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The Effects of Combinations of Intranasal Cocaine, Smoked Marijuana, and Task Performance on Heart Rate and Blood Pressure

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FOLTIN, R. W. AND M. W. FISCHMAN. *The effects of combinations of intranasal cocaine, smoked marijuana, and task performance on heart rate and blood pressure.* PHARMACOL BIOCHEM BEHAV **36**(2) 311–315, 1990.—Eight adult male research volunteers received cocaine and marijuana, alone and in combination during experimental sessions. Following the determination of baseline cardiovascular indexes, a one-gram marijuana cigarette (0–2.9% Δ^9-THC w/w) was smoked, and cocaine hydrochloride (4–96 mg) was inhaled five minutes after completion of marijuana smoking. Subjects performed a learning task 25 and 70 minutes after initiating marijuana smoking. Cocaine increased heart rate, which averaged 68 bpm under resting baseline conditions, by up to 15 bpm, marijuana increased heart rate by up to 27 bpm, and task performance increased heart rate by 5 bpm. The combination of cocaine and marijuana produced increases in heart rate that were similar to those seen with marijuana alone. During task performance in combination with cocaine and marijuana administration, however, heart rate was elevated by 37 bpm. Although more variable, the largest increases in blood pressure were observed following combinations of cocaine, marijuana, and task performance. These findings suggest that the self-administration of cocaine and marijuana under nonresting conditions has greater cardiovascular effects than the self-administration of these drugs under resting conditions.

Cocaine Marijuana Stress Human subjects Cardiovascular activity Blood pressure Heart rate Drug interaction

THE cardiovascular effects of cocaine and marijuana are well documented. Consistent increases in heart rate and blood pressure have been reported following cocaine administration by intranasal (7, 12, 21), intravenous (4,6) and inhaled freebase routes (17), with the magnitude and duration of the changes dependent on dose and route of administration. In contrast, oral (10), intravenous (18), and smoked marijuana (6,22) have been reported to consistently increase heart rate with inconsistent, or small effects on blood pressure. Although anecdotal reports indicate that these two drugs are often self-administered in close proximity (1,9), only one laboratory study has reported on the cardiovascular effects of combinations of intravenous cocaine and smoked marijuana (6). In that study (6), combinations of cocaine and marijuana increased heart rate above levels observed with either drug alone, while blood pressure changes were reflective of cocaine dose alone.

Numerous recent experiments have demonstrated that the heart rate and blood pressure changes following drug administration can be exacerbated when subjects perform learning tasks [e.g., (5, 14, 15, 19, 20)]. For example, combining intranasal cocaine and task performance (8), or combining smoked marijuana administration with task performance (2) increases heart rate and mean arterial pressure above levels observed following either drug or task performance alone. Given the significant increases in heart rate and blood pressure when cocaine and marijuana are given concomitantly (6), it was of interest to determine if task performance could further increase heart rate and blood pressure above the drug-elevated baseline.

METHOD

Subjects

Eight adult male research volunteers, 25 to 36 years of age, with histories of cocaine and marijuana use, were solicited by advertisement from a metropolitan drug-using population. All subjects received medical and psychological evaluation prior to their entry into the study and did not meet DSM-III criteria for

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drug abuse or anxiety. They received training in the computerized performance task and agreed to refrain from illicit drug and/or alcohol use for 24 hours prior to each testing session. Periodic urinalyses confirmed drug abstinence. Each subject signed a consent form that described the study, outlined any possible risks, and indicated that cocaine and marijuana, singly and in combination, would be administered, possibly on a daily basis during the study.

Procedure

The study consisted of nine experimental sessions (Mondays through Fridays) with single intranasal cocaine (4, 48 or 96 mg) and smoked marijuana doses (one-g cigarettes containing 0%, 1.3 or 1.8%, 2.7 or 2.9% Δ^9-THC, w/w) administered per session according to a three cocaine dose by three marijuana dose schedule. The 0% THC cigarette served as the marijuana placebo, while the 4 mg cocaine dose, which does not have any physiological or subjective effects, but does cause a slight numbing of the nasal mucosa (3), served as the cocaine placebo. To insure that cigarettes and caffeinated beverages were not consumed in association with testing, subjects reported to the laboratory 90 minutes prior to the scheduled drug administration time. During the first 45 minutes of this period, they rested and provided a urine sample for drug screening.

During experimental sessions, each subject was seated in a reclining chair before an Apple IIe® computer and monitor. Heart rate (HR) was continuously monitored via chest electrodes, and HR and blood pressure (systolic, SP; diastolic, DP) were recorded every two minutes (Vita-Stat 2001 automated vital signs monitor, Vita-Stat Medical Services, St. Petersburg, FL) beginning 30 minutes prior to administration of drug. A marijuana cigarette was smoked over a five-min period using a uniform puffing procedure known to produce reliable THC blood levels (6). Five min after completion of the puffing procedure, subjects were given 100 mg of white powder on a 50×50 cm mirror. Subjects prepared their own "lines" with a single edged razor blade and inhaled the powder when instructed. A serial acquisition task was repeated at 25 and 70 min following the start of marijuana smoking (15 and 60 min after cocaine administration). At 105 minutes postmarijuana administration, when vital signs had generally returned to baseline, subjects were dismissed from the laboratory. To limit the possibility of adverse effects of dosing, all of the subjects received low dose combinations prior to high dose combinations. To insure safety, the subjects were continuously monitored through one-way vision glass and could communicate with the investigators by intercom.

Serial Acquisition Task

A serial acquisition task, which has been reported to produce consistent 5 to 10 bpm increases in HR, and 5 to 8 mmHg increases in DP and SP (2, 5, 8), was presented on a CRT screen. Subjects were provided with a three-button response manipulandum which was interfaced to the Apple IIe computer. A random sequence of 25 correct response positions (left, center, or right) was available during each task presentation. The sequence of correct responses was changed each time the task was presented. Subjects were required to respond on one of three response keys (left, center, right) with each correct response producing an asterisk on the CRT. When a subject completed a sequence correctly on two consecutive occasions, a cumulative counter increased the point tally by three points per asterisk on the screen. The sequence was then increased in length by one response for the next trial. Thus, each trial required the subject to complete a sequence of responses which was one response longer than the previous trial (from 1 to 25). The task ended after 10 minutes. Points were exchanged for money at the rate of one cent per point at the end of the study.

Drug

Cocaine hydrochloride (4, 48 and 96 mg, Mallenkrodt, St. Louis, MO) was combined with lactose to total 100 mg of powder for each administration [see (13) for kinetics of this combination] by the Pharmacy Manufacturing Department of The Johns Hopkins Hospital. One-g cigarettes containing 0%, 1.3 or 1.8%, 2.7 or 2.9% Δ^9-THC (w/w) were provided by the National Institute on Drug Abuse.

Data Analysis

Heart rate and blood pressure during the task was calculated as the mean of the last three readings obtained during the ten-min task period. Heart rate and blood pressure prior to the task was calculated as the mean of the three readings obtained immediately before the task, and heart rate and blood pressure after the task was calculated as the mean of the three readings obtained between two and eight min after the task was concluded. One subject was dismissed from the study after three sessions due to elevated baseline vital signs, and two subjects were dismissed from the study after five and seven days, respectively, due to their noncompliance with the proscription against drug use. Data collected with these subjects prior to departure was used in the analysis necessitating the use of between groups analyses of variance (ANOVA). The analyses of HR, DP, and SP, expressed as change from resting baseline, were accomplished using ANOVAs with two between group and two within group factors. The between group factors were cocaine dose (0, 48, 96 mg) and THC concentration [none, low (1.3 or 1.8% THC), high (2.7 or 2.9% THC)]. The within group factors were time of task performance (performance started 25 or 70 minutes after the start of marijuana smoking) and observation (pretask baseline, task, posttask baseline). Differences were considered significant at $p<0.01$.

RESULTS

There were no significant differences among groups in resting HR, with a mean of 72.1 ± 1.3 (SEM) beats per minute (bpm). The top panel of Fig. 1 compares the effects of marijuana and task performance on HR as a function of dose of cocaine. Cocaine alone produced dose-dependent increases in HR up to a mean of 15 bpm following 96 mg, $F(2,55) = 7.93$, $p<0.001$, and marijuana alone produced concentration-dependent increases in HR up to a mean of 27 bpm following the high THC concentration cigarette, $F(2,55) = 11.05$, $p<0.001$. The increases in HR were greater during the series of vital signs associated with the first task performance after drug delivery (T1: 25 min) than those measured during the second task performance after drug delivery [T2: 70 min; $F(1,55) = 178.69$, $p<0.001$]. In the absence of drug (placebo cocaine and marijuana administration), task performance increased HR by a mean of five bpm above the values obtained immediately before and after task performance, $F(2,110) = 76.04$, $p<0.001$. There was a significant interaction between marijuana dose and HR before, during, and after task performance, $F(2,55) = 22.45$, $p<0.001$. HR after the first task performance postdrug (T1) was lower than HR before task performance, while HR was similar before and after the second postdrug task performance (T2). Finally, there was a significant interaction between time of task performance (25 min or 70 min) and HR before, during, and after task performance, $F(2,110) = 8.03$, $p<0.001$, with peak HRs

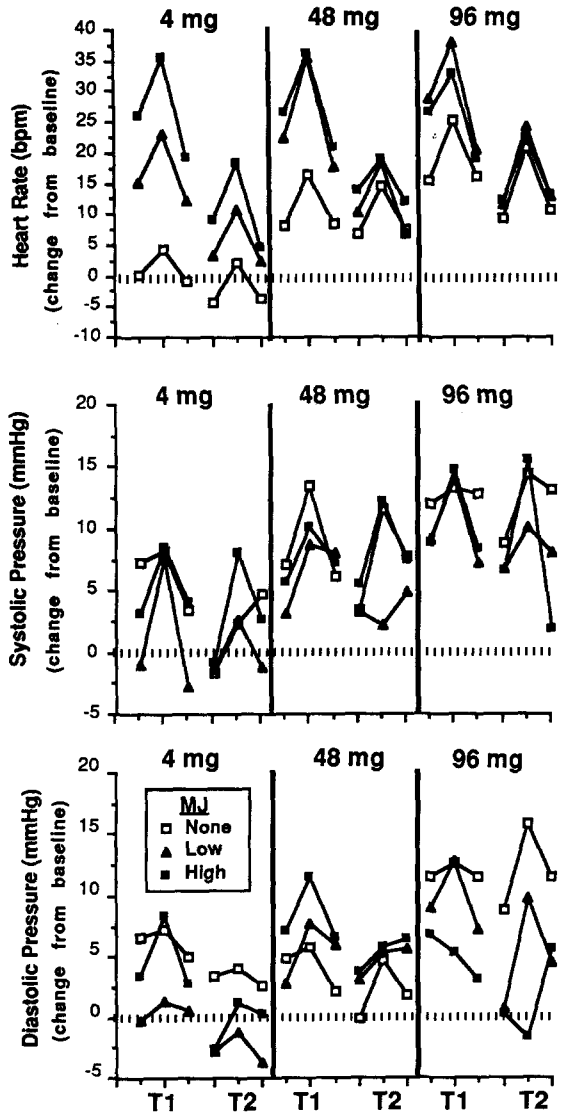

FIG. 1. Change in HR (top panel), SP (middle panel), and DP (lower panel) during experimental sessions as a function of dose of cocaine (4 mg: left panel; 48 mg: middle panel; 96 mg: right panel) and marijuana. A ten-minute performance task was started 25 (T1) and 70 (T2) minutes after the beginning of marijuana smoking. Points to the left of T1 and T2 represent HR before task performance, and the points to the right of T1 and T2 represent HR after task performance. The dashed line indicates no change from baseline. Although SEMs have been omitted for clarity, the range of SEMs for HR was 1.1 to 10.6 bpm, the range for SP was 1.3 to 8.7 mmHg, and the range for DP was 0.9 to 5.0 mmHg, with the greater SEMs being associated with the larger changes from baseline.

(about 37 bpm) during the first task performance being larger than peak HRs (18 to 24 bpm) during the second task performance after drug. Thus, task performance alone increased HR by about 5 bpm, cocaine alone increased HR by about 15 bpm, and marijuana alone increased HR by about 27 bpm. The combination of all three events resulted in a peak HR of about 37 bpm.

There were no significant differences among groups in resting SP, with a mean of 128.1 ± 1.3 mmHg. The middle panel of Fig. 1 compares the effects of marijuana and task performance on SP as a function of dose of cocaine. Cocaine alone produced dose-dependent increases in SP up to a mean of 12 mmHg following 96 mg, $F(2,55) = 7.03$, $p<0.002$, while marijuana had no significant effect on SP. In the absence of drug, task performance increased SP above the values obtained immediately before and after task performance, $F(2,110) = 20.08$, $p<0.001$. Thus, task performance alone increased SP by about 7 mmHg, and cocaine alone increased SP by about 12 mmHg. The combination of task performance, cocaine and marijuana administration increased SP to those levels seen following combinations of task performance and cocaine administration alone.

There were no significant differences among groups in resting DP, with a mean of 77.6 ± 0.8 mmHg. The bottom panel of Fig. 1 compares the effects of marijuana and task performance on DP as a function of dose of cocaine. Cocaine alone produced dose-dependent increases in DP up to a mean of 12 mmHg following 96 mg, $F(2,55) = 8.09$, $p<0.001$, while marijuana had no significant effect on DP. The increases in DP were greater during the series of vital signs associated with the first task performance after drug delivery than those measured during the second task performance after drug delivery, $F(1,55) = 23.93$, $p<0.001$. In the absence of drug, task performance increased DP above the values obtained immediately before and after task performance, $F(23,110) = 11.88$, $p<0.001$. Finally, there was a significant interaction between time of task performance and DP before, during, and after task performance, $F(2,110) = 4.42$, $p<0.014$, with peak DPs (about 12 mmHg) during the first task performance being larger than peak DPs during the second task performance after drug. Thus, as was observed with SP, task performance alone increased DP by about 8 mmHg, and cocaine alone increased DP by about 12 mmHg. The combination of task performance, cocaine and marijuana administration increased DP to those levels seen following combinations of task performance and cocaine administration alone.

There was no significant effect of either cocaine or marijuana on any dimensions of performance on the serial acquisition task.

DISCUSSION

The current study points to the importance of measuring drug effects under conditions in which some behavioral demands are being made on the drug-taker. HR and blood pressure changes were related both to the drug administered and the concurrent behavioral requirements in the test session. Inhaled cocaine, smoked marijuana, and task performance all produced significant increases in HR. Although combinations of cocaine and marijuana increased HR, these increases were no larger than those observed following the highest concentration of THC alone. Task performance in combination with all pairs of cocaine and marijuana doses increased HR 34–37 bpm, which was equivalent to the HR observed following marijuana administration and task performance alone. Thus, the cardiovascular effects of combinations of drugs, or drugs and task performance could not accurately be predicted by the effects of drugs or task performance alone. This indicates the importance of further studies evaluating drug interactions. Previous studies on the effect of marijuana or cocaine, in combination with task performance, indicated larger increases in HR following combinations of drug and task performance than following drug or task performance alone, with larger increases being associated with marijuana administration (2) than cocaine administration (8).

Inhaled cocaine, smoked marijuana, and task performance all produced significant increases in SP and DP. Combined administration of cocaine and marijuana increased blood pressure to the same degree as cocaine administration alone. As was observed with HR, task performance significantly incremented both SP and

DP above levels seen following cocaine and marijuana administration alone. Although the interactive effects of cocaine, marijuana and task performance were more variable with respect to blood pressure than HR, maximal blood pressure increases observed with combinations of all three events were similar to those observed following cocaine and task performance alone. Previous reports indicate that both marijuana (2) and cocaine (8) combined with task performance result in larger increases in blood pressure than either drug or task performance alone. This indicates that compared to HR there is greater variability in the blood pressure response to drug administration in combination with task performance both within and among studies. The duration of the task effect was limited to the period of task performance, and maximal increases were observed 25 min after marijuana smoking and 15 min after cocaine inhalation, consistent with the relatively short durations of action of these drugs (4,22). The large cardiovascular effect of task performance in combination with drug administration was not due to a drug-induced disruption of task performance per se, as neither drug alone, nor in combination, significantly affected performance.

The HR increases following cocaine, marijuana, and task performance alone, were similar to, or slightly smaller than, previously reported increases in HR (2, 4, 6, 8, 22). The failure of combinations of cocaine and marijuana to have greater chronotropic effects than marijuana alone differs from a previous report (6). In that study (6), intravenous cocaine, which alone increased HR by up to 30 bpm, in combination with inhaled marijuana, which alone increased HR by up to 28 bpm, increased HR by up to 45 bpm. The difference in the effects of cocaine and marijuana between studies may be related to the greater cardiovascular effects of IV cocaine in the earlier study with correspondingly greater cocaine blood levels (6). The increases in BP following cocaine and task performance were similar to, or slightly smaller than, previously reported increases in blood pressure (6,7).

Recently, the number of reports of adverse cardiovascular consequences of cocaine use has risen sharply [e.g., (16,23)], including reports of cardiovascular emergencies after multiple drug use (11). One possible reason for an incident rate higher than would be predicted based on laboratory studies (12, 21, 22), is that these controlled studies have analyzed drug effects under resting conditions. Clearly, individuals engaging in drug use are not all sitting quietly during periods of intoxication. It is more likely that drug use is associated with a number of stressful activities, e.g., sexual intercourse, social interactions, illegal activities, sports, which all have cardiovascular effects of their own. The present study suggests that HR and blood pressure elevations following illicit drug use can combine with ongoing behavior to further increase these physiological responses. The serial acquisition task produced small, but consistent and significant effects on heart rate and blood pressure, and, as such, was a good model of a small behavioral demand. It is likely that in the natural ecology significantly greater behavioral demands are placed on the drug taker, and significantly greater cardiovascular requirements may result. Such combinations may be one factor contributing to the adverse medical consequences of drug use. Therefore, the cardiovascular effects of illicit drug use may be best predicted by an analysis of the interactive effects of concurrent environmental and behavioral circumstances and such drug use.

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