shown).

3.3. Plasma levels

Repeated measures ANOVA revealed that there were no significant differences in plasma cocaine, BE, or EME levels as a function of nicotine pretreatment. Plasma cocaine levels peaked at 50-min post-administration during both the active nicotine and placebo nicotine pretreatment conditions. Peak plasma cocaine levels were 90.8±18.6 ng/ml during the 14-mg nicotine condition and 89.7±13.4 during the placebo nicotine condition. The highest BE levels were achieved at 180 min post-cocaine during both the active nicotine ($\bar{x}=304.54\pm25.70$) and the placebo nicotine ($\bar{x}=277.18\pm17.43$) conditions. Similarly, peak EME levels occurred at 150 min for the active nicotine ($\bar{x}=42.13\pm3.6$) and the placebo nicotine ($\bar{x}=36.18\pm14.12$) condition (Fig. 5).

4. Discussion

The findings from the present study suggest that nicotine pretreatment alters some of the positive subjective effects of acute intranasal cocaine in humans. Specifically, when treated with nicotine, subjects took significantly longer to report detecting the effects of cocaine and to report cocaine-induced euphoria compared to placebo. In addition, nicotine pretreatment attenuated the magnitude of cocaine-induced increases in reports of "stimulated" and "high."

Nicotine's modulation of cocaine's effects was most pronounced shortly after cocaine administration and did not persist beyond 40 min after cocaine. This profile of nicotine's attenuation of cocaine-induced euphoria may have important implications as it is well known that the immediate reinforcing effects of a drug are tied to the latency of onset of action and can influence a drug's abuse potential. For instance, Balster and Schuster (1973) demonstrated that increasing the infusion duration of an intravenous cocaine dose to monkeys (who were self-administering the drug) from 10 to 100 s virtually extinguished the drug-seeking behavior, even though the entire dose was still delivered. This suggests that attenuating the initial reinforcing effects of a drug may decrease subsequent self-administration. To the extent that transdermal nicotine attenuates the immediate, highly reinforcing phase shortly after cocaine administration, its potential as an adjunct to treating cocaine abuse/dependence deserves further scrutiny. Moreover, because transdermal nicotine has a demonstrated efficacy in treating tobacco dependence (Palmer et al., 1992), nicotine transdermal patches may be good candidates for individuals who are dually dependent on tobacco and cocaine.

An alternative explanation for our findings could be that nicotine deprivation during the placebo nicotine condition may have enhanced cocaine's subjective effects rather than an attenuation of cocaine's effects by active nicotine. However, the magnitude of cocaine's subjective effects during the placebo nicotine condition in the present study was comparable to that previously reported by our group in studies of male nonsmokers (Kouri et al., 2000; Lukas et al.,

1996), suggesting that this was not the case. Even though subjects in the placebo nicotine condition may have been experiencing some nicotine withdrawal, baseline levels of "anxious" and "bad" were not different between placebo-treated and nicotine-treated subjects (data not shown). Because subjects in this study were not heavy smokers, nicotine withdrawal did not appear to be severe enough to be reflected in the subjective reports of mood.

In contrast to the findings of Reid et al. (1998), we did not find increases in cocaine craving with nicotine treatment. Subject's reported "desire to use" cocaine was significantly increased in the present study, but only as a function of the cocaine dose. Methodological differences between the two studies can explain the discrepancy in results. The subjects in Reid et al.'s study had histories of heavy crack cocaine use while our subjects were recreational users with and average cocaine use of two times per month. The nicotine dose used in their study was significantly higher (two 22-mg patches) than the dose in the present study (14 mg) and cocaine craving was induced by the presentation of cues in their study while we measured spontaneous craving.

It is important to note that Reid et al. reported that nicotine reduced cocaine craving prior to cocaine cue testing, suggesting that nicotine might produce a decrease in basal levels of cocaine craving. This appears to be consistent with our finding of an attenuation of some of cocaine's effects by nicotine. Therefore, despite the methodological differences between the two studies, both support the contention that nicotine (not necessarily tobacco) and cocaine may share a number of fundamental effects that contribute to their reinforcing efficacy. Our findings also are consistent with those of a recent preliminary report (Sobel and Griffiths, 2000) indicating that nicotine pretreatment via a transdermal patch decreases some of the subjective effects of intravenous cocaine including "high," "stimulated," and "drug effect."

Another important finding from the present study is that nicotine's attenuation of cocaine's subjective effects occurred in the absence of any significant physiological or pharmacokinetic effects. Even though subjects treated with the nicotine patch had slightly elevated heart rate levels during baseline, this difference was only about 8 bpm and was not statistically significant. As subjects had the patch on for less than 24 h, it is likely that this slight elevation in heart rate simply reflects the acute effects of nicotine. The magnitude of cocaine-induced increases in heart rate (from baseline to peak) was similar during the two nicotine conditions. Similarly, nicotine did not alter cocaine-induced decreases in skin temperature. This finding is consistent with previous published reports (Reid et al., 1998).

The results from the present study should be interpreted in the context of several methodological limitations. First, the timing of nicotine patch application was a few hours different between the placebo and active conditions. This difference between the two conditions was due to the fact that we could not obtain placebo patches and had to maintain the blind by having a research assistant apply the placebo patch. However, even though subjects were treated differently during the two conditions, none of the VAS or ARCI scores during baseline reflected any differences, suggesting that this slight procedural change did not have a significant effect on behavior. Second, only one dose of nicotine was used over a relatively short period of time. It is possible that higher nicotine doses or a lower dose administered over a longer period of time may have yielded different results. We used a relatively low nicotine dose primarily for safety purposes and now that we have established that subjects can tolerate these doses, future studies in our laboratory will investigate the interaction between higher nicotine doses and cocaine's effects.

In conclusion, the present study provides some evidence that short-term treatment with a nicotine transdermal patch attenuates some of cocaine's subjective effects without affecting cocaine-induced changes in heart rate, skin temperature, blood pressure, or pharmacokinetic profiles. These findings suggest that nicotine transdermal patches have the potential for being useful adjuncts in the management of a select population of cocaine-dependent individuals. Further studies using higher nicotine doses and longer treatment intervals will be necessary to determine the role of nicotine transdermal patches in both dependence on cocaine alone as well as those who are dually dependent on cocaine and tobacco.

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