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Effects of Cocaine and Ethylcocaine on Schedule-Controlled Responding in Rats

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SHELNUTT, S., T. J. HUDZIK, D. L. LATTIN AND D. E. McMILLAN. *Effects of cocaine and ethylcocaine on schedule-controlled responding in rats.* PHARMACOL BIOCHEM BEHAV 43(2) 509–511, 1992.—The effects of cocaine and benzoylecognine ethyl ester (ethylcocaine), its metabolite found only in simultaneous users of cocaine and ethanol, were studied in rats responding for food under a multiple fixed-ratio fixed-interval schedule of food presentation. Both cocaine and ethylcocaine increased rates of responding under the fixed-interval component and decreased the quarter life. Both drugs only decreased rates of responding under the fixed-ratio component. Cocaine was approximately equipotent to ethylcocaine. Ethylcocaine may contribute to interactions between cocaine and ethanol by exerting cocaine-like effects not seen with other cocaine metabolites.

Cocaine Ethylcocaine Schedule-controlled responding Rats

RECENT reports have identified a transesterification product, benzoylecognine ethyl ester (ethylcocaine), in concurrent users of cocaine and ethanol (2,7,8). Because the concurrent use of cocaine and ethanol is quite common (15), the pharmacology of ethylcocaine is of great interest.

Ethylcocaine has been shown to be as potent as cocaine in inhibiting the binding of the specific dopamine uptake blocker, GBR 12935, to rat striatal membranes and in inhibiting dopamine uptake into rat synaptosomes (8), but it is less potent than cocaine in inhibiting the uptake of norepinephrine and serotonin (7). Little is known about the behavioral effects of ethylcocaine, although it has been shown to increase motor activity in rats and maintain lever pressing for intravenous injections in monkeys with a potency equal to that of cocaine (8).

The present study compared the effects of ethylcocaine with those of cocaine on responding under a multiple fixed-ratio fixed-interval schedule of food presentation (mult FR FI) in rats. The mult FR FI schedule has been used widely to study the effects of drugs on behavior (11) including the effects of cocaine (10,13). Cocaine increases low rates of responding under the FI component of the schedule and decreases high rates under the FR component (10,13). These effects on responding under the mult FR FI schedule do not seem to be related to the local anesthetic action of cocaine because other local anesthetics do not increase rates of responding under the FI component (10).

METHOD

Subjects

Five adult, male Sprague-Dawley rats were used as subjects. The weight of rats ranged from 300–362 g and they were maintained at these weights throughout the experiments by food pellets delivered during test sessions and supplemental feeding immediately after the sessions. Rats had unrestricted access to water in their colony cages, in which they were housed singly. Room lights in the colony room were on between 0700 and 1900 h. Rats had received other drugs prior to these experiments, but none during the 2-week period before the present experiments began.

Apparatus

The test chamber was a Gerbrands Model G7105 (Ralph Gerbrands Co., Arlington, MA) equipped with a Gerbrands lever and a food cup into which 97-mg food pellets (P. J. Noyes Co., Lancaster, NH) could be delivered. The test chamber was enclosed in a Gerbrands Model G7210 sound-attenuated chamber. The experiments were programmed and data recorded by a Radio Shack Model IV computer (Tandy Corp, Arlington, TX).

Procedure

Rats had been trained earlier to respond under a multiple fixed-ratio 30-response fixed-interval 5-min schedule of food

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presentation (mult FR 30 FI 5). Under the FI component, the first response after 5 min elapsed produced a food pellet. Responses occurring prior to that time were recorded but had no programmed consequences. Under the FR component, the 30th response produced food. A 60-s limited hold applied to both schedule components so that if a response did not occur within 60 s after 5 min in the FI component, or if 30 responses did not occur within 60 s in the FR component, the schedule switched to the other component. Two stimulus lights above the active lever were lighted only during the FR components to differentiate the components. Sessions were always initiated with the FR component and continued until each component had been presented 10 times (about 55 min).

Drugs

Cocaine HCl and ethylcocaine fumarate were dissolved in saline solution at a concentration that allowed each injection to be given in a volume of 0.1 ml/100 g body weight. Injections were intraperitoneal. Doses shown in the figure are as the free base.

Drugs were administered 5 min before the session on Tuesdays and Fridays. Saline injections were administered 5 min before Thursday sessions and data from these sessions served as an estimate of baseline (control) variability. Data following sessions on Mondays and Wednesdays were not used.

Data

Overall rates of responding were calculated for each component for an entire session by dividing the number of responses by the number of seconds. Quarter life was calculated according to the method of Gollub (5). The quarter life is the percentage of the fixed interval required for 25% of the responses to be emitted and is a measure of the temporal pattern of responding within the interval.

Data were averaged across subjects for rates of responding and quarter life. Drug means falling more than two standard deviations from the average control mean were considered statistically significant. Dose–effect curves for cocaine and ethylcocaine were tested for statistically significant differences by the nonparametric signed ranks test for paired observations (4).

RESULTS

Control performance under the multiple FI FR schedule was similar to that described previously for rats under this schedule of food presentation (1). Under the FI component, rates of responding were low early in the FI but increased gradually as time within the FI elapsed. The baseline control rate of responding under the FI component averaged across animals was 0.35 responses/s. The pattern of responding under the FI component was reflected by the quarter life value, which averaged 60% across animals for control sessions, indicating that 60% of the FI time elapsed before one quarter of the FI responses were emitted. Under the FR component, following a short pause at the beginning relatively uniform rates of responding were maintained until the food pellet was delivered. The overall rate of responding under the FR component averaged across animals for control sessions was 2.76 responses/s.

Figure 1 shows the effects of cocaine and ethylcocaine on rates of responding and quarter life under the mult FI FR

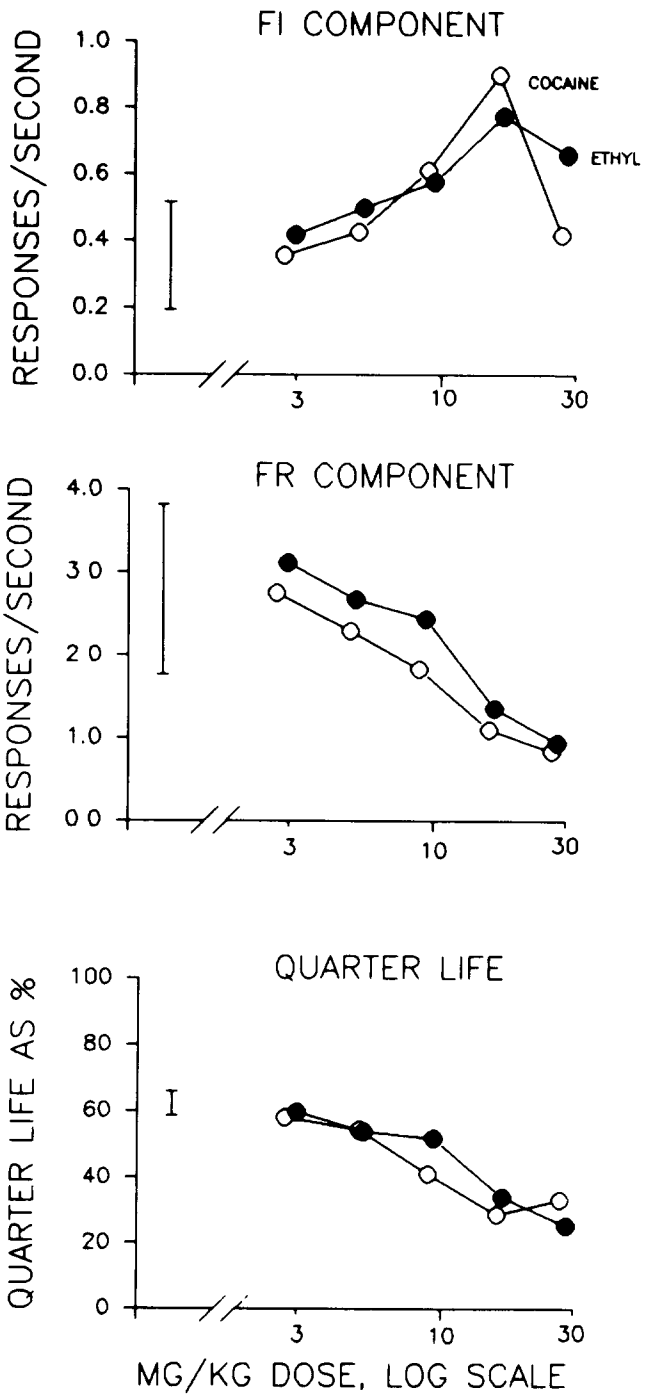

FIG. 1. Effects of cocaine (○) and ethylcocaine (●) on rates of responding under the FI component (top frame) and under the FR component (middle frame) and on the quarter life of FI responding (bottom frame). Ordinate: responses/s averaged over the session (top two frames); quarter life as percent (bottom). Abscessa: mg/kg free base, log scale. Brackets show ±2 SDs of Thursday control means. Each point represents a mean of single observations in each of five rats.

schedule. Low doses of both drugs had no effect on responding under the FI component (top frame). Higher doses increased rates of responding under the FI component with the highest dose causing the FI dose–effect curve to descend. The dose–effect curves were not significantly different.

Cocaine and ethylcocaine only decreased FR responding in a dose-dependent manner. Although the dose–effect curves for the two drugs differed significantly, cocaine was only slightly more potent than ethylcocaine. Cocaine and ethylcocaine also produced dose-dependent decreases in the quarter life. The dose–effect curves for quarter life were not statistically different.

DISCUSSION

Cocaine and ethylcocaine produced similar effects on the performance of rats whose behavior was maintained under a mult FI FR schedule. Both drugs generated an inverted U-shaped dose–effect curve for FI responding. Both drugs produced dose-dependent decreases in rates of FR responding. Both drugs produced similar decreases in the quarter life. On all measures of performance, cocaine was approximately equipotent to ethylcocaine. Many effects of cocaine on the CNS have been related to its ability to block dopamine reuptake (7,8). Cocaine and ethylcocaine are equipotent in blocking dopamine uptake into rat synaptosomes from striatum or nucleus accumbens (7,8), consistent with our data showing similar behavioral effects. In contrast, ethylcocaine is considerably less potent than cocaine at serotonin and norepinephrine uptake transport sites (7).

Despite the widespread interest in the behavioral pharmacology of cocaine (9), we were unable to find reports in the literature on the effects of cocaine on responding under mult FI FR schedules in rats; however, there are numerous reports of the effects of cocaine on responding under the mult FI FR schedule in pigeons (10,13) and monkeys (6). The effects obtained in other species were generally the same as those we obtained in rats with rate increases occurring during the FI but not during the FR component and disruption of the temporal pattern of responding under the FI component. These effects are probably not related to the local anesthetic effects of either cocaine or ethylcocaine (16) because the rate-dependent effects of cocaine on mult FR FI responding are not shared by most other local anesthetics (10).

Ethylcocaine is of interest because of its discovery in tissues of individuals using both cocaine and ethanol (2,7,14). Concurrent use of cocaine and ethanol is extremely common (15) and has been associated with a higher morbidity and mortality than occurs with cocaine alone (3,7,12). It has been proposed that the pharmacological and toxic effects of cocaine may be potentiated by ethanol through the enzymatic formation of ethylcocaine (7,8). If alcohol diminishes the metabolism of cocaine to benzoyleconine by inducing the formation of ethylcocaine as proposed by Dean et al. (2) and if cocaine and ethylcocaine exert similar effects as shown in the present study as well as others (8), then the pharmacological effect of combined exposure to ethanol and cocaine may be prolonged cocaine-like effects due to the formation of ethylcocaine. The degree to which this occurs awaits both detailed studies on the pharmacokinetics of these drug interactions and studies on the pharmacological consequences of interactions between ethanol, cocaine, and/or ethylcocaine.

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REFERENCES

1. Clark, F. C.; Steele, B. J. Effects of *d*-amphetamine on performance under a multiple schedule in the rat. Psychopharmacologia 9:315–335; 1966.
2. Dean, R. A.; Christian, C. D.; Sample, R. H. B.; Borson, W. F. Human liver cocaine esterases: Ethanol-mediated formation of ethylcocaine. FASEB J. 5:2735–2739; 1991.
3. Foltin, R. W.; Fischman, M. W. Ethanol and cocaine interactions in humans: Cardiovascular consequences. Pharmacol. Biochem. Behav. 31:877–883; 1989.
4. Goldstein, A. Biostatistics: An introductory test. New York: MacMillan; 1964.
5. Gollub, L. R. The relations among measures of performance of fixed-interval schedules. J. Exp. Anal. Behav. 7:337–343; 1964.
6. Gonzalez, F. A.; Goldberg, S. R. Effects of cocaine and *d*-amphetamine on behavior maintained under various schedules of food presentation in squirrel monkey. J. Pharmacol. Exp. Ther. 201:33–43; 1977.
7. Hearn, W. L.; Flynn, D. D.; Hime, G. W.; Rose, S.; Confino, J. C.; Mantero-Atienza, E.; Weli, C. W.; Mash, D. C. Cocaethylene: A unique cocaine metabolite displays high affinity for the dopamine transporter. J. Neurochem. 56:698–701; 1991.
8. Jatlow, P.; Elsworth, J. D.; Brodberry, C. W.; Winger, G.; Taylor, J. R.; Russel, R.; Roth, R. H. Cocaethylene: A neuropharmacologically active metabolite associated with concurrent cocaine–ethanol ingestion. Life Sci. 48:1787–1794; 1991.
9. Johanson, C.-E.; Fischman, M. W. The pharmacology of cocaine related to its abuse. Pharmacol. Rev. 41:3–52; 1989.
10. McMillan, D. E.; Dearstyne, M. R.; Engstrom, T. G. Some effects of local anesthetics on schedule-controlled behavior. Pharmacol. Ther. Dent. 2:57–64; 1975.
11. McMillan, D. E.; Leander, J. D. Effects of drugs on schedule-controlled behavior. In: Glick, S. D.; Goldfarb, J., eds. Behavioral pharmacology. St. Louis, MO: C. V. Mosby; 1976:85–139.
12. Rose, S.; Hearn, W. L.; Hime, G. W.; Wetli, C. V.; Ruttenber, A. J.; Mash, D. C. Cocaine and cocaethylene concentration in the human post mortem cerebral cortex. Neurosci. Abstr. 16:14; 1990.
13. Smith, C. B. Effects of *d*-amphetamine upon operant behavior in pigeons: Enhancement by reserpine. J. Pharmacol. Exp. Ther. 146:167–174; 1964.
14. Smith, R. M. Ethyl esters of aryhydroxy- and arylhydroxymethoxycocaines in the urines of simultaneous cocaine and ethanol users. J. Anal. Toxicol. 8:38–42; 1984.
15. Weiss, R. D.; Mirin, S. M.; Griffin, M. L.; Michael, J. L. Psychopathology in cocaine abusers: Changing trends. J. Neuro. Ment. Dis. 176:719–725; 1988.
16. Windholz, M.; Budavari, S.; Stroumtsos, L. Y.; Fertig, M. N. The Merck index. Rahway, NJ: Merck & Co.; 1976.