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Marihuana Smoking Increases Plasma Cocaine Levels and Subjective Reports of Euphoria in Male Volunteers

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LUKAS, S. E., M. SHOLAR, E. KOURI, H. FUKUZAKO AND J. H. MENDELSON. *Marihuana smoking increases plasma cocaine levels and subjective reports of euphoria in male volunteers.* PHARMACOL BIOCHEM BEHAV **48**(3) 715–721, 1994.—The reasons why individuals use this combination are not entirely clear, however, it has been speculated that marihuana may potentiate cocaine's subjective effects. Five male recreational drug users provided informed consent and volunteered to participate in this study. Each subject participated on 3 different days, separated by at least 1 week. Subjects sat in an isolated chamber and were prepared with electrocardiographic (ECG) electrodes for heart rate monitoring and an IV catheter for blood withdrawal. After adapting to the experimental chamber, they smoked a marihuana cigarette containing either 0.004% (placebo), 1.24%, or 2.64% Δ^9-tetrahydrocannabinol (THC). Thirty minutes later they received an intranasal dose of 0.9 mg/kg cocaine. On subsequent visits, the marihuana dose was varied on a random basis. Subjects continuously reported changes in their mood state via an instrumental joystick device and filled out visual analog scales. Marihuana-induced tachycardia was increased even more after cocaine. The duration of all marihuana- and cocaine-related positive subjective effects was unchanged when both drugs were given, but marihuana pretreatment significantly reduced the latency to cocaine effects, from 1.87 to 0.53 min, and decreased the duration of dysphoric or bad effects, from 2.1 to 0.5 min. Peak plasma cocaine levels were 122.8 ± 26.6 ng/ml after placebo marihuana, but pretreatment with the high-dose marihuana resulted in a significant increase in peak cocaine levels (233.8 ± 19.2 ng/ml) and the apparent bioavailability as determined by area under the curve (AUC) analysis. We conclude that marihuana-induced vasodilation of the nasal mucosa attenuates the vasoconstrictive effects of cocaine and thus increases its absorption.

Cocaine Marihuana Tetrahydrocannabinol Polydrug abuse Blood levels Human subjects

THE practice of using two or more drugs in combination (i.e., polydrug abuse) has become widespread in recent years (3,5,11). An analysis of polydrug abuse patterns indicates that marihuana is the most heavily used illicit drug (1), but use of cocaine rose sharply in the 1970s and 1980s. One of the many popular combinations identified by recreational users and abusers is marihuana and cocaine. Although it is unknown why two or more drugs are taken concurrently, there are a number of theories for why polydrug abuse is so popular. First, the individual might be using the second drug to attenuate or block undesirable side effects of the first drug. Second, the two drugs may be taken simultaneously to produce a novel effect that is perceived as more pleasurable than when either is taken alone. Third, the first drug may be taken to boost or enhance the effects of the second drug. Fourth, the second drug may be used to prolong the effects of the first drug. Although the reason for these altered effects would be expected to be due to the additive effects of physiological re-

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sponses, our previous study of marihuana and ethanol combinations revealed that marihuana treatment actually attenuated the rise in ethanol blood levels (16).

The behavioral and physiological consequences of combined marihuana and cocaine use have been reported previously (7-10) and appear to be additive. The present study was undertaken to characterize the behavioral effects of cocaine after various doses of marihuana to determine if this practice enhances cocaine's effects and minimizes the dysphoria that is frequently associated with the resultant "crash." Furthermore, we evaluated plasma drug levels to determine if pharmacokinetic changes might explain the altered behavioral responses.

METHOD

Subjects

Five healthy adult male volunteers (mean ± SD weight = 76.15 ± 9.92 kg) between the ages of 21 and 35 years (mean 24.60 ± 3.91 years) provided informed consent to participate in this study. Subjects had normal physical and psychiatric status examinations and normal hemogram and blood chemistry analyses. Subjects with histories of mental health problems or drug or alcohol abuse were excluded from the study. All subjects used marihuana on an occasional basis and reported smoking an average of 2.2 ± 1.73 marihuana cigarettes per week and reported drinking predominantly beer with an average intake of 2.32 ± 1.91 12 oz cans of beer per week. Subjects used cocaine on an occasional basis (8.8 ± 6.6 times per year), and reported using marihuana and cocaine together on an average of 2.2 ± 2.17 times per year. All urine specimens were negative for licit and illicit drugs on the morning of each experimental day.

Plasma cholinesterases or pseudocholinesterases play an important role in the metabolism of cocaine (25), and it has been suggested that individuals with low cholinesterase activity may metabolize cocaine more slowly, as predicted by in vitro tests (13). The fact that the present study was conducted as a within-subject design minimizes this possible confound. We consulted with members of the Department of Anesthesiology, Massachusetts General Hospital, who informed us that dibucaine numbers are not routinely performed on patients prior to surgery. They only perform the test on individuals who report that they, or any of their family members, have experienced difficulties in the past. This information was obtained during the physical examination before the subject enters the study. Subjects with a positive history or family history of difficult surgeries would have been excluded from studies involving cocaine, although we have yet to encounter any subject with such a history.

Experimental Design and Setting

The present study was conducted within the framework of a multidisciplinary program designed to measure brain electrical activity, physiology, behavioral responses, and plasma hormone and drug levels. Subjects returned to the laboratory on three separate occasions and smoked cigarettes containing a different concentration of THC in random order: placebo (0.004% Δ^9-THC); low-dose (1.26% Δ^9-THC); or high-dose (2.53% Δ^9-THC). They all received intranasal cocaine powder (0.9 mg/kg) on each of the 3 days.

On each study day, subjects had a light breakfast but abstained from caffeine, nicotine, milk, and egg products. They were then escorted back to the laboratory. Two standard silver electrodes were then placed on the subject's chest (Lead II montage) to record ECG activity. The recordings were collected continuously for the duration of the experiment. Subjects sat in an electrically-shielded, sound- and light-attenuated double-walled chamber (IAC, Bronx, NY) during the conduct of the experiment. The chamber was equipped with a wired intercom and a closed-circuit video camera to provide auditory and visual contact with the subjects. Subjects sat in a semisupine position and were instructed to relax, keep their eyes closed, and remain awake.

An IV catheter (Kowarski-Cormed Thromboresistant Blood Withdrawal Butterfly Needle and Tubing Set; Dak Med, Inc., Buffalo, NY) was inserted in an antecubital vein for withdrawing blood samples. The distal end of the catheter was passed outside the sound chamber and attached to a syringe pump (Harvard Apparatus) set to withdraw blood at a continuous rate of 1 ml/min. Syringes were changed every 5 min. Plasma samples were immediately prepared and frozen for subsequent integrated Δ^9-THC and cocaine quantitative analyses.

After 30 min of acclimation to the setting, subjects smoked a 100-mm-long humidified marihuana cigarette (Research Triangle Institute, NC) via a smoking device (18) that cooled and filtered the smoke (Fig. 1, top). Subjects smoked the cigarettes according to the following instructions provided via a tape recorder: "inhale" for 3 s; "hold" (their breath) for 5 s; and then "exhale." This process was repeated every 30 s until only

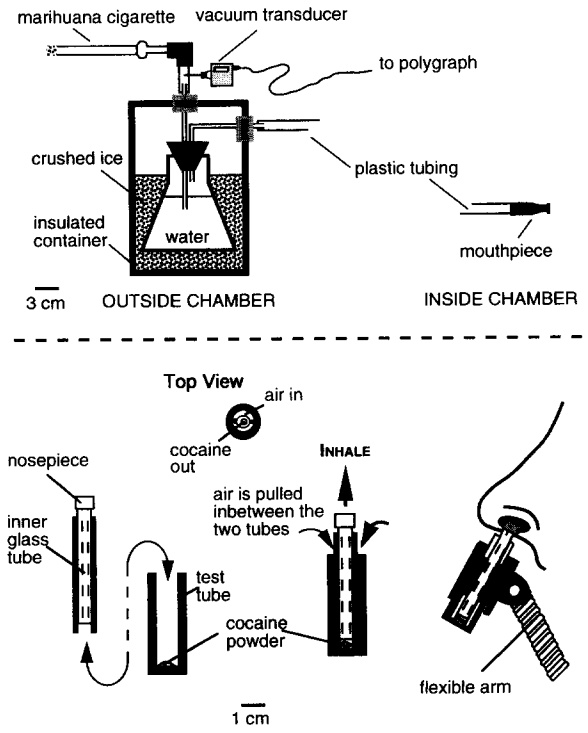

FIG. 1. Top: device for delivering marihuana smoke to subjects who are inside an isolated chamber. The smoke is cooled and humidified as it passes through the flask. The vacuum transducer transmits a signal to the polygraph to mark when inhalations (and how long they lasted) on the polygraph. Bottom: device for intranasal delivery of cocaine powder. Air is drawn in through the test tube, causing turbulence that pushes the powder up through the inner glass tube. The glass rods keep the inner glass tube from touching the cocaine powder in the test tube.

10 mm of the cigarette remained. This typically took between 3.5 and 5.0 min. A vacuum-operated transducer transmitted a signal to an event pen on the polygraph to record actual inhalations and verify compliance with the taped instructions. Thirty minutes after smoking began, subjects snorted the dose of cocaine using a modified snort-stick device (Fig. 1, bottom). Subjects reported marihuana and/or cocaine subjective effects on a continuous basis by moving an instrumental joystick device (17,19) during the entire study (120 min). Movement of the joystick or depression of either of the two buttons was recorded directly on the polygraph. Subjects were instructed to use the joystick as follows:

Forward:	"when you feel the effects of marihuana"
Backward:	"whenever you feel the effects of cocaine"
Side:	"when you feel the effects of both drugs"
Top button:	"when you experience a feeling of intense well-being, good effects, euphoria, or intense pleasure"
Bottom button:	"when you experience an intense bad feeling, dysphoria, or intense displeasure."

Subjects were also asked to fill out visual analog scales (VAS) by placing a mark on a 100-mm line that represented their answer to the following questions: "How high do you feel from the cigarette?" "How much do you feel the effects of the powder?" "How good do you feel right now?" "How bad do you feel right now?" The VAS was collected 10 min before smoking, 10 min postsmoking, and 10 and 45 min postintranasal cocaine.

Plasma Δ^9-THC Analysis

Plasma Δ^9-THC levels were measured using a radioimmunoassay (RIA) kit provided by Research Triangle Institute (Research Triangle Park, NC). The procedure was as follows: aliquots of 100 μl of blank plasma were pipetted into the control tube and duplicate 100-μl aliquots of the standards, controls, and samples were pipetted into the remaining tubes. Methanol (0.4 ml) was added to each tube that was then vortexed and allowed to stand at room temperature for 10 min. Samples were then centrifuged for 10 min at 733 $\times$ g and 50-μl aliquots of the methanol supernatant were then transferred to an assay tube and 0.4 ml of the freshly prepared radiolabeled/buffer solution was added. Freshly prepared antiserum (100 μl) was then added to the appropriate tubes and tubes were vortexed and then incubated overnight at 4°C. The immunobead/buffer solution was prepared by adding 10 ml of cold buffer to the immunobeads in a scintillation vial followed by gentle shaking. The immunobead buffer solution was added to the appropriate tubes. All tubes were then vortexed and allowed to incubate for 3 h at 4°C. After centrifugation, the supernatant was carefully poured into a waste container and the bead pellet was then washed with 1 ml of cold buffer followed by vortexing and recentrifugation as before. The supernatant was poured off and all tubes were counted in a gamma counter.

The average duplicate counts per minute values for all control tubes were calculated and properly subtracted to correct for nonspecific binding. The initial radioligand binding was defined by the ratio of the average corrected (0-dose) value to the average total value. Corrected standards, controls, and unknown counts per minute (CPM) values were divided by the average corrected CPMs for the 0-dose tubes to determine the percent radioligand bound for each tube. A standard curve was then generated by logit transformation followed by weighted least squares regression analysis. Concentrations of Δ^9-THC in controls and unknowns were determined from the calculated percent bound by interpolating from the standard curve.

The quality control sheet provided with the kit includes a record of total CPM, nonspecific counts, 0-dose and total ratio, slope, 50% intercept, standard deviation, and coefficient of variation for each assay. The inter- and intra-assay coefficient of variations were 11.2% and 7.0%, respectively. The precision and sensitivity of radioimmunoassays for measuring plasma levels of Δ^9-THC has been reported in studies of controlled marihuana smoking by men and women (23). Verification of this RIA was carried out via analysis of 5% random samples of plasma by gas liquid chromatography-mass spectrometry (Center for Human Toxicology, University of Utah School of Medicine). Only minor variations were found and the results of the two analytic techniques were highly correlated (r = 0.98), although the RIA kit consistently detected 2.2% more Δ^9-THC (Fig. 2). This is most likely due to the cross-reactivity with other cannabinoids.

Plasma Cocaine Analysis

Plasma cocaine was measured using a modification of the procedure described by Jacob et al. (12). Samples were run in duplicate using a Hewlett-Packard model 5890A gas chromatograph equipped with a nitrogen-phosphorus detector. Sensitivity was less than 5 ng of cocaine from 1 ml of plasma. A stock external standard solution was made by dissolving 10 mg of cocaine HCl (Sigma, St. Louis, MO) in 10 ml of 0.01 M sulfuric acid. This solution was diluted to appropriate concentrations with 0.01 M sulfuric acid and added to drug-free plasma containing sodium fluoride to provide several concentration ranges (5–500 ng/ml cocaine and 200 ng/ml internal standard). All standards were extracted by organic solvent and injected into the gas chromatograph. The computing integrator was calibrated to prepare a standard curve by using the internal standard method.

The internal standard (n-propyl ester of benzoylecgonine) was prepared as follows: one ml of 1-iodopropane was added

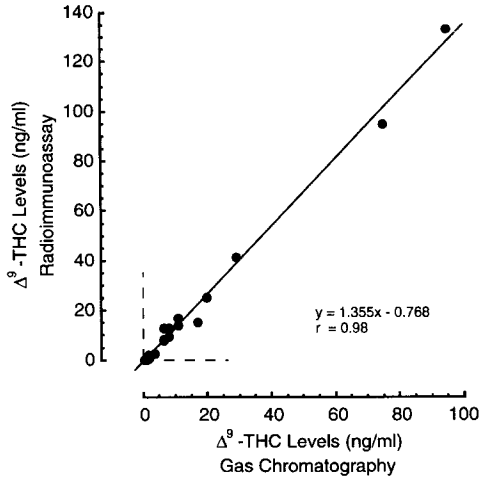

FIG. 2. Linear regression analysis comparing plasma Δ^9-THC levels measured via a radioimmunoassay procedure (Alcohol and Drug Abuse Research Center) with a gas chromatographic procedure (University of Utah).

to a solution containing 100 mg of benzoylecgonine in 100 ml of the organic base. The reaction mixture was stirred at 50°C for 1 h, after which the reaction was terminated by adding 100 ml of 0.75 sodium carbonate/sodium bicarbonate buffer (pH 9.6). The product was extracted with three 25-ml portions of chloroform, and the combined extracts were washed with three 50-ml portions of carbonate buffer. The organic phase was dried over anhydrous sodium sulfate and concentrated in a rotary evaporator. The gum obtained was crystallized from ethanol with a 75% overall yield. The residue was then prepared for thin-layer chromatography (TLC) by dissolving it in *n*-propanol. The TLC was conducted on 20 cm × 20 cm × 0.5 mm Anasil H plates (Analabs, Inc., North Haven, CT) that were placed in ethyl acetate : methanol : concentrated ammonium hydroxide (85 : 10 : 0.5 by volume). The purified *n*-propyl ester of benzoylecgonine was obtained by removing and evaporating the supernate and reconstituting it in 5 ml of 0.01 M sulfuric acid.

The internal standard was purified as follows: a solution of *n*-propyl ester of benzoylecgonine was made basic with saturated potassium carbonate. The extract was evaporated to dryness on a vacuum vortex-evaporator and dissolved with 2 ml of hexane : isopropyl alcohol : concentrated ammonium hydroxide (4 : 15 : 0.25). The solution was purified by column chromatography on Lipidex-5000 (12 × 1.5 cm column), eluting with hexane : isopropyl alcohol : concentrated ammonium hydroxide (4 : 15 : 0.25). Fractions (0.5 ml) were removed and evaporated. The resulting solid was reconstituted in 1 ml of butyl acetate and monitored by gas chromatography (GC) for purity determination. Those fractions containing pure product were combined and dried in a vacuum vortex-evaporator. The product was then dissolved in 0.01 M sulfuric acid. An aliquot of the internal standard was diluted with 0.01 M sulfuric acid to provide a concentration corresponding to 100 ng/ml of cocaine.

Plasma samples were prepared as follows: a 200-μl aliquot of plasma was placed in a polypropylene (12 × 75 mm) culture tube to which 10 μl of the internal standard (1000 ng in 1 ml of 0.01 M sulfuric acid) was added. Samples were alkalinized with 20 μl of saturated potassium carbonate. Toluene (1 ml) : tert-amyl alcohol (90 : 10) was added and mixed for 5 min. The tubes were centrifuged for 15 min at 2000 rpm to break emulsions and then placed in a dry ice/isopropyl alcohol bath to freeze the aqueous layer. The organic phase was transferred to a clean polypropylene tube. A 0.5-ml aliquot of 0.1 M sulfuric acid was added, extracted for 3 min, centrifuged, and then frozen as above. The organic phase was poured off and discarded; the aqueous layer was thawed and then washed with 1 ml toluene : tert-amyl alcohol (90 : 10). Sufficient saturated potassium carbonate buffer was added to alkalinize the aqueous phase, and extracted with 1.0 ml of toluene and tert-amyl alcohol. After centrifugation, the sample was frozen and the organic phase was poured into a clean polypropylene tube. The solvent was evaporated in a vacuum vortex evaporator at room temperature. The residue was dissolved in 50 μl of butyl acetate.

Samples (2 ml) were injected into the GC using the following settings: a 1.8-m × 2 mm i.d. glass column was packed with 3% OV-17 on 100–120 mesh chromosorb W-HP. Flow rates for carrier gas (helium), detector air, and hydrogen were 20, 150, and 3.5 ml/min, respectively. The injector, detector, and oven temperatures were 280, 260, and 300°C, respectively. Chromatograms were recorded on a Hewlett-Packard 3393A integrator interfaced with a Hewlett-Packard 7673A automatic sampler. Concentrations were calculated from the relative peak areas, inter- and intra-assay coefficient of variations were 11.2% and 2.8%, respectively.

Data Analysis

Instrumental subjective responses for detecting cocaine and marihuana effects were analyzed separately using a one-factor analysis of variance (ANOVA) with marihuana dose as the independent variable and responses as the dependent variable. Plasma cocaine levels were analyzed using a (two-within, zero-between) repeated-measures ANOVA design. Marihuana dose and time were within the subject factors and plasma cocaine was the dependent variable. All calculations were performed on a Macintosh computer using Super ANOVA software. Because a significant overall effect was found on plasma cocaine levels, a one-factor ANOVA, followed by Dunnett's *t*-test (two-tailed), was performed to determine which time points after marihuana inhalation were significantly different from placebo marihuana administration. Probabilities were adjusted using both the Greenhouse-Geisser and the Hunyh-Feldt epsilon because the former tends to be conservative and the latter may be too liberal. Area under the curve analysis was performed using a trapezoidal rule method (15). For all statistical analyses, plasma level changes and behavioral effects were considered significant at the $p < 0.05$ level.

RESULTS

Subjective Reports of Cocaine Effects

The continuously available joystick device provided a continuous measure of the onset and offset of marihuana and cocaine effects as well as the appearance of good or positive (e.g., "euphoric") and negative or bad (e.g., "dysphoric") effects. The latency to cocaine-induced effects was shorter in four of the five subjects who smoked high-dose marihuana compared to low-dose marihuana and placebo (Table 1). The effects of marihuana/cocaine combinations on good and bad feelings are shown in Fig. 3.

The profile of good or "euphoric" feelings was paroxysmal in nature. Subjects who smoked placebo marihuana depressed the "euphoria" button of the joystick an average of 14.2 ± 7.2 times after cocaine. Although the number of "good" or euphoric events increased to 42.2 ± 22.8 when high-dose marihuana was smoked, the wider variability prevented this from reaching statistical significance. Four of the five subjects reported at least twice as many good or euphoric events after

TABLE 1

LATENCY TO DETECTION OF COCAINE EFFECTS VIA JOYSTICK RESPONDING AFTER VARIOUS DOSES OF THC

	Latency to Cocaine Detection (min)		
Subject Number	2.64% THC	1.24% THC	Placebo
049	1.13	1.07	4.02
051	0.45	0.32	1.05
055	0.49	1.10	1.55
057	0.20	2.54	2.41
059	0.36	0.13	0.31
Mean ± SD	0.53 ± 0.41	1.03 ± 0.99	1.87 ± 1.56

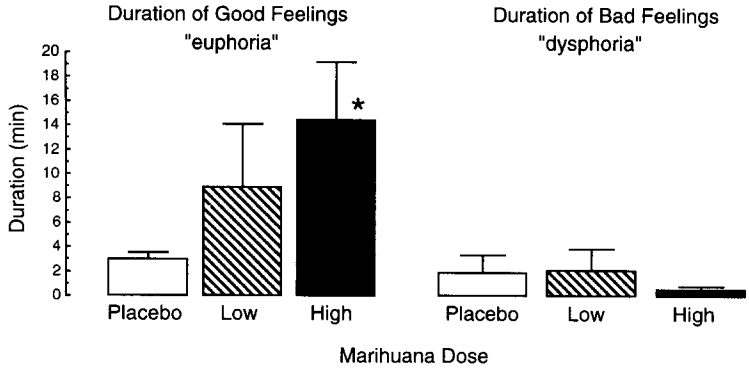

FIG. 3. Duration of good (left side) and bad (right side) feelings after marihuana/cocaine combinations. Data are generated via the instrumental joystick device and reflect the cumulative number of minutes subjects move the joystick to indicate the subjective effects of good, high, rush, or intensely pleasurable effects. Alternatively, subjects could also report feeling bad, dysphoric, and unpleasant. Both behaviors could be reported at the same time. Values are mean ± SD of five subjects who received either placebo or high-dose marihuana and 0.9 mg/kg cocaine 30 min later.

cocaine/high-dose marihuana. The overall duration of cocaine effects was unaffected by marihuana pretreatment, but the duration of good effects or "euphoria" was increased from 2.96 ± 0.6 to 14.43 ± 4.8 min after placebo and high-dose marihuana, respectively ($p < 0.05$). The duration of bad feelings or "dysphoria" after cocaine was reduced from 1.85 ± 1.49 min after placebo marihuana to 0.50 ± 0.31 min after the high-dose marihuana. However, these differences were not statistically significant after Greenhouse-Geisser adjustments.

Heart Rate

Marihuana caused a dose-related increase in heart rate that peaked 15 and 25 min after smoking the low- and high-dose cigarettes, respectively (Fig. 4). The magnitude of the change never exceeded 20 bpm. Cocaine caused a further increase in heart rate (up to a maximal increase of 30 bpm) that peaked about 25 min after cocaine administration. These changes after cocaine remained proportional to the already elevated heart rate after marihuana. There were no significant differences except at the $t = 30$ time point.

Plasma Drug Levels

Plasma concentrations of Δ^9-THC peaked 10 min after smoking began and achieved levels of 25.00 ± 9.12 and 76.80 ± 19.76 ng/ml after the low and high dose, respectively. Levels quickly decreased and were unaffected by the subsequent cocaine dose (Fig. 5). When subjects smoked high-dose marihuana, plasma cocaine levels were significantly higher than

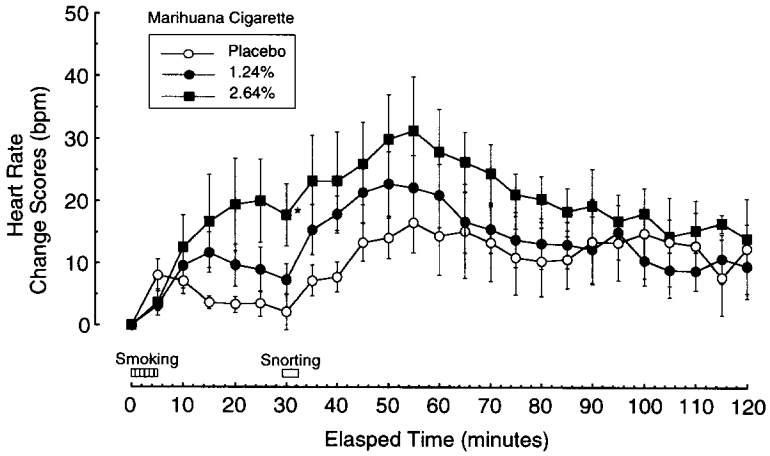

FIG. 4. Effects of marihuana pretreatment and cocaine on heart rate changes from baseline. Heart rates were tabulated from ECG recordings on a polygraph and plotted at 5-min intervals. Data represent the mean ± SD of five subjects over the course of the 2-h experiment. Marihuana smoking occurred from time 0–5 min while the cocaine was snorted from 30–31 min into the study. *Indicates significantly different from placebo marihuana.

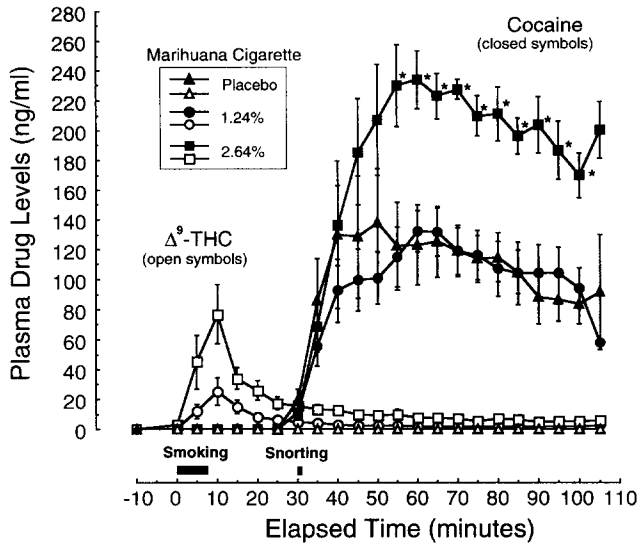

FIG. 5. Plasma Δ^9-THC and cocaine levels after smoking various doses of marihuana and receiving an intranasal 0.9-mg/kg dose of cocaine, respectively. Filled-in symbols represent cocaine plasma levels and open symbols represent Δ^9-THC levels. Integrative plasma samples were removed at 5-min intervals and processed as described in the text. *Indicates values significantly different from placebo Δ^9-THC at $p < 0.01$ or less. Values represent mean ± SD of five subjects.

when subjects smoked either the low dose or placebo marihuana cigarette. Significant increases in plasma cocaine levels began 25 min after cocaine administration, $F(28) = 5.365$, $p = <0.001$, although a clear dissociation between the rate of increase in cocaine levels was evident 15 min after snorting. Plasma cocaine levels remained significantly higher for the duration of the experiment. The area under the plasma cocaine level curve (AUC) for each of the three treatment conditions was 17.55 ± 3.61, 16.54 ± 2.59, and 29.95 ± 2.63 ng/ml/min after the placebo, low-dose marihuana, and high-dose marihuana, respectively. The AUC after high-dose marihuana was significantly greater than placebo ($p = 0.012$) and low-dose marihuana ($p = 0.008$).

DISCUSSION

The most striking finding of the present study was that plasma cocaine levels were significantly elevated when subjects smoked a high-dose marihuana cigarette 30 min before snorting cocaine. The increase in plasma cocaine levels was paralleled by an alteration in cocaine-induced subjective effects. As would be expected from an increase in plasma levels, the duration of good effects was increased and the latency to detecting cocaine effects was reduced. These findings were possible because they were recorded using an instrumental joystick device that provided a continuous assessment of drug effects. The lack of any significant changes on the VAS suggests that the joystick device may be superior to detecting the rapid onset of both good and bad effects of cocaine.

The change in latency to detect cocaine effects occurred before significant elevations in plasma cocaine were observed. Because the brain receives over 20% of the blood circulation, it is likely that brain levels may have been elevated prior to the observed changes in plasma. However, the increased number of good or "euphoric" effects did occur 15–45 min after cocaine. These changes in the behavioral responses after cocaine suggest that there is a pharmacodynamic mechanism supporting the notion that the combined use of these two drugs may be more desirable among drug abusers.

The vasoconstrictor properties of cocaine accounts for its limited absorption (and reduced effects) of subsequent intranasal doses. The most likely explanation for the elevated plasma cocaine levels in the present study is that marihuana decreased the tone of the capillaries in the nasal mucosa and blocked the usual cocaine-induced vasoconstriction of these vessels. Although there is no direct evidence for this effect, Δ^9-THC does reduce the tone of other smooth muscle such as human bronchioles (22). The significant increase in the area under the plasma cocaine curve is further evidence of its increased bioavailability and that more cocaine is absorbed in the presence of high-dose marihuana. This interpretation of the mechanism behind marihuana's effects on cocaine absorption is strengthened by the fact that plasma cocaine levels after IV administration are not affected by smoking marihuana (7,8,10).

It is unlikely that the increased plasma cocaine levels were due to THC-induced alterations of cocaine metabolism. Because the slopes of the plasma cocaine decay curves from $t = 65$–105 min were identical, $t(76) = 0.38$ and 1.327, NS. Although THC has a high affinity for, and is metabolized by, microsomal drug-metabolizing enzymes (4,20), cocaine is metabolized primarily by plasma cholinesterase or pseudocholinesterase enzymes (25). It is more likely that this enzyme contributes to the apparent inconsistencies in the cocaine literature relating to tolerance and dependence. However, the differential effects on cocaine metabolism may be due to species variations in cholinesterase activity. These distinctions are more apparent when comparisons are made across species because intraspecies differences seem to be less problematic due to the low incidence of atypical enzymes (14). Plasma cholinesterase activity in humans is genetically determined and the activity of these enzymes is fairly well understood (6,21). The incidence of individuals with atypical, dibucaine-resistant plasma cholinesterase is 1 : 2500 (26), whereas the incidence of other genetic variants (e.g., fluoride, chloride, formaldehyde) is in the range of 1 : 154,000–1 : 300,000 (26). The fact that the present study was conducted as a within-subject design minimized this possible confound.

The present finding that marihuana increases cocaine bioavailability is interesting in light of the reports that marihuana actually decreases plasma ethanol levels (2,16). This effect was most likely a result of a marihuana-induced reduction in gastric emptying and gastrointestinal propulsion and motility (24).

In conclusion, marihuana has profound psychoactive effects of its own, but its unique pharmacodynamic profile on other organs and peripheral vascular systems contribute to its effects on the bioavailability (and subjective responses) of other drugs of abuse. Marihuana appears to not only increase the duration of the positive or good effects of cocaine, but to also decrease the duration of bad effects. Together, these wide range of actions on other systems modulates the effects of cocaine and, thus, may account for its popularity in polydrug abuse.

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