Subjective and Physiological Effects of Intravenous Nicotine and Cocaine in Cigarette Smoking Cocaine Abusers

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ABSTRACT

The subjective and physiological effects of intravenously administered cocaine and nicotine were compared in 10 cigarette-smoking cocaine abusers. Subjects abstained from smoking at least 8 h before each session. Under double blind conditions, subjects received placebo, cocaine (10, 20, and 40 mg/70 mg), or nicotine (0.75, 1.5, 3.0 mg/70 kg) in mixed order. Physiological and subjective data were collected before and repeatedly after each intravenous drug administration. Subjects also completed a drug versus money multiple-choice procedure in which they chose between that day’s drug and 44 monetary values. Both drugs increased blood pressure and heart rate and decreased skin temperature. Nicotine showed a more rapid onset of subjective effects than cocaine. Overall, although both cocaine and nicotine increased subjective ratings of “drug effect”, “rush”, “good effects”, “liking”, “high”, and “stimulated”, only nicotine increased ratings of “bad effects” and “jittery”. Although the highest nicotine dose produced greater effects than the highest cocaine dose on most subjective measures, the highest cocaine dose produced somewhat greater ratings of drug liking. At doses that produced comparable ratings of drug effect (40 mg/70 kg cocaine versus 1.5 mg/70 kg nicotine), cocaine produced significantly greater good effects, whereas nicotine produced greater bad effects. All three cocaine doses and the intermediate and high nicotine doses were frequently categorized as producing effects similar to those of cocaine or amphetamine. The drug versus money measure showed that the highest cocaine dose was worth twice as much as the highest nicotine dose. Thus, intravenous nicotine and cocaine can be differentiated by their subjective and reinforcing effects.

Cocaine and nicotine are two of the most widely abused stimulant drugs in the world. Cocaine is self-administered by a variety of routes, including inhalation, insufflation, and intravenous administration. Nicotine, the active ingredient in tobacco that leads to addiction (U.S. Department of Health and Human Services, 1988), is commonly self-administered by the inhalation of tobacco smoke and by insufflation and chewing of tobacco. Although nicotine is not self-administered i.v. by users of this drug, for research purposes, rapid i.v. injection closely mimics the swift transport of nicotine into the systemic circulation that is provided by cigarette smoke inhalation (Henningfield et al., 1985; Evans et al., 1993). Previous human laboratory studies using i.v. administration of nicotine suggest that nicotine produces central effects similar to the prototypical abused stimulants such as cocaine and amphetamine. Similar to i.v. cocaine, i.v. nicotine produces dose-related increases in heart-rate and blood pressure as well as dose-related increases in subjective ratings of “drug liking” in participants with histories of drug abuse and cigarette smoking (Henningfield et al., 1985, 1983; Soria et al., 1996; Garrett and Griffiths, 1997). In these studies, i.v. nicotine was categorized as producing effects like cocaine on a questionnaire that contained the names of 10 commonly abused drugs (Henningfield et al., 1983, 1985). Although nicotine and cocaine have been examined separately in clinical pharmacology studies, these drugs have yet to be compared within the same experiment.

Although both nicotine and cocaine are known to alter dopaminergic activity, it is not known whether their subjective and physiological effects are related to this central mechanism of action. Evidence suggests that dopaminergic neurotransmission is essential for the psychostimulant actions of these drugs. For example, cocaine has been shown to produce its reinforcing and psychostimulant actions through the blockade of dopamine reuptake (Koe, 1976; Ritz et al., 1987; Bergman et al., 1989). Nicotine, like cocaine, increases dopaminergic activity by inhibiting dopamine reuptake (Izenwas-
ser et al., 1991) and increases dopamine release (Hart and Kair, 1996; Nisell et al., 1997). Self-administration of nicotine and cocaine in rats was associated with similar patterns of neuronal activation (i.e., expression of Fos-related protein) in discrete structures of the mesocorticollimbic dopamine system, thus suggesting a common substrate for these addictive drugs (Pich et al., 1997).

Although both clinical and preclinical evidence support the idea that cocaine and nicotine have similar pharmacologic profiles, to our knowledge, these drugs have not been directly compared in humans. Thus, the purpose of the present investigation was to directly compare the subjective, physiological, and reinforcing effects of i.v. cocaine and nicotine in human subjects. The subject population selected for study were individuals with histories of exposure to both cocaine and nicotine—cocaine abusers who smoke cigarettes.

Materials and Methods

Subjects. Participants were 15 adult volunteers (3 women and 12 men) who were recruited through newspaper advertisements and word of mouth. For inclusion in the study, subjects had to report a minimum of 6 months of cocaine abuse and report using either smoked or i.v. cocaine use at least 2 days a week for the previous 6 weeks. All subjects had a Diagnosis and Statistical Manual of Mental Disorders diagnosis of cocaine dependence (American Psychiatric Association, 1994). All subjects smoked at least 20 tobacco cigarettes per day for at least 1 year before participation, had a Fagerstrom questionnaire score (a measure of nicotine dependence and tolerance) of at least 6, and an afternoon carbon monoxide level of at least 10 ppm at screening. All participants were in good health, without any significant medical or psychiatric illness with the exception of drug and nicotine dependence. Before enrollment, participants were screened for medical problems and drug use via assessment of medical history, physical examination, laboratory tests of blood chemistry, ECG, blood pressure, and urinalysis. A battery of psychiatric instruments was used to screen for psychiatric disorders. Participants were not enrolled if they had histories of seizure disorders, hypertension, abnormal ECG, significant risk factors for heart disease, or poor venous access. Women were excluded from the study if they were pregnant.

Participants were informed that the purpose of the study was to learn more about the effects of certain drugs and the extent to which these drugs are liked. Participants were told that they could receive low to moderate doses of various types of drugs. They were told the various types of drugs they might receive included sedatives (e.g., alprazolam, diazepam, lorazepam, triazolam, and methocarbamol), antihistamines (e.g., diphenhydramine and promethazine), stimulants and weight loss medications (e.g., caffeine, d-amphetamine, cocaine, diaethylpropion, methylphenidate, nicotine, phentermine, and phenylpropanolamine), opioids (e.g., heroin, morphine, codeine, and buprenorphine), antipsychotics (e.g., chlorpromazine and haloperidol), and miscellaneous drugs, including alcohol and marijuana. Participants were told that their daily drug dose could consist of any of the drugs listed above or a placebo (a blank, no drug).

This study was approved by the Institutional Review Board of the Johns Hopkins Bayview Medical Center. Participants gave their written consent before beginning the study and were paid for participation.

Five volunteers did not complete the study due to personal reasons. A total of 10 volunteers completed the study; all were African American. The 10 subjects ranged in age from 25 to 43 years (mean, 35 years), and their weight ranged from 56 to 85 kg (mean, 69.4 kg). Subjects reported 3 to 14 years (mean, 9 years) of cocaine use and estimated using from $30 to $200 per occasion (mean, $67) three to six times a week (mean, four times a week). All subjects reported some other occasional use of a wide range of drugs, including alcohol, marijuana, opiates, stimulants, and sedatives. Three of the 10 subjects reported using i.v. cocaine; the remaining 7 subjects reported using cocaine via smoking and/or the intranasal route but not the i.v. route. The 10 subjects reported smoking tobacco cigarettes for 7 to 30 years (mean, 18 years) before the study, and the number of cigarettes smoked ranged from a half a pack to two packs a day (mean, 1.25 packs). Initial CO readings ranged from 10 to 20 ppm (mean, 15.5 ppm).

Study Design and General Procedures. This study was conducted while subjects resided on a residential research facility at the Behavioral Pharmacology Research Unit of the Johns Hopkins University School of Medicine for approximately 4 weeks. Before admission, and when informed consent was obtained, subjects were informed that the objective of the study was to learn more about the behavioral effects of certain drugs. Subjects were oriented to the residential unit, and then written consent for research participation was obtained. Although cigarette smoking was permitted for the duration of the study, subjects were restricted from smoking at least 8 h before each session. Carbon monoxide levels were assessed at baseline (at least 8 h before each session) and then immediately before each session to verify compliance with the smoking restriction.

The study consisted of 11 sessions. All sessions were conducted under double blind conditions. The purpose of the first four sessions was to assess the safety and tolerability of the stimulant doses (dose run-up). The remaining seven sessions were experimental sessions.

The testing room consisted of a desk and chair for the research assistant, a cushioned chair for the participant, a microcomputer (Apple IIGS, Cupertino, CA), a computer keyboard, a joystick, and physiological monitoring equipment (blood pressure, heart rate, skin temperature, respirations, and ECG). The microcomputer was used to obtain subjective and physiological measures. For subjective measures, participants entered their responses using the computer keyboard or the joystick. The research assistant was seated behind the computer and used the keyboard to initiate tasks.

Drug Preparation and Administration. Cocaine HCl powder (Mallinckrodt Inc., St. Louis, MO) and nicotine hydrogon tartrate (Gallard-Schlesinger Chemical Company, Carle Place, NY) were dissolved in the appropriate amount of saline (0.9% sodium chloride) and filtered through a 0.22-µm pore size filter (Millipore Products Division, Bedford, MA) into a sterile pyrogen-free vial. Cocaine (10, 20, and 40 mg/70 kg), nicotine (0.75, 1.5, and 3.0 mg/70 kg), and placebo (0.9% sodium chloride sterile saline) were administered through an indwelling venous catheter in a total volume of 5 ml at a 10-s infusion rate. Doses of both drugs are expressed as the base. All drugs were infused manually by a physician.

Dose Run-up Sessions. The first four experimental sessions for all subjects were 2- to 3-h dose run-up sessions to determine the safety and tolerability of the drug doses to be administered in the remaining seven experimental sessions. Although all dose run-up sessions were conducted in the morning, the exact time that the sessions were conducted varied among subjects but was consistent for an individual subject. Subjects ate a light breakfast approximately 2 h before each session. Before the start of each session, subjects had an i.v. catheter inserted into the dominant arm. A slow-drip i.v. line was maintained throughout each session. During the four dose run-up sessions, participants received two or three injections separated by 60 min. The order of exposure to cocaine and nicotine was counterbalanced across subjects (half of the subjects received the two cocaine dose run-up sessions first, and the other half received the two nicotine dose run-up sessions first). The doses administered in the two cocaine run-up sessions were (1) placebo, 10 and 20 mg/70 kg and (2) placebo and 40 mg/70 kg. The doses administered in the two nicotine dose run-up sessions were (1) placebo, 0.75 and 1.5 mg/70 kg and (2) placebo and 3.0 mg/70 kg. All doses of each drug were administered over a 10-s infusion period. Each dose-run up session was separated by at least 48 h. During each dose-run up
session, baseline physiological and subjective data were collected before the first injection. Immediately after each injection and in 2-min intervals thereafter, subjects completed subjective questionnaires relating to the drug effect for the duration of the session. Physiological data were collected continuously (minute-by-minute), 20 min before each drug injection, and for 60 min after the injection. Self-report and physiological data were collected for 60 min after the injection.

**Experimental Session.** After the four dose run-up sessions, seven experimental sessions were conducted up to 5 days a week (Monday through Friday). Although all experimental sessions were conducted in the afternoon, the exact time that the sessions were conducted varied among subjects but was consistent for an individual subject. Subjects ate a light lunch approximately 2 h before each session. Before the start of each experimental session, subjects had an i.v. catheter inserted into the dominant arm. During each experimental session, a single dose of either placebo, cocaine (10, 20, or 40 mg/70 kg), or nicotine (0.75, 1.5, or 3.0 mg/70 kg) was administered. The sequence of the seven dose conditions across subjects was mixed. All drug doses were administered over a 10-s infusion period. Each experimental session was separated by at least 24 h. Data collection in the experimental sessions was the same as that in the dose run-up sessions.

**Visual Analog Scales.** Subjects completed a set of 11 visual analog scales (VAS) asking, “Do you feel a rush?” “Do you feel a drug effect?” “Does the drug have any good effects?” “Does the drug have any bad effects?” “Do you like the drug?” “How high are you?” “How drowsy/leepy are you?” “How alert/energetic are you?” “Do you feel jittery?” “Do you feel relaxed?” and “Do you feel stimulated?” Participants responded by positioning an arrow along a 100-mm line marked from 0 (“Not at all”) to 100 (“Extremely”). These visual analog scales were completed once before the drug injection and every 2 min for 30 min after the injection.

**Addiction Research Center Inventory.** Participants completed the short form of the Addiction Research Center Inventory (ARCI), which is a 49-item questionnaire that is consists of five subscales: amphetamine (A), an amphetamine scale that provides an assessment of amphetamine-like effects; benzodiazepine group (BG), an amphetamine-sensitivity scale that provides a measure of benzodrine-like effects, intellectual efficiency, and energy; lysergic acid diethylamide (LSD), a scale that provides a measure of euphoria and somatic complaints; morphine-benzodiazepine group (MBG), a scale that provides a measure of euphoria; and pentobarbital-chlorpromazine alcohol group (PCAG), a scale that provides a measure of sedation (Martin et al., 1971). Subjects completed the ARCI once before the injection and at approximately 35 min after the drug injection. Because most drug effects had dissipated by approximately 15 min after drug administration, subjects were instructed to answer the questions on the ARCI retrospectively for how they felt since drug injection.

**Pharmacological Class Identification Questionnaire.** Approximately 40 min after each drug injection, subjects completed a pharmacological class identification questionnaire on which they were asked to select the drug class that best described which drug they had received that day. After participants selected the drug class option, the computer screen displayed the names of specific drugs of that drug class. Subjects then chose, from the list of specific drugs, which compound was most similar to the drug they had received. The drug class options included sedatives or muscle relaxants (diazepam (Valium; Roche; Puerto Rico), alprazolam (Xanax; Pharmacal & Upjohn, Piscataway, NJ), lorazepam (Ativan; Wyeth-Ayerst), triazolam (Halcion; Pharmacal & Upjohn), methohexital (Robaxin; Robins), barbiturates, alcohol, or other), antihistamines [diphenhydramine (Benadryl; Parke-Davis, Atlanta, GA), promethazine (Phenergan; Wyeth-Ayerst) or other], stimulants or weight loss medications [amphetamine, cocaine, nicotine, caffeine, methylphenidate (Ritalin; Ciba-Geigy, Basel, Switzerland), dietyropipion (Tenuate; Merrell Dow, Cincinnati, OH), phenmetrazine (Preludin; Boehringer Ingelheim, Ridgefield, CT), phenylpropanolamine (control), or other], opiates [heroin, morphine, codeine, Percodan (DuPont Merck, Wilmington, DE), methadone, or other], hallucinogens [phencyclidine (PCP), LSD, marijuana, mescaline, 3,4-methylenedioxyamphetamine (MDMA; “Ecstasy” or street name “Extasy”), or other], and blank or placebo.

**Sensory Assessment Questionnaire.** At the end of each session, immediately after the completion of the Pharmacological Class Identification Questionnaire, participants were asked by the research assistant to describe any unusual visions, tastes, or smells that they experienced during the session. The research assistant wrote, in detail, the subject’s response onto a sensory assessment questionnaire form.

**Physiological Measures.** Participants were monitored continuously on a number of physiological measures that included blood pressure (systolic and diastolic), heart rate, respiration rate, and skin temperature with data output recorded minute-by-minute. Blood pressure and heart rate were measured automatically with a Sentron Automatic Blood Pressure Monitor (Bard Biomedical Division, Lombard, IL) for the first three subjects and with a Criticare noninvasive patient monitor (Criticare Systems Inc., Waukesha, WI) for the remaining seven subjects. The blood pressure cuff was placed on the nondominant arm. Respiration rate (breaths/min) was measured with a bellows (Pneumo Chest Assembly, Lafayette, IN) that was placed around the lower chest and connected to a pressure-sensitive switch (Micro Pneumatic Logic, Inc., Fort Lauderdale, FL). Skin temperature was monitored using a skin-surface thermometer (Yellow Springs Instrument Co., Yellow Springs, OH) taped to the index finger of the nondominant hand. Data for each of these measures were collected and stored using the previously described microcomputer. In addition to the above physiological parameters, ECG was monitored before and periodically after the drug injection by a physician.

**Drug versus Money Multiple-Choice Questionnaire.** The Multiple-Choice Procedure was developed as a tool to efficiently assess drug reinforcement in humans (Griffiths et al., 1993, 1996). The present study used a modified version of the drug versus money version of the multiple-choice procedure, which provided a contingency-based assessment of the monetary value for each drug condition (Mumford et al., 1995). After completing the Pharmacological Class Identification Questionnaire, volunteers completed the Drug versus Money Multiple-Choice Questionnaire, which consisted of 44 drug versus money choices; on each form, the volunteer was required to make 44 discrete choices between the drug received that day and 44 monetary values arranged on an increasing scale. The scale started with $0.25 and increased in $0.25 increments until $20.00 was reached, at which point the scale increased in $0.50 increments with the last value being $20.00. This form was completed after each of the seven drug conditions. Thus, during the course of the crossover experiment, subjects made 308 discrete choices (i.e., 44 choices on each Drug versus Money Multiple-Choice Questionnaire × seven drug conditions), which were numbered consecutively from 1 to 308. A “reinforcement session” was conducted 24 h after the last of the seven drug conditions. On the reinforcement session, subjects drew one number from a container holding numbers from 1 to 308 with each number corresponding to each drug versus money choice. The choice corresponding to the randomly selected number was reinforced (i.e., if the subject had chosen drug, then that specific dose of drug was readministered; if the subject had chosen money, then the indicated amount of money was added to his or her study earnings). After learning the outcome of the Drug versus Money Multiple-Choice Questionnaire, subjects completed a standard experimental session; subjects who chose drug received that drug, and subjects who chose money did not receive a drug during this session. Before beginning the study, volunteers received explicit instructions on the operation of the multiple-choice procedure, including that their drug versus money choice performance would be randomly reinforced on the final experimental session. Results from the Drug versus Money
Multiple-Choice Questionnaire are presented as the maximum dollar amount at which subjects chose drug over money. That dollar amount is defined as the “crossover point”.

Subjects were informed that multiple-choice forms from the safety assessment sessions 1 through 4 would be used for practice purposes only. Multiple-choice forms from the seven drug conditions (experimental sessions 5–11) were used for the reinforcement session.

Data Analyses. Data from the dose run-up session were used for safety assessment purposes only and were not analyzed statistically. Time course data from the experimental sessions for VAS and physiological data were analyzed using univariate two-factor repeated measures analysis of variance (ANOVA). The factors in the analysis were drug condition (placebo; 10, 20, and 40 mg/70 kg cocaine; and 0.75, 1.5, and 3.0 mg/70 kg nicotine) and time (predrug and 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, and 30 min postdrug). Data from the ARCI were expressed as change scores (postdrug minus predrug values) and analyzed by ANOVA with drug condition as the within-subject factor. Tukey’s post hoc tests were used to conduct pairwise comparisons. Results were considered significant when $P \leq .05$ and marginally significant when $P \leq .1$. For repeated measures ANOVAs, Huynh-Feldt corrected $P$ values are reported.

Results

VAS. Both cocaine and nicotine produced orderly dose- and time-related changes on several of the VAS (Figs. 1 and 2). Cocaine produced dose-related increases in ratings of “drug effect”, “rush”, “good effects”, “like drug”, “high”, and “stimulated”. Maximum drug effects were generally observed 4 min after drug injection. The low dose of cocaine (10 mg/70 kg) generally produced small but nonsignificant increases over placebo ratings. The intermediate (20 mg/70 kg) and the high (40 mg/70 kg) cocaine doses produced significant increases over placebo ratings with significant effects lasting up to 8 and 12 min after injection, respectively.

Nicotine produced dose- and time-related increases in “drug effect”, “rush”, “good effects”, “bad effects”, “like drug”,

![Fig. 1. Time-action functions for i.v. cocaine and nicotine on subject ratings of “Do you feel a drug effect?” “Do you feel a rush?” “Does the drug have any good effects?” “Does the drug have any bad effects?” X-axes, time after drug injection in minutes; 0 indicates predrug. Y-axes, subjects ratings in millimeters. Data points show mean values for 10 subjects. • and ▲, values that are significantly different from the corresponding placebo value at the same time point ($P \leq .05$, Tukey’s post hoc test).](image-url)
“high”, “stimulated”, and “jittery”. Maximum drug effects were generally observed approximately 2 min after drug injection. Across the measures shown in Figs. 1 and 2, the low dose of nicotine (0.75 mg/70 kg) did not produce significant increases over placebo ratings. The intermediate (1.5 mg/70 kg) and high doses (3.0 mg/70 kg) of nicotine produced significant increases over placebo ratings with effects lasting up to 4 and 6 min after injection, respectively.

The remaining ratings from the VAS (“alert/energetic”, “drowsy/sleepy”, and “relaxed”) were not significantly affected by either cocaine or nicotine.

Comparing across cocaine and nicotine, both quantitative and qualitative differences are apparent. In Figs. 1 and 2, the high dose of nicotine (3.0 mg/70 kg) produced larger magnitude increases than the high dose of cocaine (40 mg/70 kg) on all ratings except for drug liking. Tukey’s post hoc values of maximal effects in Figs. 1 and 2 showed that the high dose of nicotine produced significantly (“rush”, “good effects”, “bad effects”, “high”, “stimulated”, and “jittery”) or marginally significantly (“drug effect”) greater ratings than the high dose of cocaine. For example, ratings of rush and high were 69% and 100% larger, respectively, after the high dose of nicotine than after the high dose of cocaine. These differences suggest that a relatively higher dose of nicotine than cocaine was studied.

Inspection of these data also show qualitative differences between cocaine and nicotine. Nicotine, but not cocaine, produced dose- and time-dependent increases in the ratings of “bad effects” and “jittery”. Although the high dose of nicotine produced greater effects than the high dose of cocaine on most measures, this was not the case with drug liking. In
fact, the maximal liking produced by the high dose of cocaine was somewhat larger than that produced by the high dose of nicotine (Tukey’s $P < .1$). The relatively smaller ratings of “drug liking” compared with the other subjective effects observed with nicotine suggest that the aversive subjective effects (i.e., “bad effects”) may modulate the positive subjective effects and culminate in lower ratings of “drug liking” with nicotine. Although the high dose of cocaine and the intermediate dose of nicotine (1.5 mg/70 kg) produced quite comparable increases in ratings of drug effect, the high cocaine dose produced greater ratings of “good effect” (Tukey’s $P < .05$) and “liking” (Tukey’s $P < .1$) than the intermediate dose of nicotine. This intermediate dose of nicotine also produced greater increases in ratings “bad effects” than the high dose of cocaine (Tukey’s $P < .05$).

**ARCI.** Figure 3 shows the results from the ARCI. There was a main effect of drug condition on the PCAG ($F(6, 54) = 3.79, P = .003$), MBG ($F(6, 54) = 3.02, P = .022$), and LSD ($F(6, 54) = 7.15, P < .001$) scales. Post hoc values revealed that the high dose of nicotine (3.0 mg/70 kg) produced significant increases over placebo on the PCAG scale (a measure of sedation) and the LSD scale (a measure of dysphoria and somatic complaints) of the ARCI. Neither drug significantly increased scores on either stimulant scale (A and MBG) relative to placebo. As seen in Fig. 3, in general, cocaine tended to increase and nicotine to decrease MBG scale scores. There was a trend (Tukey’s $P = .1$) for the MBG scale scores with the intermediate nicotine dose (1.5 mg/70 kg) to be lower than the intermediate (20 mg/70 kg) and high (40 mg/70 kg) cocaine doses.

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**Fig. 3.** Dose-effect curves for nicotine and cocaine on the scales of the ARCI. X-axes: drug dose (mg/70 kg); 0 indicates placebo. Y-axes, scale scores. Data points show mean ± S.E.M. for 10 subjects. ■, Values that are significantly different from the corresponding placebo value ($P < .05$, Tukey’s post hoc test).
Pharmacological Class Identification Questionnaire. Table 1 shows the results from the Pharmacological Class Identification Questionnaire. Placebo administration was correctly identified as a blank or placebo on 70% of occasions. The highest doses of cocaine and nicotine were never identified as blank or placebo. This table also shows that doses of 10, 20, and 40 mg/70 kg of i.v. cocaine were identified as stimulants on 60%, 60%, and 70% of occasions, respectively. When subjects identified a dose of cocaine as a stimulant, they usually (63%) further identified the stimulant as being cocaine or amphetamine and they never identified it as being nicotine.

In contrast to the lowest dose of cocaine, the lowest dose of nicotine (0.75 mg/70 kg) was more often identified as placebo (50% of occasions) than a stimulant (30% of occasions). The intermediate nicotine dose (1.5 mg/70 kg) resulted in the greatest number of stimulant identifications (80% of occasions). The highest dose of nicotine (3.0 mg/70 kg) was identified as a stimulant and an opiate on 50% and 40% of occasions, respectively. As with cocaine, when subjects identified a dose of nicotine as a stimulant, they usually (75%) further identified the stimulant as being cocaine or amphetamine and they rarely (6%) identified it as being nicotine.

Sensory Assessment Questionnaire. As shown in Table 2, increasing doses of i.v. cocaine and nicotine produced increases in the frequency of positive responses on the Sensory Assessment Questionnaire (i.e., experience of any unusual tastes, visions, or smells). Placebo and 10, 20, and 40 mg/70 kg of cocaine resulted in 10%, 40%, 40%, and 70%, respectively, of affirmative responses on one or more occasions on the sensory measure questionnaire. For nicotine, 0.75, 1.5, and 3.0 mg/70 kg resulted in 10%, 60%, and 80%, respectively, of subjects responding affirmatively on one or more occasions on the sensory measure questionnaire. The onset of these sensory experiences generally occurred 1 min after the injection and did not exceed 5 min. Table 2 shows individual subject responses, which were generally visual and gustatory in nature, on the sensory measure questionnaire after administration of the highest doses of cocaine and nicotine. The responses at the lower doses of i.v. cocaine and nicotine were generally qualitatively similar to those shown in Table 2.

Physiological Measures. Physiological effects (systolic and diastolic blood pressure, heart rate, skin temperature, and respirations) for i.v. cocaine and nicotine were generally qualitatively similar to those shown in Fig. 4. Both the highest doses of cocaine and nicotine in-

<table>
<thead>
<tr>
<th>Category</th>
<th>Placebo</th>
<th>Cocaine (mg/70 kg)</th>
<th>Nicotine (mg/70 kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blank or placebo</td>
<td>70</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Stimulant</td>
<td>30</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>Sedative/muscle relaxant</td>
<td>0</td>
<td>10</td>
<td>10</td>
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<tr>
<td>Antihistamine</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Opiate</td>
<td>0</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Hallucinogen</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Table 1. Pharmacological class identification across 10 subjects. Data are derived from 10 subjects; each value in the table shows the percentage of subjects selecting a given drug category.*

<table>
<thead>
<tr>
<th>Subject</th>
<th>Cocaine</th>
<th>Nicotine</th>
</tr>
</thead>
<tbody>
<tr>
<td>S01 Blurry vision</td>
<td>Blurry vision</td>
<td></td>
</tr>
<tr>
<td>S02 None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>S03 Blurry vision and dry mouth</td>
<td>Blurry vision</td>
<td></td>
</tr>
<tr>
<td>S04 None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>S05 Sour taste</td>
<td>Sour taste</td>
<td></td>
</tr>
<tr>
<td>S06 None</td>
<td>Blurry vision</td>
<td></td>
</tr>
<tr>
<td>S07 Bitter taste</td>
<td>Blurry vision, bitter taste</td>
<td></td>
</tr>
<tr>
<td>S08 Dizzy, blurry vision, and bitter taste</td>
<td>Blurry vision, dry mouth</td>
<td></td>
</tr>
<tr>
<td>S09 Lights bright, vinegar taste and sedative smell</td>
<td>Blurry vision, medicine</td>
<td></td>
</tr>
<tr>
<td>S10 Blurry vision and dry mouth, bitter taste</td>
<td>Blurry vision, dry mouth</td>
<td></td>
</tr>
</tbody>
</table>

*Table 2. Subject response on Sensory Measure Questionnaire after administration of 40 mg/70 kg of intravenous cocaine and 3.0 mg/70 kg of intravenous nicotine.*

Fig. 4. Time-action functions for i.v. cocaine and nicotine on selected physiological measures. X-axes: time after drug injection in 2-min blocks (P indicates predrug injection). Y-axes, systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg), heart rate (beats/min), respiration (breaths/min), and skin temperature (°C). Data points show mean values for 10 subjects. A, O, and • values that are significantly different from the corresponding placebo value at the same time point. *Significant difference between the high dose of nicotine and the high dose of cocaine (P = .05, Tukey’s post hoc test).
creased systolic blood pressure relative to placebo; cocaine (40 mg/70 kg) significantly increased systolic blood pressure from 4 to 6 min and at 16 min after injection; and nicotine (3.0 mg/70 kg) increased systolic blood pressure at 2 min. Cocaine increased diastolic blood pressure from 4 to 6 min after injection. There was a trend (Tukey’s $P < .1$) for nicotine to also increase diastolic blood pressure 2 min after injection. The intermediate dose of cocaine increased heart rate from 2 to 18 min after injection, whereas the intermediate nicotine dose increased heart rate from 2 to 6 min after injection. The high dose of cocaine elevated heart rate from 2 to 30 min, and the high nicotine dose increased it from 2 to 30 min after injection. Relative to placebo, the low, intermediate, and high nicotine doses decreased skin temperature from 8 to 26 min, 8 to 30 min, and 6 to 30 min after injection, respectively. The highest nicotine dose produced a significant decrease in skin temperature from 8 to 20 min after injection relative to placebo. Comparisons of the highest doses of cocaine and nicotine revealed that cocaine produced greater decreases in skin temperature. Neither drug produced significant changes in respiration.

**Drug versus Money Choice Questionnaire.** Ordinarily dose-associated effects were observed in the amount subjects were willing to pay for each drug injection (i.e., crossover points on Drug versus Money Multiple Choice Questionnaire; Fig. 5). Subjects were willing to pay an average of less than $1 for the low dose of cocaine and the low and intermediate nicotine doses. They were also willing to pay a little over $3 for both the high dose of nicotine and the intermediate dose of cocaine. The highest dose of cocaine was worth the greatest amount of money ($6.23), almost twice that of the high dose of nicotine. The placebo injection was worth an average of $2; however, this was a result of one individual selecting $20 and all other subjects selecting $0.00.

**Fig. 5.** Mean ± S.E.M. monetary values (crossover points) from the multiple-choice forms after placebo, cocaine, and nicotine i.v. administration. X-axis, drug dose. Y-axis, amount of money ($) subjects were be willing to pay to receive that injection again. *Significant difference ($P ≤ .05$, Tukey's post hoc test) between cocaine 40 mg/70 kg and low doses of cocaine and nicotine.

**Discussion**

The administration of i.v. cocaine and nicotine produced dose- and time-related effects on a number of physiological, subjective, and behavioral responses. On many measures, the doses of nicotine and cocaine produced qualitatively similar effects, with the highest dose or doses resulting in significant effects relative to placebo. Nicotine showed a more rapid onset of effects than cocaine, with peak effects usually occurring at 2 and 4 min, respectively. Direct effects of nicotine on the heart and brain occur within 1 to 2 min (e.g., Benowitz and Jacob, 1987). In contrast, effects of cocaine have been shown to peak approximately 5 min after injection (Ashley and Hitzemann, 1990; Preston et al., 1992, 1993). The duration of the subjective effects were shorter with nicotine than cocaine. The effects of nicotine on VAS measures dissipated to placebo levels approximately 8 min after injection, whereas the effects of cocaine dissipated approximately 12 min after injection.

In the present study, cocaine produced dose- and time-associated increases in positive subjective reports (i.e., “rush”, “good effects”, “liking”, and “high”). These results are consistent with previous reports of dose-related increases in subjective ratings of “drug effect”, “rush”, “good effects”, “liking”, “high”, and “positive effects” (Fischman et al., 1983, 1990; Kumor et al., 1989; Foltin and Fischman, 1991; Preston et al., 1992, 1993; Walsh et al., 1994) after i.v. administration of cocaine. Similar to other studies, the peak changes in subjective effects with 16 to 48 mg of cocaine occurred approximately 4 min after injection.

Similar to cocaine, i.v. nicotine produced dose-related increases in “drug effect”, “rush”, “good effects”, “liking”, and “high”. However, nicotine was differentiated from cocaine by showing dose-related increases in ratings of “bad effects” and “jittery”. The positive subjective effects in the present study with nicotine are consistent with previous reports of pleasurable effects of nicotine when administered i.v. to cigarette smokers (Henningfield et al., 1983, 1985; Soria et al., 1996; Garrett and Griffiths, 1997).

Results from the present study suggest that relatively higher doses of nicotine than cocaine were studied. In ratings of overall drug effect, the high dose of nicotine was associated with greater ratings of drug effect relative to the high dose of cocaine. In fact, as shown in Figs. 1 and 2, on all measures except for “liking”, the high dose of nicotine produced relatively greater effects than the high dose of cocaine.

Nicotine and cocaine produced qualitatively different subjective effects. Nicotine, but not cocaine, produced dose- and time-dependent increases in ratings of “bad effects” and “jittery”. In contrast to the negative subjective effects produced by nicotine, the high dose of cocaine produced maximal ratings of liking that tended to be greater than those produced by the high dose of nicotine. The observations that nicotine produced greater negative subjective effects whereas cocaine produced greater positive subjective effects was also evident when doses of the two drugs that produced comparable ratings of drug effect were compared (e.g., 1.5 mg/70 kg versus 40 mg/70 kg). The intermediate dose of nicotine produced greater increases in the ratings of “bad effects” relative to the high dose of cocaine, in contrast, the high cocaine dose was associated with greater ratings of “good effect” and “liking” relative to the intermediate dose of nicotine.

The present results, which failed to show significant effects of cocaine on the ARCI, are in contrast with a number of studies reporting consistent increases in MBG, A, and BG scores (see Foltin and Fischman, 1991, for review). One explanation for the insensitivity of the ARCI in the present...
study may be the delay between the drug effect and time of the administration of the ARCI. In previous studies demonstrating significant changes in the ARCI after cocaine administration, data were collected approximately 5 min after drug administration (Fischman et al., 1983, 1985). The present study used data collected approximately 35 min after drug administration. Although the participants were instructed to complete the questionnaire based on how they felt since the drug injection, this time lapse may have affected the sensitivity of the ARCI. The elevations in LSD and PCAG scales with nicotine are similar to those previously reported (Henningfield et al., 1985; Soria et al., 1996). However, previously observed dose-related increases in MBG scale scores (Henningfield et al., 1985; Soria et al., 1996) were not demonstrated in the present study.

At all three doses, cocaine was identified as a stimulant by the majority of subjects. Nicotine was also identified as a stimulant by 80% and 50% of subjects at the intermediate and high doses, respectively. It is interesting that when subjects were asked to identify the type of stimulant they had been administered, subjects usually identified both cocaine and nicotine as being cocaine or amphetamine and almost never identified either drug as being nicotine. Thus, despite these subjects' familiarity with both cocaine (through histories of either i.v. or smoked/intranasal use) and nicotine (through tobacco cigarette smoking) the subjects were not able to correctly identify nicotine. Interestingly, the high dose of nicotine was also identified as an opiate by 40% of the subjects. The identification of 3.0 mg/70 kg nicotine as an opiate may be related to its subjective effects of sedation and somatic effects, which were elevated on the ARCI.

In the present study, increasing doses of both cocaine and nicotine produced significant increases in the frequency of responses on the sensory questionnaire (i.e., experienced any unusual visions, tastes, feelings or smells); the responses were generally visual or gustatory in nature. This instrument was used in a previous study with caffeine, which yielded primarily olfactory responses (Rush et al., 1995). Relative to the previous study in which 60% of the subjects reported olfactory responses after the highest caffeine dose, the highest dose of cocaine and nicotine resulted in 10% and 0% of the subjects report an olfactory response, respectively. Thus, such information may differentiate these drugs. For nicotine, some of the dysphoric and somatic effects (i.e., light-headedness, coughing, irritation of the throat, tingling and sedation) have been reported in other investigations (Henningfield et al., 1983, 1985) and are consistent with the elevations on the LSD scale. The mechanisms mediating these responses are unknown and worthy of further investigation.

Previous studies have demonstrated that i.v. cocaine (Preston et al., 1992; 1993; Walsh et al., 1994) and nicotine (Henningfield et al., 1985; Soria et al., 1996) produce increased heart rate, increased systolic and diastolic blood pressures, and decreased skin temperature. Consistent with previous findings, in the present study, cocaine (40 mg/70 kg) and nicotine (3.0 mg/70 kg) produced significant increases in diastolic (12 and 15 mm Hg, respectively) and systolic (15 and 27 mm Hg, respectively) blood pressure shortly after injection (Fig. 4). The high doses of cocaine and nicotine also increased heart rate (approximately 20 and 19 beats/min, respectively) and decreased skin temperature (approximately 5° and 3°C, respectively). Thus, findings from the present study show that the cardiovascular profile of effects are similar for both cocaine and nicotine. In contrast to cardiovascular effects and subjective effects, skin temperature was affected more by cocaine than by nicotine. All three active doses of cocaine produced prolonged effects lasting approximately 30 min after injection; in contrast, only the highest dose of nicotine produced significant effects, and those were no longer significant 22 min after injection.

The present study used a multiple-choice procedure to assess the reinforcing effects of cocaine and nicotine. The current version of the procedure used a final reinforcement session to reinforce choices between the administered drugs and various amounts of money. In previous studies, the multiple-choice procedure has been used to evaluate reinforcement with pentobarbital (Griffiths et al., 1993), alprazolam (Mumford et al., 1995), triazolam (Silverman et al., 1993), caffeine (Silverman et al., 1994; Garrett and Griffiths, 1997; Schuh and Griffiths, 1997), and tobacco cigarettes (Griffiths et al., 1996). The multiple-choice procedure provides a measure of drug reinforcement that corresponds well with more conventional measures of drug reinforcement such as choice and self-administration (Griffiths et al., 1993). The present results, in which subjects reported higher monetary values for increasing cocaine doses, are similar to those previously reported (Fischman et al., 1990; Preston et al., 1992, 1993; Haberny et al., 1995). Other studies that asked what the subjects would pay for a single i.v. injection of 40 mg of cocaine found that it was rated three times as valuable as placebo (Daffe et al., 1989). Additionally, the results from the multiple-choice procedure concur with the other subjective effects measured in the present study. The fact that nicotine produced a mixed profile of good and bad subjective effects, whereas cocaine produced only good subjective effects, appeared to be reflected in the multiple-choice procedure results, which showed that the subjects were willing to pay more money for the high dose of cocaine than they were for the high dose of nicotine.

In conclusion, this is the first report to compare directly the subjective, physiological, and behavioral effects of i.v. cocaine and nicotine in humans. Although cocaine and nicotine appear to produce similar effects on several physiological and subjective measures, the two stimulant drugs produced different effects on a number of measures. Both drugs produced increases in subjective ratings of "rush", "good effects", "liking", "high", and "stimulated", but only nicotine produced increases in ratings of "bad effects" and "jittery". Although the highest dose of nicotine produced a greater magnitude of effects than the high dose of cocaine on most subjective measures, the high cocaine dose was associated with somewhat greater ratings of drug liking. At doses that produced comparable ratings of drug effect (e.g., 40 mg/70 kg cocaine versus 1.5 mg/70 kg nicotine), cocaine produced significantly greater good effects, whereas nicotine produced greater bad effects. Cocaine also tended to increase reports of euphoria as measured by MBG scale scores, whereas nicotine decreased MBG scores and increased feelings of discomfort and sedation as measured by LSD and PCAG scale scores, respectively. Finally, the highest dose of cocaine was observed to be the most reinforcing to subjects and was worth twice as much money as the highest nicotine dose.
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References


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