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Ethanol and Cocaine Interactions in Humans: Cardiovascular Consequences

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FOLTIN, R. W. AND M. W. FISCHMAN. *Ethanol and cocaine interactions in humans: Cardiovascular consequences.* PHARMACOL BIOCHEM BEHAV 31(4) 877–883, 1988.—Intranasal cocaine (COC) and oral ethanol (ETOH) were administered to nine research volunteers during daily experimental sessions. Following the determination of baseline cardiovascular indexes, an ETOH cocktail (0, 19.4, 38.7, or 58.1 g of ETOH in lemonade) was consumed over a ten-minute period. Cocaine hydrochloride (4, 48, 96 mg) was inhaled 25 minutes after the start of ETOH drinking. Breath samples were collected 50 minutes after the start of ETOH drinking to estimate blood alcohol level (BAL). The effect of these doses, alone and in combination, on heart rate (HR) and blood pressure (BP), while resting and while performing a serial acquisition task, were determined. COC and ETOH alone significantly increased HR up to 6 bpm without affecting BP. Combining the two highest doses of COC with the highest BAL increased HR by 20 bpm. During task performance, in the absence of drug, HR was increased up to 5 bpm, and BP was unchanged. Combining the highest COC dose and BAL with task performance increased HR by 40 bpm. Small increases in BP were also observed under these conditions. These results indicate that combinations of ETOH, COC and task performance produce greater increases in HR than BP, and, in addition, this increase in HR is greater than that observed following COC, ETOH, or task performance alone.

Ethanol Cocaine Heart rate Blood pressure Drug interaction Humans

THE cardiovascular effects of cocaine (COC) and ethanol (ETOH) are well documented. Consistent increases in heart rate (HR) and blood pressure (BP) have been reported following intranasal (13,28), intravenous (6,7) and inhaled freebase administration (24) of COC, with the magnitude and duration of the changes dependent on dose and route of administration. Compared to COC, the effects of oral ETOH on HR and BP are more variable. ETOH has been reported to both increase and decrease HR and BP [e.g., (5, 10, 11, 27, 36, 38)]. However, the most consistent findings are small (4–6 beats per minute) increases in HR accompanied by small (5–8 mmHg) decreases in BP with breath alcohol levels (BAL) of 0.030–0.080 g/dl (15).

In contrast to the research on the cardiovascular effects of these drugs when given alone, surprisingly little research has concentrated on the effects of these drugs in combination. Anecdotal reports indicate that it is common for COC users to drink ETOH in close proximity to COC self-administration (3, 30–32). Given the likelihood of concurrent use of these drugs, an analysis of their cardiovascular effects, when taken in combination, is warranted. In addition, these drugs are commonly self-administered under social conditions when users might be engaged in a number of other activities which may affect the cardiovascular system. Analysis of the effects of COC and ETOH under resting and nonresting conditions, therefore, would provide useful information about the interactive effects of drug and environmental conditions on cardiovascular responsivity.

Nonresting conditions can be examined under controlled laboratory conditions by having subjects perform behaviorally demanding tasks. Performance of a variety of such tasks results in significant increases in HR and BP [e.g., (19, 20, 23)]. Task performance in combination with nicotine (25), marijuana (4), or COC (8) administration results in significantly greater increases in HR and BP than observed following either drug administration or task performance alone. The significantly higher HR following administration of COC and task performance (8) was probably related to the inhibition, by COC, of the reuptake of norepinephrine (9,22) that was released in response to task performance [e.g., (23)]. Increases in HR following ETOH are due to either a direct sympathomimetic effect of ETOH, or a compensatory response to the decrease in BP caused by the vasodilatory effect of ETOH (15, 17, 18). If increases in HR are a direct effect of ETOH, it would be predicted that combinations of ETOH and COC would have greater effects than either drug alone. Previous research using rats supports the possibility that combining ETOH and COC can increase, rather than decrease the effects of either drug (1,26). In addition, Zsoter and Sellers (38) have reported that ETOH enhances cardiovascular reflex responses, suggesting that task-elicited cardiovascular changes may be exacerbated by ETOH. The

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present study investigated the interaction between changes in HR and BP following COC and ETOH alone, and in combination, as well as in combination with task performance.

METHOD

Subjects

Nine healthy male volunteers, ranging in age from 21 to 45 years and each with a history of both ETOH and intranasal COC use, participated. Prior to acceptance, each subject was given a drug history interview and physical examination. All of the subjects were admitted to the Clinical Research Unit of The Johns Hopkins Hospital 24 hours before the first test day and remained in the hospital for the duration of the 11- to 14-day study. Each subject signed a consent form that described the study, outlined any possible risks, and indicated that COC and ETOH, singly and in combination, would be administered, possibly on a daily basis during the study. When not participating in experimental sessions subjects were free to engage in nondrug-related recreational activities of their own choice on the ward. Subjects had either breakfast or lunch prior to each daily session.

Procedure

Subjects were individually tested in daily three-hour sessions, Monday through Friday. A 14-min period of resting baseline was followed by the experimental session which consisted of 1) ten min of task performance, 2) administration of ETOH (0, 19.4, 38.7, or 58.1 g), 3) 35 min of ETOH baseline, 4) administration of cocaine hydrochloride (4, 48, 96 mg), 5) 20 min of ETOH and COC baseline, 6) ten min of task performance, 7) 40 min of resting, 8) ten min of task performance, and 9) 6 min of resting. The order of dose-dose combinations was mixed so that all subjects were tested with low dose combinations prior to testing with high dose combinations. A breath sample was obtained 50 minutes after the start of ETOH drinking for determination of breath alcohol levels (BAL, e.g., (34,35)] using an Alco-Sensor III® (Intoximeter Inc., St. Louis, MO).

During each session, electrocardiogram was monitored continuously through bipolar chest leads. BP (diastolic—DP, systolic—SP, and mean arterial—MAP) and HR were sampled every two minutes via a Vita-Stat Model 900-S monitor (Vita-Stat Medical Services Inc., St. Petersburg, FL). The subjects were continuously monitored through one-way glass and could communicate with the investigators by intercom.

Serial Acquisition Task

A modified repeated acquisition task (4,8) 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. Incorrect responses were followed by a one-second timeout when the screen was blank, after which the sequence started at the beginning with the first asterisk again. The task required subjects to associate each asterisk on the screen with its button location, e.g., asterisk# 1—left, asterisk#2—middle. 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. Points were exchanged for money at the rate of 3 cents 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 (14) for kinetics of this combination] by the Pharmacy Manufacturing Department of The Johns Hopkins Hospital. The 4 mg dose of cocaine hydrochloride which has no subjective or cardiovascular effects, but does produce a slight numbing of the nasal mucosa (13) functioned as the placebo cocaine dose. The cocaine-lactose powder was 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. Pure grain alcohol (0, 25, 50, and 75 ml) was mixed with a noncarbonated lemon-flavored drink (Giant Food Products, Washington, DC) to a total volume of 200 ml. Subjects were given 10 min to consume the drink. All subjects were tested with three or four ETOH doses in combination with all of the cocaine doses.

Data Analysis

Due to differences in body weight and possible differences in rate of ETOH metabolism, the distribution of BALs determined 50 min after ETOH consumption was used to determine the ETOH groups for analyses. All results were analyzed as a function of four BALs: BAL < 0.002 (i.e., no ETOH), 0.002 g/dl $<$ BAL < 0.030 g/dl, 0.030 g/dl $<$ BAL < 0.060 g/dl, BAL > 0.060, g/dl. As a consequence of this post hoc distribution, not all subjects had data points in all cells, necessitating the use of between-groups analyses of variance (7). HR and BP during task performance were measured as the mean of the last three readings obtained during the ten-min task period. HR and BP prior to the task were measured as the mean of the three readings obtained immediately before the task, and HR and BP after the task were measured as the mean of the three readings obtained between two and eight minutes after the task was concluded. Changes in HR, SP, DP and MAP were analyzed using analyses of variance with two between-group and two within-group factors. The between-group factors were dose of COC (4, 48, 96 mg) and BAL. The within-group factors were time of task performance (55 or 105 minutes after ETOH administration) and observation (pretask, task, posttask). Changes in length of maximum sequence, total rate and correct rate during task performance were analyzed using analyses of variance with two between-group and one within-group factors. The between-group factors were dose of COC and BAL, and the within-group factor was time of task performance. Post hoc tests were accomplished using Newman-Keuls comparisons. Results were considered statistically significant if $p<0.01$.

RESULTS

Cardiovascular

There were no significant differences among groups in resting HR, which ranged from 71 to 80 beats per minute (bpm). Figure 1 compares the effects of ETOH and task

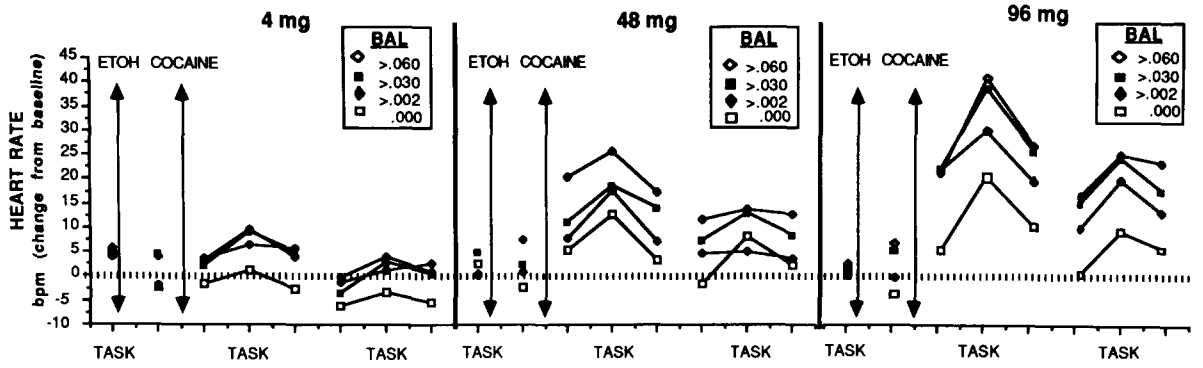

FIG. 1. Change in HR during experimental sessions as a function of dose of cocaine (4 mg—left panel, 48 mg—middle panel, 96 mg—right panel) and BAL. ETOH was administered at time zero, and cocaine was inhaled at 35 min as indicated by the double-arrow lines. A ten-minute performance task was completed at −5, +65 and +115 minutes relative to ETOH intake. The abscissa represents events during each session, not real time.

performance on HR, expressed as change from baseline, as a function of dose of COC. There was a significant effect of COC dose, $F(2,85)=47.57$, $p<0.001$, with 48 and 96 mg increasing HR to a greater extent than 4 mg, and a significant effect of BAL, $F(3,85)=11.31$, $p<0.001$, with the three BALs above zero increasing heart rate to a greater extent than observed in the zero BAL groups. The increases in HR were greater during the series of vital signs associated with the first task performance after drug delivery (55 min) than those measured during the second task performance after drug delivery, $F(1,85)=129.75$, $p<0.001$. Task performance increased HR above the values obtained immediately before task performance, and HR after task performance was elevated statistically compared to HR before task performance, $F(2,170)=56.63$, $p<0.001$. There was a significant interaction between COC dose and HR before, during, and after task performance, $F(4,170)=5.46$, $p<0.001$. The HR increases during task performance following 48 and 96 mg of COC were greater than those observed following 4 mg of COC, and HR remained elevated after task performance only in subjects receiving 96 mg COC. Finally, there was a significant interaction between time of task performance (55 min, 105 min) and HR before, during and after task performance, $F(2,170)=8.6$, $p<0.001$, with greater increases in HR during the first task performance after drug than during the second task performance after drug.

Figure 2 compares the effects of combinations of ETOH and COC on HR under resting conditions (at 45 min after the start of the session, and prior to the first task performance), and during the first task performance after drug administration (at 55 min after the start of the session). Forty-eight and 96 mg of COC significantly increased resting HR by about 6 bpm, while all BALs increased HR by about 4 bpm. Combining 48 or 96 mg of COC with the highest BAL increased HR by 20 bpm. Task performance alone had no effect on HR (data point represented by 4 mg COC with 0 BAL), while COC in combination with task performance produced dose-dependent increases in HR up to 22 bpm, and all BALs in combination with task performance increased HR by 6 bpm. The combination of 96 mg COC, a BAL of >0.060 g/dl and task performance increased HR by 40 bpm.

There were no significant differences among groups in resting MAP, which ranged from 88 to 94 mmHg. Figure 3 compares the effects of ETOH and task performance on

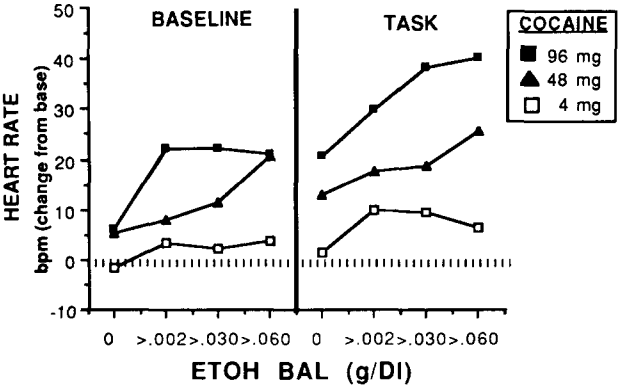

FIG. 2. Change in HR during ETOH and COC resting baseline and during the first task performance after drug delivery as a function of BAL and dose of cocaine.

MAP, expressed as change from baseline, as a function of dose of COC. There was a significant effect of COC dose, $F(2,86)=11.99$, $p<0.001$, with 96 mg increasing MAP to a greater extent than 4 or 48 mg, and a significant effect of BAL, $F(3,86)=4.82$, $p<0.004$, with the zero BAL groups having higher MAPs than the other BAL groups. The increases in MAP were greater during the series of vital signs associated with the first task performance after drug delivery (55 min) than those measured during the second task performance after drug delivery, $F(1,86)=14.45$, $p<0.001$. Task performance increased MAP above the values obtained immediately before task performance, and MAP remained elevated after task performance, $F(2,172)=15.80$, $p<0.001$.

DP and SP were differentially affected by combinations of COC, ETOH and task performance. Baseline levels of these measures prior to drug administration were stable with DP ranging between 68 and 80 mmHg, and SP ranging between 124 and 134 mmHg. COC increased DP, $F(2,86)=5.78$, $p<0.004$, with 96 mg increasing DP to a greater extent than 4 or 48 mg, while BAL did not affect this measure. Task performance increased DP above the values obtained immediately before task performance, and DP remained elevated after task performance, $F(2,172)=10.48$, $p<0.001$.

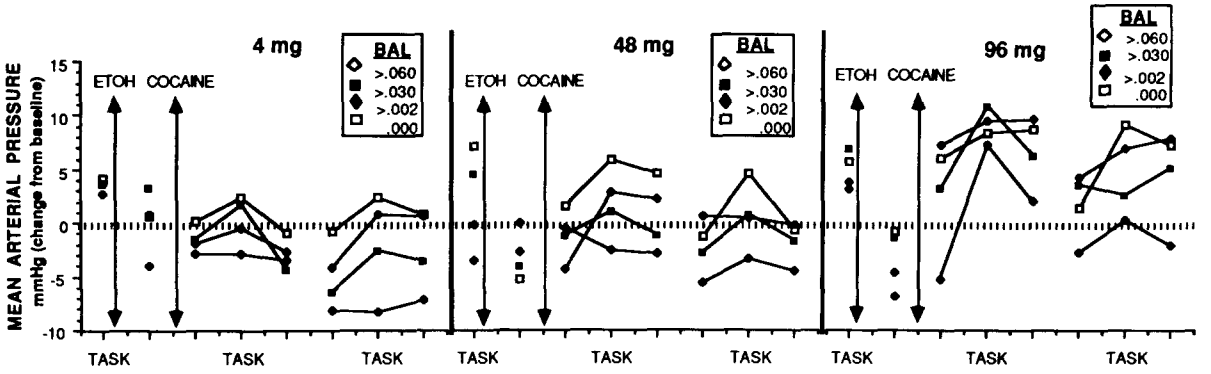

FIG. 3. Change in MAP during experimental sessions as a function of dose of cocaine (4 mg—left panel, 48 mg—middle panel, 96 mg—right panel) and BAL. ETOH was administered at time zero, and cocaine was inhaled at 35 min as indicated by the double-arrow lines. A ten-minute performance task was completed at −5, +65 and +115 minutes relative to ETOH intake. The abscissa represents events during each session, not real time.

There was also a significant COC dose, by time of task performance by observation (before, during, and after task performance) interaction, $F(2,172)=5.03$, $p<0.001$. Only 96 mg of COC increased DP during task performance, and this increase was only observed during the first task performance after drug delivery (55 min).

COC dose significantly increased SP, $F(2,86)=13.09$, $p<0.001$, with 48 and 96 mg increasing SP to a greater extent than 4 mg, and, in contrast to DP, BAL had a significant effect on SP, $F(3,86)=4.23$, $p<0.004$, with increases after the two lowest BALs and decreases after the two highest BALs. SP was greater during the series of vital signs associated with the first task performance after drug delivery (55 min) than those measured during the second task performance after drug delivery, $F(1,86)=44.66$, $p<0.001$. Task performance increased SP above the values obtained immediately before and after task performance, $F(2,172)=10.86$, $p<0.001$. Finally, there was also a significant BAL by time of task performance by observation (before, during, after task performance) interaction, $F(6,172)=2.75$, $p<0.01$. As BAL increased, SP during task performance decreased with no significant task effect observed during the second task performance after drug delivery.

Figure 4 compares the effects of combinations of ETOH and COC on BP under resting conditions (left portion of each panel), and also during the first task performance after drug administration (right portion of each panel). Neither COC dose nor BAL had significant effects on resting DP (top panel), but 96 mg of COC in combination with task performance significantly increased DP by about 10 mmHg. Ninety-six mg of COC significantly increased resting SP by about 5 mmHg, while 96 mg of COC in combination with task performance significant increased SP by about 10 mmHg. Neither COC dose nor BAL had significant effects on resting MAP (bottom panel), but 96 mg of COC in combination with task performance significantly increased MAP by about 10 mmHg. Thus, while task performance alone increased DP and MAP by 3 mmHg without affecting SP (data points represented by 4 mg COC with 0 BAL), combining task performance with the highest dose of COC increased DP, SP, and MAP by 10 mmHg.

Task Performance

There were no differences among groups in task performance prior to drug delivery. On average, the maximum sequence length completed was 18.05 with a response rate of 1.50 responses/second, and a correct response rate of 0.87 responses/second. Figure 5 compares the length of the maximum sequence (top panel) and correct rate (bottom panel), expressed as change from baseline, as a function of combination of COC dose and BAL. There was no significant effect of time of task performance, and the data are presented as the mean of task performance 55 min and 105 min after drug delivery. BAL produced blood-level-dependent decreases in the length of the maximum sequence completed, $F(3,84)=15.67$, $p<0.001$. Overall response rate was not affected by COC dose or BAL, but BAL produced blood-level-dependent decreases in correct rate, $F(3,84)=4.90$, $p<0.003$.

DISCUSSION

The results of this experiment demonstrated clearly that IN COC increases resting HR and BP, and oral ETOH increases resting HR and decreases resting BP. Though significant, the increases in HR (6 bpm) and MAP (7 mmHg) were smaller than previously reported following similar dosages of IN COC (8, 13, 28). The effects of ETOH alone replicate the majority of previous studies which reported similar small increases in HR (5, 27, 29, 36, 38) and small decreases in SP (10,27).

Although COC users often report ETOH use, alone or in combination with COC (3, 30–32), there have been no controlled studies on the effects of these drugs in combination in humans. The present study found that combinations of ETOH and COC increased resting HR up to 20 bpm, which was three to five times the increase in HR observed following the independent administration of either drug. The large HR increases following combinations of ETOH and COC suggest that each of these drugs is facilitating the chronotropic effect of the other. Two studies using laboratory rats reported similar effects of combinations of ETOH and COC (1,26). In the first of these experiments (26), COC, which alone had no effect on rotorod performance in mice, significantly increased the disruption of

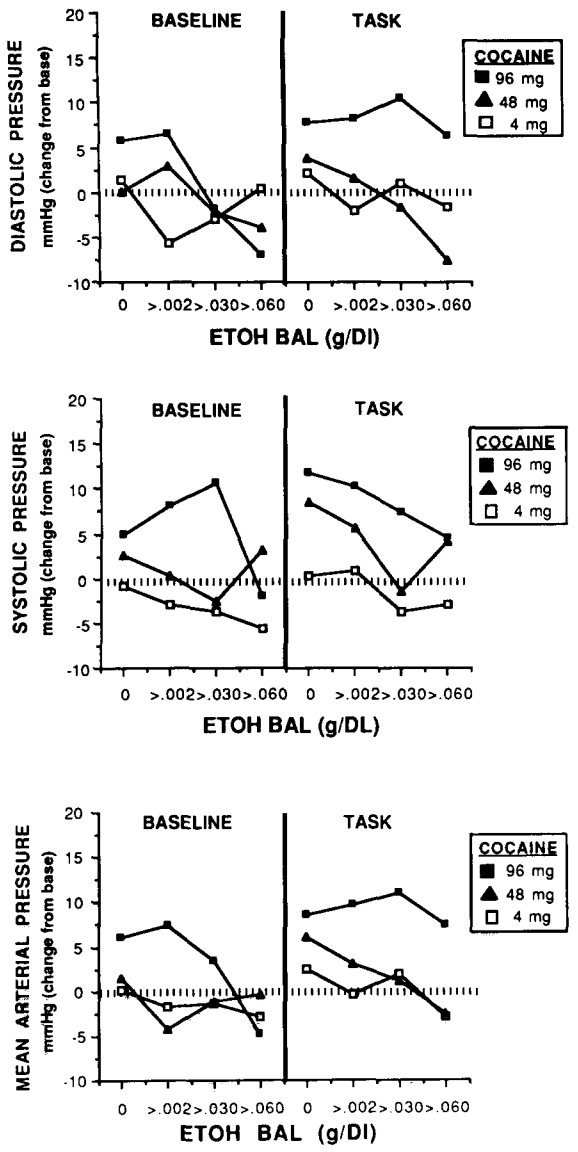

FIG. 4. Top panel: Change in DP during ETOH and COC resting baseline and during the first task performance after drug delivery as a function of BAL and dose of cocaine. Middle panel: Change in SP during ETOH and COC resting baseline and during the first task performance after drug delivery as a function of BAL and dose of cocaine. Bottom panel: Change in MAP during ETOH and COC resting baseline and during the first task performance after drug delivery as a function of BAL and dose of cocaine.

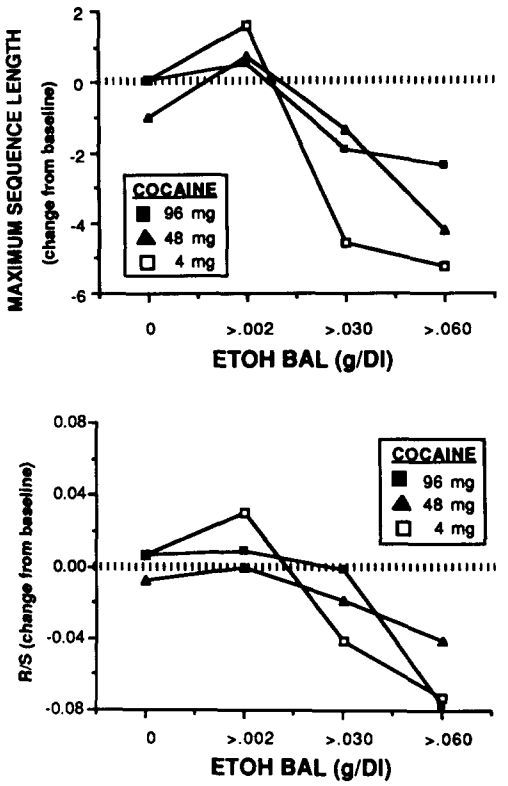

FIG. 5. Top panel: Change in the maximum completed sequence length during both task performances after drug delivery as a function of BAL and dose of cocaine. Bottom panel: Change in correct rate during both task performances after drug delivery as a function of BAL and dose of cocaine.

rotorod performance induced by ETOH. In the latter experiment (1), COC decreased the rate-increasing effect of ETOH on punished behavior while simultaneously increasing the ataxic effects of ETOH. In contrast to the increase in the HR following combinations of ETOH and COC, however, increasing BAL decreased the BP increase following 96 mg COC. Thus, the effect of combinations of ETOH and COC varied as a function of the dependent variable.

Performance of a serial acquisition task prior to drug delivery had no effect on HR and increased MAP by 3 mmHg. These changes were smaller than previously reported using the same task (4,8). Either drug in combination with the first task performance after drug delivery (55 min) resulted in HRs that were about three times greater than those produced by drug alone. Task performance in combination with the highest dose of COC increased HR by 20 bpm and MAP by 8 mmHg, while task performance in combination with ETOH produced maximal increases in HR of 10 bpm and had no effect on MAP. The effect of COC and task performance replicates an earlier report (8). Although other studies have not specifically analyzed the combined effects of ETOH and task performance on cardiovascular activity, the effect of ETOH on the cardiovascular response to exercise in normal volunteers has been examined (29). A BAL equivalent to the highest BAL measured here had no effect on the hemodynamic response to 5 min of exercise 90 min after drug ingestion. This difference in ETOH effects suggests that the cardiovascular response to exercise and a behaviorally demanding task may differ.

The combination of COC, ETOH and task performance 20 min after cocaine administration produced maximal HR increases of 40 bpm and maximal MAP increases of 8 mmHg. The increase in HR was two to four times greater than that produced by either drug alone in combination with task performance, while the increase in MAP was equivalent to that produced by cocaine in combination with task performance. As described previously, combinations of ETOH and COC had greater

chronotropic effects than either drug alone, and, in addition, resulted in increased cardiovascular reactivity to behaviorally demanding task performance. However, combining ETOH and COC did not increase reactivity to the pressor effects associated with task performance.

It has been shown that peak HR and self-report of cocaine's effects after IN administration occurs 20–30 minutes after the drug is inhaled (13). This was the time of the first task performance. The increase in cardiovascular reactivity seen in the present study was only evident during this period of peak cocaine effect. When the task was performed 70 minutes after cocaine inhalation, significantly smaller increases in HR and BP were observed. In addition, COC alone had no effect on task performance, while ETOH produced blood-level-dependent decreases in the length of the maximum completed sequence and correct response rate regardless of the time of task performance after drug delivery. Therefore, since the effects of COC and ETOH on performance of the task were not related to time since drug was administered, while the interactive effect of drug with task on HR was related to the time since administration, it is unlikely that the increase in HR during the first task performance following COC and ETOH administration was related to quality of task performance. COC and ETOH alone had no effect on the resting cardiovascular baseline prior to the second task performance after drug. However, ETOH did have an effect on the second task performance indicating that ETOH, but not COC, had measureable effects at that time. Further evidence for the short-lived effects of IN COC are provided by a previous study on the interaction between COC and task performance (8). In that study HR increased above levels observed following task performance alone when task performance occurred 15 min, but not 60 min after cocaine administration. Alternatively, the decrease in task effect during the second performance after drug delivery may represent acute tolerance (16).

It is difficult to speculate about the physiological mechanisms underlying the interaction between COC, ETOH and task performance. The mechanisms of action of both COC and ETOH are complex, with both central and peripheral mechanisms involved in the cardiovascular response to each drug (15, 17, 33). It is possible that the HR increase following this combination is a consequence of the inhibition, by cocaine (9,22), of the reuptake of norepinephrine released during task performance (23) interacting with the acute stimulatory effect of ETOH on the sympathetic nervous system (15). A similar increase in cardiovascular reactivity following ETOH administration has been reported by Zsoter and Sellers (38). BALs equivalent to the higher two BALs measured here increased the reactivity of cardiovascular reflexes to hyperventilation, deep breath, and the Valsalva maneuver in normal volunteers. The present increase in HR following combinations of COC, ETOH and task performance supports the possibility that ETOH increases cardiovascular reactivity.

Recently, the number of reports from emergency rooms on the adverse cardiovascular effects of COC has been increasing [e.g., (12, 21, 37)]. The present results suggest a possible basis for increased cardiovascular toxicity associated with using combinations of ETOH and COC. When HR and BP are already elevated following ETOH and COC administration, performance of a behaviorally demanding task can increase HR and BP even more. These data, in combination with other studies indicating similar large increases in BP and HR following drug use and task performance (4, 8, 25), suggest the importance of further research investigating the effects of environmental conditions on the cardiovascular effects of drugs.

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REFERENCES

1. Aston-Jones, S.; Aston-Jones, G.; Koob, G. F. Cocaine antagonizes anxiolytic effects of ethanol. Psychopharmacology (Berlin) 84:28–31; 1984.
2. Brod, J.; Fencl, V.; Hejl, Z.; Jirka, J. Circulatory changes underlying blood pressure elevation during acute emotional stress (mental arithmetic) in normotensive and hypertensive subjects. Clin. Sci. 18:269–279; 1959.
3. Burglass, M. E. The use of marijuana and alcohol by regular users of cocaine: Patterns and use and style of control. In: Milkman, H. B.; Shaffer, H. J., eds. The addictions. Lexington, MA: D. C. Heath & Co.; 1985:111–120.
4. Capriotti, R.; Foltin, R.; Brady, J.; Fischman, M. Effects of marijuana and task performance on cardiovascular responsivity. Drug Alcohol Depend. 21:183–187; 1988.
5. Dafters, R.; Anderson, G. Conditioned tolerance to the tachycardia effect of ethanol in humans. Psychopharmacology (Berlin) 78:365–367; 1982.
6. Fischman, M. W.; Schuster, C. R.; Resnekov, L.; Shick, J. F. E.; Krasnegor, N. A.; Fennell, W.; Freedman, D. X. Cardiovascular and subjective effects of intravenous cocaine administration in humans. Arch. Gen. Psychiatry 33:983–989; 1976.
7. Foltin, R. W.; Fischman, M. W.; Pedroso, J. J.; Pearlson, G. D. Marijuana and cocaine interactions in humans: Cardiovascular consequences. Pharmacol. Biochem. Behav. 28:459–464; 1987.
8. Foltin, R. W.; McEntee, M. A.; Capriotti, R. M.; Pedroso, J. J.; Fischman, M. W. Effects of cocaine, alone and combination with task performance, on heart rate and blood pressure. Pharmacol. Biochem. Behav. 31(2): in press; 1988.
9. Furchgott, R. F.; Kirpekar, S. M.; Rierer, M.; Schwab, A. Actions and interactions of norepinephrine, tyramine and cocaine on aorta of rabbit and left atria of guinea pig and cat. J. Pharmacol. Exp. Ther. 142:39–58; 1963.
10. Gould, L.; Reddy, R.; Goswani, K.; Venkataraman, K.; Gomprecht, R. F. Cardiac effects of two cocktails in normal man. Chest 63:943–947; 1973.
11. Gould, L.; Zahir, M.; DeMartino, A.; Gomprecht, R. F. Cardiac effects of a cocktail. JAMA 218:1799–1802; 1971.
12. Isner, J. M.; Estes, M., III; Thompson, P. D.; Costanzo-Nordin, M. R.; Subramanian, R.; Miller, G.; Katsas, G.; Sweeney, K.; Sturner, W. Q. Acute cardiac events temporally related to cocaine abuse. N. Engl. J. Med. 315:1438–1443; 1986.
13. Javaid, J. J.; Fischman, M. W.; Schuster, C. R.; Dekirmenjian, H.; Davis, J. M. Cocaine plasma concentrations: Relation to physiological and subjective effects in humans. Science 202:227–228; 1978.
14. Javaid, J. I.; Musa, M. N.; Fischman, M. W.; Schuster, C. R.; Davis, J. M. Kinetics of cocaine in humans after intravenous and intranasal administration. Biopharm. Drug Dis. 4:9–18; 1983.

15. Johnson, R. H.; Eisenhofer, G.; Lambie, G. H. The effects of acute and chronic ingestion of ethanol on the antonomic nervous system. Drug Alcohol Depend. 18:319–328; 1986.
16. Kalant, H.; LeBlanc, A. E.; Gibbins, R. J. Tolerance to, and dependence on, some non-opiate psychotropic drugs. Pharmacol. Rev. 23:135–191; 1971.
17. Knott, D. H.; Beard, J. D. Changes in cardiovascular activity as a function of alcohol intake. In: Kissin, B.; Begleiter, H., eds. The biology of alcoholism. vol. 2. Physiology and behavior. New York: Plenum Press; 1972:345–365.
18. Kupari, M. Acute cardiovascular effects of ethanol A *controlled noninvasive study* (sic). Br. Heart J. 49:174–182; 1983.
19. Lane, J. D. Caffeine and cardiovascular response to stress. Psychosom. Med. 45:447–451; 1983.
20. Light, K. C.; Obrist, P. A. Cardiovascular reactivity to behavioral stress in young males with and without marginally elevated casual systolic pressures. Hypertension 2:802–808; 1980.
21. Mathias, D. W. Cocaine-associated myocardial ischemia. Am. J. Med. 81:675–678; 1986.
22. Muscholl, E. Effect of cocaine and related changes on the uptake of noradrenaline by heart and spleen. Br. J. Pharmacol. 16:352–361; 1961.
23. Obrist, P. A.; Light, K. C.; James, S. A.; Strogatz, D. S. Cardiovascular responses to stress: I. Measures of myocardial response and relationship to high resting systolic pressure and parental hypertension. Psychophysiology 24:65–78; 1987.
24. Perez-Reyes, M.; Guiseppi, S. D.; Ondrusek, G.; Jeffcoat, A. R.; Cook, C. E. Free-base cocaine smoking. Clin. Pharmacol. Ther. 32:459–465; 1982.
25. Ray, R. L.; Nellis, M J.; Brady, J. V.; Foltin, R. W. Nicotine and caffeine effects on the task-elicited blood pressure response. Addict. Behav. 11:31–36; 1986.
26. Rech, R. H.; Vomachka, M. K.; Rickert, D. E. Interactions between depressants (alcohol-type) and stimulants (amphetamine-type). Pharmacol. Biochem. Behav. 8:134–151; 1978.
27. Reed, T. E.; Hanna, J. M. Similarities and differences in acute cardiovascular responses to alcohol among normal men of European, Japanese, and Chinese ancestry: A univariate and multivariate analysis. Alcohol.: Clin. Exp. Res. 10:560–563; 1986.
28. Resnick, R. B.; Kestenbaum, R. S.; Schwartz, L. K. Acute systematic effects of cocaine in man: A controlled study by intranasal and intravenous routes. Science 195:696–698; 1977.
29. Riff, D. P.; Jain, A. C.; Doyle, J. T. Acute hemodynamic effects of ethanol on normal human volunteers. Am. Heart J. 78:592–597; 1969.
30. Schnoll, S. H.; Karrigan, J.; Kitchen, S. B.; Daghestani, A.; Hansen, T. Characteristics of cocaine abusers presenting for treatment. In: Kozel, N. J.; Adams, E. H., eds. Cocaine use in America: Epidemiologic and clinical persepectives. NIDA Research Monograph #61. Washington, DC: U.S. Government Printing Office; 1985:171–181.
31. Schuckit, M. A.; Bogard, B. Intravenous drug use in alcoholics. J. Clin. Psychiatry 47:551–554; 1986.
32. Schuster, C. R.; Fischman, M. W. Characteristics of humans volunteering for a cocaine research project. In: Kozel, N. J.; Adams, E. H., eds. Cocaine use in America: Epidemiologic and clinical perspectives. NIDA Research Monograph #61. Washington, DC: U.S. Government Printing Office; 1985:158–170.
33. Stimmel, B. Cardiovascular effects on mood-altering drugs. New York: Raven Press; 1979:239–251.
34. Sutker, P. B.; Goist, K. C., Jr.; Allain, A. N.; Bugg, F. Acute alcohol intoxication: Sex comparisons on pharmacokinetic and mood measures. Alcohol.: Clin. Exp. Res. 11:507–512; 1987.
35. Sutker, P. B.; Tabakoff, B.; Goist, K. C., Jr.; Randall, C. L. Acute alcohol intoxication, mood states and alcohol metabolism in women and men. Pharmacol. Biochem. Behav. 18(Suppl. 1):349–354; 1983.
36. Timmis, G. C.; Ramos, R. G.; Gordon, S.; Parikh, R.; Gangadharan, V. Ethanol-induced changes of myocardial performance in healthy adults. Cardiology 59:184–189; 1974.
37. Zimmerman, F. H.; Gustafson, G. M.; Kemp, H. G., Jr. Recurrent myocardial infarction associated with cocaine abuse in a young man with normal coronary arteries: Evidence for coronary artery spasm culminating in thrombosis. J. Am. Coll. Cardiol. 9:964–968; 1987.
38. Zsoter, T. T.; Sellers, E. M. Effect of alcohol on cardiovascular reflexes. J. Subst. Abuse 38:1–10; 1977.