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Effects of Cocaine, Alone and in Combination With Task Performance, on Heart Rate and Blood Pressure

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FOLTIN, R. W., M. A. McENTEE, R. M. CAPRIOTTI, J. J. PEDROSO AND M. W. FISCHMAN. *Effects of cocaine, alone and in combination with task performance, on heart rate and blood pressure.* PHARMACOL BIOCHEM BEHAV 31(2) 387–391, 1988.—Eleven adult male subjects with histories of cocaine use participated in daily experimental sessions consisting of resting cardiovascular (heart rate, blood pressure) baseline measures followed by intranasal cocaine (4, 48 or 96 mg) administration and further cardiovascular monitoring. Subjects in Group I performed a learning task before and after cocaine administration, while subjects in Group II rested. Cocaine administration alone significantly increased heart rate up to 10 beats per minute (bpm) and mean arterial pressure (MAP) up to 15 mm/Hg. Task performance alone increased heart rate up to 8 bpm and MAP up to 10 mm/Hg. In combination, increases in heart rate up to 19 bpm and MAP up to 18 mm/Hg were observed. Thus, combinations of cocaine administration and task performance increased heart rate and blood pressure above levels observed following the occurrence of either activity alone. These results indicate the importance of understanding the effects of drugs within the environmental context in which they are taken.

Cocaine Stress Human subjects Cardiovascular activity Blood pressure Heart rate

THE cardiovascular effects of cocaine are well documented. Consistent increases in heart rate and blood pressure have been reported following intranasal (11,20), intravenous (4,5) and inhaled freebase administration (18), with the magnitude and duration of the changes dependent on dose and route of administration. Although most of these laboratory evaluations have been carried out under resting or baseline conditions, cocaine is commonly self-administered under nonresting conditions (e.g., socially). It is therefore important to investigate the cardiovascular effects of cocaine under nonresting or "stressful" conditions to better evaluate the cardiovascular consequences of such drug use.

Performance of a variety of behavioral tasks results in significant increases in heart rate and blood pressure [e.g., (14, 15, 19)]. The task-elicited cardiovascular response combines additively with caffeine or nicotine administration (19) and supra-additively with marijuana smoking (2). This task-elicited cardiovascular response may be increased by the presence of cocaine since this drug increases sensitivity to circulating catecholamines by inhibiting reuptake (7,16). The present study investigated the interaction between the effects of cocaine and task performance on cardiovascular activity.

METHOD

Subjects

Eleven adult males 21 to 38 years of age with histories of cocaine 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 current axis 1 disorders. All subjects had resting blood pressures of less than 140/85 mm/Hg. They received training in a 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. All subjects signed consent forms which described the study and outlined its risks.

Apparatus

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 heart rate and blood pressure (systolic, SP; diastolic DP) were recorded every two minutes via a Dinamap 825XT automated vital signs monitor (Critikon, Tampa, FL).

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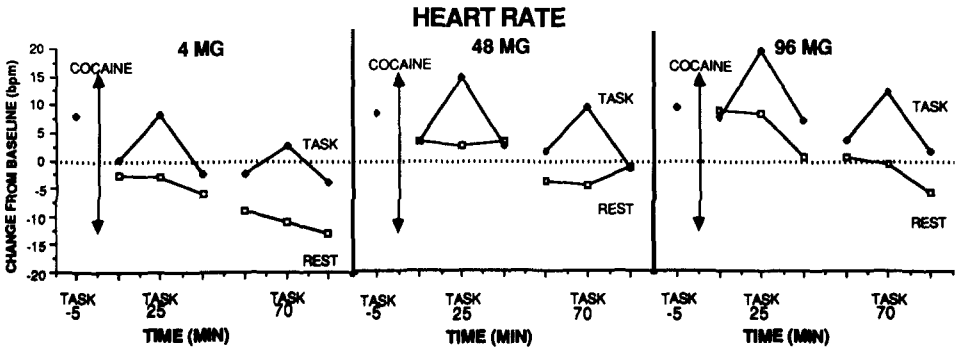

FIG. 1. Change in heart rate during experimental sessions. Cocaine (4 mg—left panel, 48 mg—middle panel, 96 mg—right panel) was inhaled at time zero as indicated by the double-arrow lines. A ten minute performance task was completed at −5, +25 and +70 minutes relative to drug delivery by subjects in Group I (closed symbols labeled TASK). Points to the left of the cocaine administration symbol indicate the effect of task prior to drug administration. Subjects in Group II rested during the session (Open symbols labeled REST).

Mean arterial pressure (MAP) was derived by adding one third of the pulse pressure to the diastolic pressure DP + [0.33(SP) − (DP)]. The subjects were continuously monitored through one-way glass and could communicate with the investigators by intercom.

Procedure

Subjects were assigned to one of two groups. Group I consisted of the first seven subjects that passed the screening procedure. They were tested with cocaine in combination with task performance. The next four subjects who passed the screening procedure and the only two subjects from the first group who were available for participation were assigned to Group II. Group II subjects, tested two months after Group I subjects, were given cocaine alone, in the absence of task performance.

For Group I, the study consisted of six experimental sessions with a single cocaine dose (4, 48 or 96 mg) administered per session. 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 completed questionnaires and provided a urine sample for drug screening. Cardiovascular monitoring equipment was then attached, and vital signs recording began 30 minutes prior to administration of drug. A 15 minute resting baseline period was followed by a 10 minute period of serial acquisition task performance. Cocaine (mixed with lactose) was then administered as 100 mg of white powder handed to the subject on a 50×50 cm mirror. Subjects prepared their own "lines" with a single edged razor blade and inhaled the powder when instructed. The performance task was repeated at 15 and 60 minutes following drug inhalation. At 90 minutes postdrug administration, when vital signs had generally returned to baseline, subjects were dismissed from the laboratory. Each dose was administered twice, first in an ascending series and then in a randomly assigned order. The initial dosing was done in an ascending order as a safety precaution to insure that any subject with an exaggerated response to a combination of a low cocaine dose and task performance would not receive a higher dose. The second dosing was done in a randomized order to minimize the possibility that dose order would alter the effect of each dose. One subject left the study after completion of the first dose determination, i.e., three sessions.

For Group II, the study consisted of three experimental sessions with a single cocaine dose (4, 48 or 96 mg) administered per session. Sessions were identical to those of Group I, with the exception that performance of the serial acquisition task was not included. Since cocaine alone produced only small increases in heart rate and blood pressure in Group I subjects, each dose was tested only once in a random order.

Serial Acquisition Task

A modified repeated acquisition task (3) was presented on a CRT screen to the subjects in Group I. Subjects were provided with a three-button response manipulandum which was interfaced to the Apple IIe computer. Subjects were required to respond on one of three response keys (left, center, right) with a correct response producing an asterisk on the CRT. The task required subjects to associate each asterisk on the screen with it's button location, e.g., asterisk No. 1—left, asterisk No. 2—middle. Incorrect responses were followed by a one-second timeout when the screen was blank, after which the sequence started with the first asterisk again. The initial sequence consisted of a single asterisk-key location pair. When a subject completed a sequence correctly on two consecutive occasions, a cumulative counter increased the point tally by two-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. Subjects were paid upon completion of each daily session.

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 (12) for kinetics of this combination] by the Pharmacy Manufacturing Department of the Johns Hopkins Hospital.

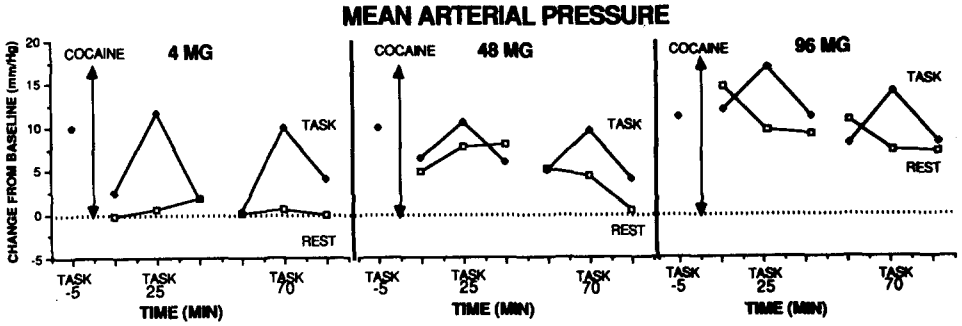

FIG. 2. Change in mean arterial pressure during experimental sessions. Cocaine (4 mg—left panel, 48 mg—middle panel, 96 mg—right panel) was inhaled at time zero as indicated by the double-arrow lines. A ten minute performance task was completed at −5, +25 and +70 minutes relative to drug delivery by subjects in Group I (closed symbols labeled TASK). Points to the left of the cocaine administration symbol indicate the effect of task prior to drug administration. Subjects in Group II rested during the session (open symbols labeled REST).

Data Analysis

Heart rate and blood pressure during the task were measured as the mean of the last three readings obtained during the ten minute task period. Heart rate and blood pressure prior to the task were measured as the mean of the three readings obtained immediately before the task, and heart rate and blood pressure after the task were measured as the mean of the three readings obtained between two and eight minutes after the task was concluded. Due to the mixed design, changes in heart rate and mean arterial pressure (MAP) were analyzed using an analysis of variance (ANOVA) with one between group and three within group factors. The first dose-response determination in the Group I subjects was analyzed as one level of the grouping factor, distinct from the second dose-response determination in this group which was the second level, while the dose-response determination for the no task group (Group II) was the third level of the grouping factor. The within group factors were dose (4, 48, 96 mg), time (task performance started 15 or 60 minutes after drug administration) and observation (pretask baseline, task, posttask baseline). A planned comparison evaluated the task effect across grouping factors (13).

RESULTS

There were no significant differences in resting baseline cardiovascular values prior to drug administration between the three groups (Group I—first dosing, Group I—second dosing, Group II). All data are presented as change from the baseline obtained prior to drug administration or task performance. Because there were no significant differences between the first and second dose response determinations in Group I, the cardiovascular changes observed in this Group were averaged across the two dose-response determinations for graphic presentation.

Figure 1 compares the change from the baseline heart rate during the experimental session for task (Group I) and control (Group II) subjects as a function of dose of cocaine. Data are presented separately for the change in heart rate during the task performance prior to cocaine, and for each observation (before, during, and after task) for the two tasks presented 15 minutes and 60 minutes after cocaine administration. Task performance prior to drug administration (isolated symbol to the left of the lines indicating cocaine delivery) reliably produced a heart rate increase of about 9 beats per minute (bpm). There was a significant main effect of cocaine on heart rate, $F(2,32)=11.89$, $p<0.0001$, with an increase of up to 9 bpm following the 96 mg dose in both groups. The main effect of time was significant, $F(1,16)=73.61$, $p<0.0001$, with the increase in heart rate being smaller during the second period of task performance compared to the first. Finally, there was also a significant main effect of observation, $F(2,32)=6.38$, $p<0.005$. The task effect was seen as an increase in heart rate during task performance above the resting values before and after task performance. This effect was marked in Group I, but absent in Group II, i.e., the triangles associated with task performance for Group I compared with the flat or descending lines for Group II in Fig. 1. The results of the planned comparison of the differences between groups at each of the observations that make up the task effect (pretask, task, posttask) indicated a significant difference between groups only during task performance, $F(2,16)=4.47$, $p<0.03$. Thus cocaine produced dose-dependent increases in heart rate, which were further increased in the presence of task performance.

Figure 2 compares the change in mean arterial pressure (MAP) from baseline during the experimental session for task (Group I) and control (Group II) subjects as a function of dose of cocaine. Task performance prior to drug administration produced an increase in mean pressure of 10 mm/Hg with no difference over days. There was a significant main effect of cocaine on MAP, $F(2,32)=16.12$, $p<0.0001$, with increases of up to 12 mm/Hg following the 96 mg dose in both groups. The main effect of time was significant, $F(1,16)=11.83$, $p<0.003$, with the increase in MAP being smaller during the second period of task performance compared to the first. Finally, there was also a significant main effect of observation, $F(2,32)=20.55$, $p<0.0001$. As with heart rate, the task effect was seen as an increase in MAP during task performance above the resting values reported prior to and after task performance. This effect was marked in Group I, but absent in Group II, i.e., the triangles associated with task performance for Group I compared with the flat or descending lines for Group II in Fig. 2. The results of the planned comparison of the effect of group at each of the observations that make up the task effect (pretask, task, posttask) indicated a significant difference between groups

only during task performance, $F(2,16)=10.65$, $p<0.001$. Task performance produced further increases in mean arterial pressure above those produced by cocaine alone and, as with heart rate, recovery from this effect was rapid.

The effects of cocaine on task performance were also analyzed. Cocaine did not produce significant dose-dependent changes in correct response rate, incorrect response rate, overall response rate, or length of the response sequence completed. The number of responses completed was 17.3+1.28 (mean with S.E.M.) following 4 mg, 16.8+1.1 following 48 mg and, 16.9+0.79 following 96 mg of cocaine.

DISCUSSION

The results of this experiment show clearly that both the administration of inhaled cocaine and performance of a behavioral task for monetary gain significantly increased heart rate and blood pressure in normal human volunteers. When task performance and cocaine administration were combined, the resultant heart rate and blood pressure increases were greater than observed following the single occurrence of either event. In contrast to the effects on heart rate and blood pressure, cocaine administration had no effect on task performance. This lack of effect on task performance indicates that the increases in heart rate and blood pressure following cocaine and task performance in combination were not due simply to an alteration in task performance. Similar cardiovascular effects of both single doses of cocaine [e.g., (5,20)] and task performance [e.g., (1, 2, 15, 19)] have been reported.

It is difficult to speculate about the physiological mechanisms underlying the interaction between cocaine and task performance. The mechanism of action of cocaine is complex, and both central and peripheral mechanisms are involved in its cardiovascular effects (21). However, it is likely that the interaction involves the inhibition, by cocaine, of the reuptake of norepinephrine (7,16) that was released in response to task performance [e.g., (17)]. Further studies of the interactive effects of task performance and cocaine administration are required in order to characterize the mechanisms subserving the differential interactive effects of cocaine and task performance on heart rate and blood pressure.

Although other studies have not specifically analyzed the combined effects of cocaine and task performance on cardiovascular activity, there have been several studies on the effects of coca leaf chewing and exercise on cardiovascular functioning. An initial study (8) reported that following coca chewing, experienced coca chewers exhibited lower exercise and recovery heart rate than nonchewers. However, the groups were not well matched, and in a subsequent study (9) the chewing of coca leaves was found to elevate both exercise and recovery heart rate.

Reports from emergency rooms suggest that cocaine use may be associated with a range of severely adverse cardiovascular consequences [e.g., (10)]. The present results suggest a possible basis for cardiovascular toxicity associated with cocaine. When heart rate and blood pressure are already elevated following cocaine administration, performance of a behaviorally-demanding task can increase heart rate and blood pressure even more. These data provide important information about the complex interaction between drug administration and prevailing environmental stimuli, and suggest a need for more research in this area.

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