Pharmacology Biochemistry and Behavior, Vol. 61, No. 3, pp. 291–296, 1998
© 1998 Elsevier Science Inc.
Printed in the USA. All rights reserved
0091-3057/98 $19.00 + .00

ELSEVIER

PII S0091-3057(98)00092-6

Cocaine and Caffeine: Conditioned Place Preference, Locomotor Activity, and Additivity

J. BRENT BEDINGFIELD, DAVID A. KING[1] AND FRANK A. HOLLOWAY

Department of Psychiatry and Behavioral Sciences, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73190-3000

Received 28 September 1997; Revised 16 March 1998; Accepted 25 March 1998

BEDINGFIELD, J. B., D. A. KING AND F. A. HOLLOWAY. *Cocaine and caffeine: Conditioned place preference, locomotor activity, and additivity.* PHARMACOL BIOCHEM BEHAV **61**(3) 291–296, 1998.—Conditioned place preference (CPP) was employed to clarify the reinforcing and locomotor stimulating effects of several doses of cocaine and caffeine (0.32, 1.0, 3.2, 5.6, and 10.0 mg/kg) and to explore the possibility of additive effects between the two drugs. Additionally, the hypothesis that the reinforcing effects of psychostimulants are mediated by the same systems that control psychostimulant-induced locomotor activity was examined by conducting correlational studies between drug-induced locomotor activity and time spent in the drug-conditioned compartments. Several doses of cocaine (1.0, 3.0, 5.6, 10.0 mg/kg), and caffeine (0.32, 1.0, 3.2, 5.6, 10.0) were found to condition place preference and stimulate locomotor activity. A combination of low doses (0.32 mg/kg) of each drug appeared to be additive. A positive relationship between locomotor activity observed during conditioning and time spent in the conditioned compartment during testing was found for cocaine but not caffeine or the low-dose combination of cocaine and caffeine. © 1998 Elsevier Science Inc.

Cocaine Caffeine Conditioned place preference Locomotor activity Additivity

MANY effects produced by psychostimulants such as cocaine are known to be mediated through dopamine systems. Though indirectly, a portion of caffeine's effects may also be mediated by dopamine [for review, see (12)]. Caffeine antagonizes the adenosine receptor which, when activated, produces results that are generally opposite to those of the dopamine receptors. For example, both striatal dopamine (24) and spontaneous locomotor activity (18) are reduced following activation of the adenosine receptor. Conversely, antagonizing the adenosine receptor with an antagonist like caffeine (8,32) augments striatal dopamine (26) and locomotor activity (33,39). That dopamine mediates many of the effects of caffeine is further supported by reports that dopaminergic antagonists (high doses) block caffeine-induced motor activity (13) and cocaine-discriminating rats will partially generalize to a caffeine lever (14–17). On the other hand, though dopamine may play a role in caffeine-induced motor activity, the exact participation is not clear because there is considerable evidence that caffeine-induced locomotor activity is not mediated by the identical mechanisms that mediate cocaine-induced locomotor activity (29,37,38). If dopamine participates in mediating the effects of both cocaine and caffeine, additive or synergistic effects on reinforcement or motor activity may be observed between the two drugs. Conversely, because there is considerable difference between the pharmacology of the two drugs, differences in the way they interact should be expected, and identifying any differences may enhance our understanding of drug reinforcement and locomotor activity.

The reinforcing efficacy of cocaine in laboratory animals is well established (10,20,27,28). However, similar confidence in the reinforcing efficacy of caffeine has not been forthcoming. Caffeine self-administration has proven equivocal (1,8,9), and data derived from conditioned place preference (CPP) experiments is limited, suggesting that low doses (1–3 mg/kg) of caffeine are reinforcing (3,40), while high doses (20–30 mg/kg) are aversive (3,36,40). Although caffeine is known to enhance locomotor activity induced by amphetamine (30,41), methamphetamine (21), and cocaine (25), little is known about what effect caffeine might have on the reinforcing efficacy of cocaine.

Given the small number of CPP (3,36,40) experiments reported, we have reexamined the reinforcing efficacy of low

[1]Now at the Department of Psychology, University of Vermont, Burlington, VT.
Requests for reprints should be addressed to J. B. Bedingfield, Dept. of Pharmacology, School of Medicine, University of Utah, Salt Lake City, UT 84132.

doses (0.32, 1.0, 3.2, 5.6, 10 mg/kg) of caffeine within a "biased" CPP paradigm. Identical doses of cocaine were also examined. To investigate possible interacting effects of these drugs on reinforcement and locomotor activity, a combination of the lowest dose of each drug (0.32 mg/kg) was tested.

The reinforcing effects of psychostimulants have been proposed to be mediated by the same dopaminergic systems that mediate the motor stimulant qualities of the drugs (42). If correct, a positive relationship between drug-induced locomotor activity and reinforcement as measured by the amount of time spent in the drug-paired compartment would be expected. Consequently, our CPP apparatus was also designed to enable recording of locomotor activity during conditioning. Correlational comparisons between these two measures were conducted.

METHOD

The subjects were 117 male, Sprague–Dawley rats (Sasco, Inc. Omaha, NE), weighing 250–300 g; group housed (two to a cage) in a colony room, under a 12 L:12 D cycle. All habituation, training, and testing was conducted between 1300 and 1800 h. Rat chow and tap water was available ad lib. Animal care was provided by Animal Resources and Facilities, Department of Comparative Medicine, University of Oklahoma, an AAALAC accredited facility. The subjects were weighed and handled daily for 3 days prior to the first habituation and daily thereafter.

Drugs

Cocaine hydrochloride and caffeine were purchased from Sigma Chemical Company (St. Louis, MO). They were dissolved in 0.9% normal saline and injected intraperitoneally immediately before the subject was placed in the drug conditioning chamber. When an animal received injections of both caffeine and cocaine, they were administered separately on either side of the abdomen.

Place Conditioning Task

The place conditioning apparatus consisted of two main conditioning compartments (40 × 16 × 24 cm), connected to each other by a third compartment (10 × 16 × 24 cm) in a straight alleyway configuration. The apparatus was constructed of Plexiglas (Cope Plastics, Oklahoma City, OK) and included a transparent hinged top. The central chamber had opaque gray walls and a transparent floor. The two conditioning compartments were distinguished by horizontal or vertical white and black stripes on the walls and textured or smooth indoor/outdoor carpeting on the floor. The apparatus was cleaned between rats by removing feces and wiping the walls, ceiling, and carpeting with warm soapy water. To sequester animals to a specific compartment for conditioning, removable partitions could be inserted between individual compartments. During testing, the partitions were removed and partial walls (10 cm high) were inserted between the central compartment and the two conditioning compartments. These partial walls remained in place during testing sessions to facilitate a clear, quantitative change in location of the rat from one compartment to the other. The number of compartment entries, time in each compartment, and general activity of the subjects were assessed and recorded by sets of infrared photobeams located near the floor of each compartment and linked by a photobeam controller (DIG-723, Med. Associates, Inc., East Fairfield, VT) to a Commodore 64C microcomputer system. The microcomputer system controlled experimental contingencies and recorded all measures from four sets of conditioning chambers simultaneously (American Neuroscience Research Foundation, Oklahoma City, OK).

Habituation to the apparatus was accomplished during the first 3 days when animals were allowed free access to all three compartments of the apparatus for 20 min each day. Baseline side preference was established on the fourth day during a 20-min test (tests 1 and 2 were conducted in an identical manner). Initially, the animal was confined to the central compartment, which was sealed off from the two distal compartments by placement of both partitions. Once the computer program was started the partitions were removed, completing a photo beam-controlled circuit that initiated the recording of chamber data. A "preference score" was calculated by dividing the total time spent in the least-preferred compartment by total time spent in both conditioning compartments (CS+/(CS− + CS+). This score reflects shifts in compartment preference independently from the time an animal may spend in the nonconditioned center compartment and appears to be an effective measure of compartment preference (11,19). The least-preferred compartment, established at the baseline test, was designated as the conditioned stimulus (CS+) side, which was paired with cocaine, caffeine, or a combination of the two during conditioning [biased design, cf. (2,31)]. The preferred compartment was paired with saline injections in volumes equivalent to the drug injections. Control animals received saline injections in both compartments. Groups (n = 9) were formed on the basis of time spent in the least-preferred compartment and were comprised of an approximately equal number of rats preferring one compartment over the other; to this extent they were matched groups and counterbalanced for side preference.

The conditioning trials began on the day following the baseline test. During conditioning, each rat was injected with the drug or saline and immediately placed into the requisite compartment and confined for 20 min. Conditioning was accomplished in a 3-day cycle, beginning on day 1 with saline in the preferred compartment followed on day 2 with drug in the nonpreferred compartment. On day 3 the animals were left in their home cages to ensure that any residual drug effects did not carry over into the saline conditioning sessions. Control animals receiving saline injections only were also left in their home cage on the third day of the cycle. Two training cycles preceded test 1, which was followed by two more training cycles and test 2.

DATA ANALYSIS

Preference scores (CS+/(CS− + CS+) were calculated and used as the indicator of side preference. The scores were analyzed separately for cocaine and caffeine groups by a mixed factors ANOVA [between Ss: doses (6); within Ss: tests (3)]. The effects of the 0.32 mg/kg cocaine and caffeine combination was compared in a separate analysis to the 0.32 mg/kg cocaine and caffeine groups; mixed factors ANOVA [between Ss: drug treatments (4); within Ss tests (3)]. Duncan's New Multiple Range Test was used to compare changes in side preference for specific treatments. Statistical significance was set at $p < 0.05$.

Locomotor activity recorded during conditioning trials was averaged over the four drug-CS$^+$ pairings and analyzed by one-way ANOVA [between Ss: doses (6)]. In the case of the

cocaine/caffeine combination, one-way ANOVA [between Ss: drug treatments (4)] was utilized. Duncan's New Multiple Range Test was used to compare the effects of individual treatments on locomotor activity. Statistical significance was set at $p < 0.05$. Possible relationships between locomotor activity and time spent in the conditioned compartments were examined by Pearson correlation coefficients. Statistical significance was set at $p < 0.01$.

RESULTS

Cocaine Effects

In comparison to baseline, cocaine-conditioned rats significantly increased the relative time spent in the drug-paired compartments, $F(2, 96) = 23.5$, $p < 0.0005$ (Fig. 1A); an effect observed during both tests ($p < 0.05$). Experience with cocaine appeared to further enhance its reinforcing effects because overall, animals spent a greater amount of time in the drug-conditioned compartments during test 2 than during test 1 ($p < 0.05$). The significant increase in preference scores was dependent on dose, as evidenced by a significant main effect of dose, $F(5, 48) = 2.75$, $p < 0.03$ and a dose by tests interaction, $F(10, 96) = 2.42$, $p < 0.01$. Individual group comparisons indicated that rats receiving doses of 3.2, 5.6, and 10.0 mg/kg cocaine during test 1 and 1.0, 3.2, 5.6 and 10.0 mg/kg during test 2, significantly increased the time spent in the drug-paired compartments compared to baseline. Locomotor activity was stimulated by cocaine, $F(5, 48) = 11.6$, $p < 0.0005$. As depicted in Fig. 1B, rats receiving 3.2, 5.6, and 10.0 mg/kg cocaine were significantly more active than animals administered saline, 0.32 or 1.0 mg/kg (Fig. 1B).

Caffeine Effects

Overall, caffeine was also found to be reinforcing as the amount of time the subjects spent in the drug-conditioned compartments increased significantly compared to baseline, $F(2, 96) = 18.6$, $p < 0.0005$. During both tests, subjects spent significantly greater amounts of time in the drug-conditioned compartments than they did at baseline ($p < 0.05$). However, in contrast to cocaine, two additional conditioning sessions between test 1 and test 2 did not significantly enhance side preference of animals at test 2 compared to test 1. The effect of dose on caffeine-conditioned place conditioning was not significant, $F(5, 48) = 1.3$, $p = 0.28$, nor was there a significant dose by test interaction, $F(10, 96) = 1.5$, $p = 0.17$. Figure 2A presents the change in preference scores exhibited by animals administered different doses of caffeine. Subjects receiving 1.0, 3.2, 5.6, and 10.0 mg/kg caffeine during test 1 and 0.32, 1.0, 3.2, 5.6, and 10.0 mg/kg during test 2 spent significantly greater amounts of time in the drug-paired compartments following conditioning ($ps < 0.05$). Caffeine significantly increased locomotor activity, $F(5, 48) = 3.95$, $p < 0.005$. However, only animals receiving 3.2, 5.6, or 10.0 mg/kg exhibited locomotor activity significantly greater than saline (Fig. 2B).

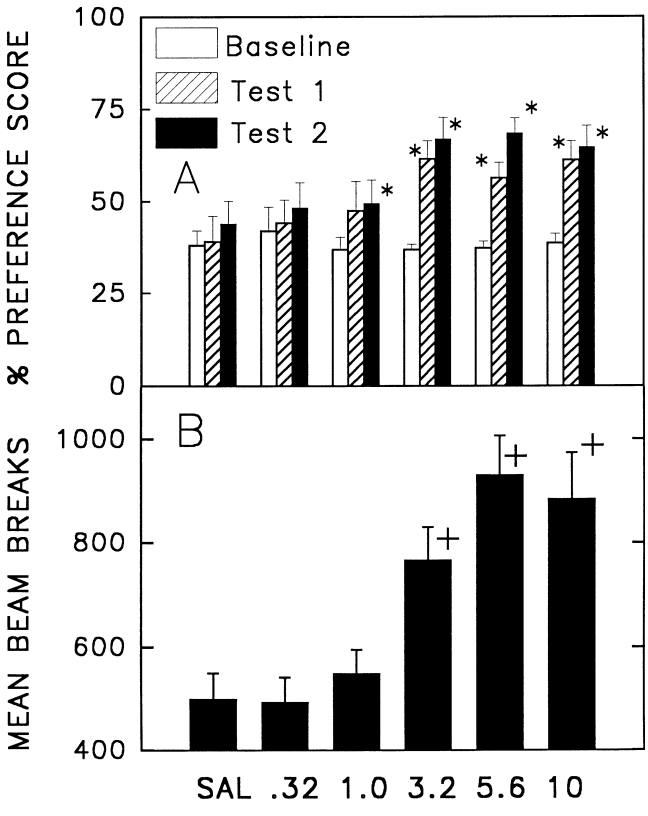

FIG. 1. (A) Test 1 and test 2 preference scores (±SEM) conditioned by different doses of cocaine (mg/kg). Legend is the same for all figures. *$p < 0.05$ compared to baseline. (B) Cocaine-induced locomotor activity recorded during conditioning sessions. Each bar represents the mean of four conditioning trials (±SEM). $^{+}p < 0.05$ compared to the saline control group.

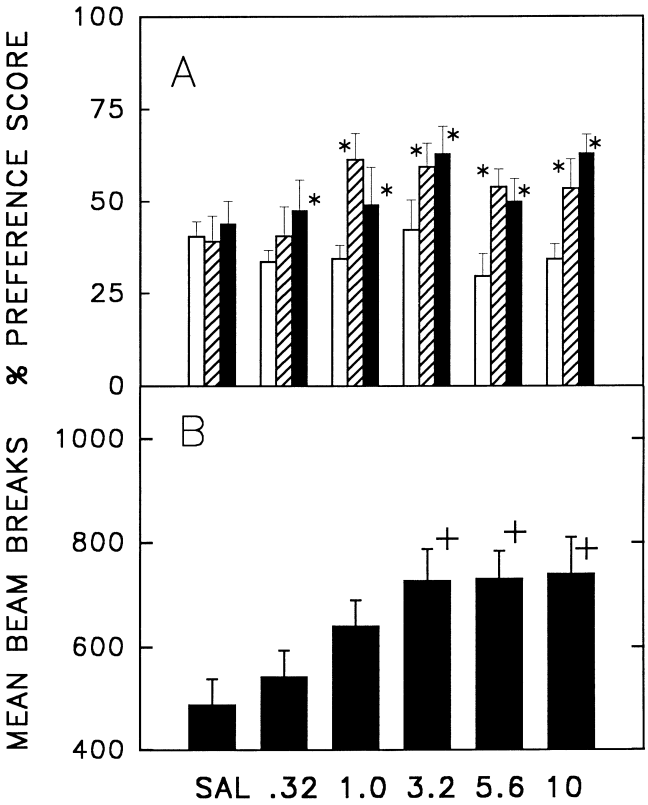

FIG. 2. (A) Caffeine-conditioned place preference. Details are same as Fig.1A. *$p < 0.05$ compared to baseline. (B) Caffeine-induced locomotor activity. $^{+}p < 0.05$ compared to saline control group.

Combined Drug Effects

The data in Fig. 3A, indicate that when combined, low-doses of cocaine and caffeine may enhance approach behavior to cues paired with their administration, suggesting that reinforcement induced by these drugs is additive. Overall, subjects increased the amount of time spent in the conditioned compartments, $F(2, 64) = 3.8$, $p < 0.03$. However, only animals receiving 0.32 mg/kg caffeine during test 2 and the combination of 0.32 mg/kg cocaine and caffeine at tests 1 and 2 increased side preference significantly ($p < 0.05$). Although subjects receiving the combination of 0.32 mg/kg cocaine and caffeine did appear more active than subjects administered the low doses of either cocaine or caffeine, the effect was not significant (Fig. 3B).

The results of the correlational analysis are presented in Table 1.

DISCUSSION

The data indicate that both cocaine (1.0, 3.2, 5.6, and 10 mg/kg) and caffeine (0.32, 1.0, 3.2, 5.6, and 10.0 mg/kg) condition positive place preferences when examined within a biased CPP paradigm, a design thought to facilitate expression of the reinforcing effects of a drug (2,31). The cocaine data is in general agreement with previous reports employing a similar design (11,28). The caffeine results are also similar to earlier reports in that low doses (1.0–3.0 mg/kg) are reinforcing (3,40). However, the present data extends the dose range of the reinforcing effects of caffeine from 0.32 mg/kg to 10.00 mg/kg.

By test 2 (following four conditioning sessions and test 1) animals treated with 0.32 mg/kg caffeine did exhibit significant approach behavior for the caffeine-conditioned compartment. However, subjects receiving the combined drug treatment of 0.32 mg/kg cocaine and caffeine displayed comparatively robust side preferences for the drug-conditioned compartments during both tests 1 and 2; suggesting that at these low doses the reinforcing effects of caffeine and cocaine are additive.

It is interesting that cocaine-conditioned animals spent a greater amount of time in the conditioned compartments during test 2 than test 1, while caffeine animals failed to exhibit a difference between test 1 and test 2. Although speculative, it is possible that in comparison to caffeine, greater familiarity with cocaine enhances its reinforcing effects. Similar hypotheses have been suggested previously (22).

It is difficult to understand why animals treated with the larger doses of either cocaine or caffeine did not spend significantly more time in the conditioned compartment than animals receiving lesser doses or why animals receiving the combined treatment did not spend significantly more time in the conditioned chamber than animals treated with 0.32 mg/kg of either drug. The CPP paradigm is quite informative in determining the reinforcing efficacy of a particular drug, but a dose–response curve or potentiation of one drug by another is

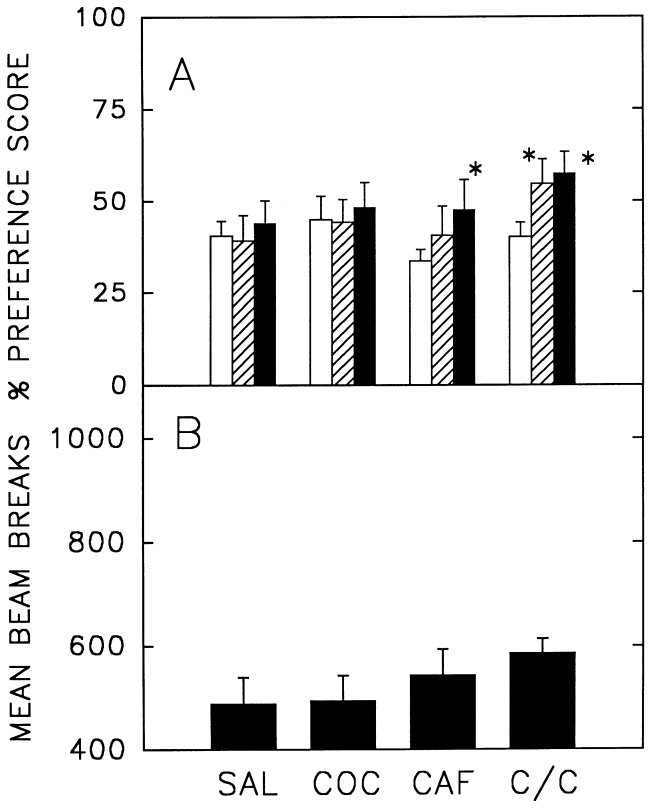

FIG. 3. (A) Test 1 and test 2 preference scores produced by a combination of 0.32 mg/kg of each drug (C/C) compared to animals receiving 0.32 mg/kg cocaine (COC), 0.32 mg/kg caffeine (CAF), or saline (SAL). *$p < 0.05$ compared to baseline. (B) Locomotor activity recorded during conditioning sessions following drug treatment explained in A.

TABLE 1

CORRELATIONS BETWEEN PREFERENCE SCORES AND LOCOMOTOR ACTIVITY RECORDED DURING CONDITIONING

	Preference Scores			
Motor Activity	Baseline	Test 1	Test 2	Mean
Overall N 117				
Cond 1	0.06	0.10	0.10	0.10
Cond 2	−0.07	0.06	0.19	0.14
Cond 3	0.05	0.17	0.28*	0.26*
Cond 4	0.05	0.15	0.29*	0.25*
Mean	0.02	0.14	0.28*	0.23*
Cocaine N 54				
Cond 1	0.09	0.17	0.28	0.25
Cond 2	−0.05	0.14	0.34*	0.27
Cond 3	0.04	0.26	0.38*	0.36*
Cond 4	0.03	0.31	0.42†	0.41†
Mean	0.02	0.26	0.41†	0.38*
Caffeine N 54				
Cond 1	0.09	0.09	0.02	0.06
Cond 2	−0.09	0.05	0.1	0.08
Cond 3	0.02	0.16	0.19	0.19
Cond 4	0.1	0.06	0.16	0.12
Mean	0.03	0.1	0.14	0.13
Caf/Co N 36				
Cond 1	0.27	−0.04	0.02	−0.01
Cond 2	0.2	−0.26	−0.02	−0.21
Cond 3	0.2	0.02	0.03	0.03
Cond 4	0.32	−0.15	0.14	−0.01
Mean	0.26	−0.14	0.05	−0.05

*$p < 0.01$; †$p < 0.001$.

sometimes difficult to demonstrate (23,28,34,35) but by no means, impossible (5). It is quite common, as supported by the present data, for a low dose of a particular drug to be ineffective, while the next higher dose conditions near maximal increases in side preference (5). This "stepup" phenomena has not received much attention and is not well understood. However, it should be pointed out that when reinforcing stimuli (e.g., food) are conditioned to the neutral cues of a box or cage, animals will find subsequent confinement without food in the same box or cage, aversive, an outcome thought to result from frustrative nonreward (7). Though subjects in a CPP experiment are not confined to the conditioned compartment during the drug-free test, the absence of drug reinforcement in the conditioned compartment may actually prove somewhat aversive to the animals (frustrative nonreward) and contribute to the modest increase in side preferences reported by many authors as well as the similar preference scores observed among subjects conditioned to a wide spectrum of drug doses. Furthermore, in the CPP paradigm animals are tested during extinction, therefore, intervening behaviors may occur that interfere with observing a direct relationship between drug dose and time spent in the conditioned chamber. This is an area that requires further attention.

Interestingly, the locomotor stimulus effects of both drugs appear to manifest in the area of 0.32–3.2 mg/kg, a range similar to the reinforcing effects of both drugs, suggesting the effects of cocaine and caffeine on locomotor activity and side-preference scores are remarkably similar. Although 0.32 mg/kg of each drug did not significantly stimulate locomotor activity compared to saline, the observation that caffeine-treated animals were slightly more active than cocaine-treated animals and that subjects treated with the combination of both drugs tended to be more active than the caffeine-treated subjects suggests that the effects of the low-dose combination on locomotor activity is additive and may be synergistic. Others have reported that caffeine enhanced cocaine-induced locomotor activity, but higher doses were examined (25).

Perhaps more supportive of the hypothesis that the locomotor activity and reinforcing effects of psychostimulants are mediated by the same dopaminergic systems is the correlational data presented in Table 1. The significant correlations between cocaine-stimulated locomotor activity and preference test scores are suggestive of the possibility that for cocaine, systems underpinning these activities may be identical (42). A similar phenomenon was previously reported when the intensity of amphetamine-induced stereotypy, a behavior thought to be mediated by dopaminergic systems in the caudate putamen, was observed to correlate with memory consolidation of a tone-shock association, a phenomenon the authors hypothesized to be mediated by identical systems in the caudate (5).

That cocaine-induced locomotor activity does not correlate with preference scores during test 1 is difficult to explain, although the failure to observe a correlation between drug-induced locomotor activity and test 1 with other drug treatments we have investigated (unpublished date) has been an emerging pattern. It is possible that after being sequestered to specific compartments during two drug pairings and two saline pairings, the relative novelty of the entire apparatus and testing procedure interferes with the animal's expression of side preference during the first preference test but not the second.

The failure of caffeine-stimulated locomotor activity to correlate with side-preference scores may be related to reports that caffeine-induced locomotor activity is not mediated by the identical neural mechanisms that mediate cocaine-induced locomotor activity (29,37,38). If correct, this hypothesis would suggest that neural mechanisms underlying the locomotor stimulating efficacy of a specific drug might be distinguished on the basis of behavior in the CPP paradigm.

It must be pointed out that caution is required when interpreting the present correlational data. First, although statistically significant, the largest correlations only account for approximately 16% of the variance, i.e., only 16% of the variance in one variable is predictable from the other. It may be that with more tests, greater correlations may emerge, but that is only conjecture at this point. Second, the significant correlations between cocaine-induced locomotor activity and time spent in the drug-conditioned compartment could be an artifact of examining multiple doses of cocaine that increase locomotor activity simultaneously but independently from conditioning a side preference. Third, the shape and limited size of the present conditioning compartments may, depending on the drug, differentially constrain drug-induced motor behavior. Clearly, to be completely confident in accepting correlations between drug-induced locomotor activity and time spent in the drug-paired compartment, much more experimentation and replication will be required. Perhaps, a better test of the hypothesis might be to examine relationships between drug-induced motor activity and place preference using only a single drug dose and a larger *n.*

In conclusion, the motor-stimulating and reinforcing effects of both drugs occur at approximately the same doses. Additionally, the effects of a low dose combination of the drugs appear to be additive. However, in view of these similarities, it is quite surprising that the motor-stimulating effects of caffeine do not correlate with time spent in the conditioned compartments. The latter observation suggests that in contrast to cocaine, the reinforcing effects of caffeine are not mediated by the same systems that mediate its motor effects. Though strictly speculative, it has to be questioned whether the addicting efficacy of drugs like cocaine, in comparison to caffeine, is related to the possibility that the reinforcing effects of these drugs are, in fact, mediated by the same systems that mediate approach behaviors.

ACKNOWLEDGEMENTS

This research was supported in part by NIDA 5R01DA04444 to F. A. Holloway.

REFERENCES

1. Atkinson, J.; Enslem, M.: Self-administration of caffeine by the rat. Drug Res. 26:2059–2061; 1976.
2. Bozarth, M. A.: Conditioned place preference: A parametric analysis using systemic heroin injections. In: Bozarth, M. A., ed. Methods of assessing the reinforcing properties of abused drugs . New York City: Springer Verlag; 1987:241–273.
3. Brockwell, N. T.; Eikelboom, R.; Benninger, R. J.: Caffeine-induced place and taste conditioning: Production of dose-dependent preference and aversion. Pharmacol. Biochem. Behav. 38:513–517; 1991.
4. Carr, G. D.; Fibiger, H. C.; Phillips, A. G.: Conditioned place preference as a measure of drug reward. In: Liebman, J. M.; Coo-

per, S. J., eds. Topics in experimental psychology: The neuropharmacological basis of behavior, vol. 1. Oxford: Clarendon Press; 1989:264–319.
5. Carr, G. D.; White, N. M.: The relationship between stereotypy and memory improvement produced by amphetamine. Psychopharmacology (Berlin) 82:203–209; 1984.
6. Collins, R. J.; Weeks, J. R.; Cooper, M. M.; Good, P. I.; Russell, R. R.: Prediction of abuse liability of drugs using IV self-administration by rats. Psychopharmacology (Berlin) 82:6–13; 1984.
7. Daly, H. B.: Reinforcing properties of escape from frustration aroused in various learning situations. In: Psychology of learning and motivation: Advances in research and theory. San Diego: Academic Press; 1974:187–231.
8. Daly, J. W.; Bruns, R. F.; Snyder, S. H.: Adenosine receptors in the central nervous system: Relationship to the central actions of methylxanthines. Life Sci. 28:2083–2097; 1981.
9. Deneau, G.; Yanagita, T.; Seevers, M. H.: Self-administration of psychoactive substances by the monkey: A measure of psychological dependence. Psychopharmacologia 16:30–48; 1969.
10. De Vry, J.; Donselaar, I.; van Ree, J. M.: Food deprivation and acquisition of intravenous cocaine self-administration in rats: Effect of naltrexone and haloperidol. J. Pharmacol. Exp. Ther. 251:735–740; 1989.
11. Durazzo, T. C.; Gauvin, D. V.; Goulden, K. L.; Briscoe, R. J.; Holloway, F. A.: Cocaine-induced conditioned place approach in rats: The role of dose and route of administration. Pharmacol. Biochem. Behav. 49:1001–1005; 1994.
12. Ferre, S.; Fuxe, K.; Von Euler, G.; Johansson, B.; Fredholm, B. B.: Adenosine–dopamine interactions in the brain. Neuroscience 51:501–512; 1992.
13. Garrett, B. E.; Holtzman, S. G.: D_1 and D_2 dopamine receptor antagonists block caffeine-induced stimulation of locomotor activity in rats. Pharmacol. Biochem. Behav. 262:65–75; 1994.
14. Gauvin, D. V.; Criado, J. R.; Moore, K. R.; Holloway, F. A.: Potentiation of cocaine's discriminative effects by caffeine: A time–effect analysis. Pharmacol. Biochem. Behav. 36:195–197; 1990.
15. Gauvin, D. V.; Harland, R. D.; Michaelis, R. C.; Holloway, F. A.: Caffeine–phenylethylamine combinations mimic the cocaine discriminative cue. Life Sci. 44:67–73; 1989.
16. Gauvin, D. V.; Holloway, F. A.: The subjective effects of caffeine: Bridging the gap between animal and human research. Pharmacopsychoecologia 7:179–200; 1994.
17. Harland, R. D.; Gauvin, D. V.; Michaelis, R. C.; Carney, J. M.; Seale, T. W.; Holloway, F. A.: Behavioral interaction between cocaine and caffeine: A drug discrimination analysis in rats. Pharmacol. Biochem. Behav. 32:1017–1023; 1989.
18. Heffner, T. G.; Wiley, J. N.; Williams, A. E.; Bruns, R. F.; Coughenour, L. L.; Downs, D. A.: Comparison of the behavioural effects of adenosine agonists and dopamine antagonists in mice. Psychopharmacology (Berlin) 98:31–37; 1989.
19. Holloway, F. A.; King, D. A.; Bedingfield, J. B.; Gauvin, D. V.: Role of context in ethanol tolerance and subsequent hedonic effects. Alcohol 9:109–116; 1992.
20. Koob, G. F.; Weiss, F.: Pharmacology of drug self-administration. Alcohol 7:193–197; 1990.
21. Kuribara, H.: Caffeine enhances the stimulant effect of methamphetamine, but may not affect induction of methamphetamine sensitization of ambulation in mice. Psychopharmacology (Berlin) 116:125–129; 1994.
22. Lett, B. T.: Repeated exposures intensify rather than diminish the rewarding effects of amphetamine, morphine, and cocaine. Psychopharmacology (Berlin) 98:357–362; 1989.
23. Martin-Iverson, M. T.; Ortmann, R.; Fibiger, H. C.: Place preference conditioning with methylphenidate and nomifensine. Brain Res. 332:59–67; 1985.
24. Meyers, S.; Pugsley, T. A.: Decrease in rat striatal dopamine synthesis and metabolism in vivo by metabolically stable adenosine receptor agonists. Brain Res. 375:193–196; 1986.
25. Misra, A. L.; Vadlamani, N. L.; Pontani, R. B.: Effect of caffeine on cocaine locomotor stimulant activity in rats. Pharmacol. Biochem. Behav. 24:761–764; 1986.
26. Morgan, M. E.; Vestal, R. E.: Methylxanthine effects on caudate dopamine release as measured by in vivo electrochemistry. Life Sci. 45:2025–2039; 1989.
27. Mucha, R. F.; van der Kooy, D.; O'Shaughnessy, M.; Bucenieks, P.: Drug reinforcement studied by the use of place conditioning in the rat. Brain Res. 243:91–105; 1982.
28. Nomikos, G. G.; Spyraki, C.: Cocaine-induced place conditioning: Importance of route of administration and other procedural variables. Psychopharmacology (Berlin) 94:119–125; 1988.
29. Pulvirenti, L.; Swerdlow, N. R.; Koob, G. F.: Nucleus accumbens NMDA antagonist decreases locomotor activity produced by cocaine, heroin or accumbens dopamine, but not caffeine. Pharmacol. Biochem. Behav. 40:841–845; 1991.
30. Schechter, M. D.: Caffeine potentiation of amphetamine: Implication for hyperkinesis therapy. Pharmacol. Biochem. Behav. 6:359–361; 1977.
31. Schechter, M. D.; Calcagnetti, D. J.: Trends in place preference conditioning with a cross-indexed bibliography; 1957–1991. Neurosci. Biobehav. Rev. 17:21–41; 1993.
32. Snyder, S. H.; Katims, J. J.; Annau, A.; Bruns, R. F.; Daly, J. W.: Adenosine receptors in the central nervous system: Relationship to the central actions of methylxanthines. Life Sci. 28:2083–2097; 1981.
33. Snyder, S. H.; Katims, J. J.; Annau, Z.; Bruns, R. F.; Daly, J. W.: Adenosine receptors and behavioural actions of methylxanthines. Proc. Natl. Acad. Sci. USA 78:3260–3264; 1981.
34. Spyraki, C.; Fibiger, H. C.; Phillips, A. G.: Cocaine-induced place preference conditioning: Lack of effects of neuroleptics and 6-hydroxydopamine lesions. Brain Res. 253:195–203; 1982.
35. Spyraki, C.; Fibiger, H. C.; Phillips, A. G.: Dopaminergic substrates of amphetamine-induced place preference conditioning. Brain Res. 253:185–193; 1982.
36. Steigerwald, E. S.; Rusiniak, K. W.; Eckel, D. L.; O'Regan, M. H.: Aversive conditioning properties of caffeine in rats. Pharmacol. Biochem. Behav. 31:579–584; 1989.
37. Swerdlow, N. R.; Koob, G. F.: Separate neural substrates of the locomotor-activating properties of amphetamine, heroin, caffeine and corticotropin releasing factor (CRF) in the rat. Pharmacol. Biochem. Behav. 23:303–307; 1985.
38. Swerdlow, N. R.; Vaccarino, F. J.; Koob, G. F.: Effects of naloxone on heroin-, amphetamine- and caffeine-stimulated locomotor activity in the rat. Pharmacol. Biochem. Behav. 23:499–501; 1985.
39. Thithapandha, A.; Maling, H. M.; Gillette, J. R.: Effects of caffeine and theophylline on activity of rats in relation to brain xanthine concentrations. Proc. Exp. Biol. Med. 139:582–586; 1972.
40. Tuazon, D. B.; Suauki, T.; Misawa, M.; Watanabe, S.: Methylxanthines (caffeine and theophylline) blocked methamphetamine-induced conditioned place preference in mice but enhanced that induced by cocaine. Ann. NY Acad. Sci. 654:531–533; 1992.
41. White, B. C.; Keller, G. E.: Caffeine pretreatment: Enhancement and attenuation of d-amphetamine-induced activity. Pharmacol. Biochem. Behav. 20:383–386; 1984.
42. Wise, R. A.; Bozarth, M. A.: A psychomotor stimulant theory of addiction. Psychol. Rev. 94:469–492; 1987.