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# Continuous or Intermittent Cocaine Administration: Effects of Flupenthixol Treatment During Withdrawal

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KING, G. R., C. J. JOYNER AND E. H. ELLINWOOD, JR. *Continuous or intermittent cocaine administration: Effects of flupenthixol treatment during withdrawal.* PHARMACOL BIOCHEM BEHAV **49**(4) 883–889, 1994.—Research indicates that chrnoic daily cocaine injections produce sensitization to, while the chronic continuous infusion of cocaine produces tolerance to, its behavioral and neurochemical effects. The present experiments examined whether flupenthixol administration during withdrawal would attenuate/eliminate the behavioral effects produced by these administration regimens. The rats were pretreated for 14 days with either continuous or intermittent daily injections of cocaine, and were then withdrawn from the pretreatment regimen for 7 days. On days 1–5 of the withdrawal period, subjects received a daily 0.125–2.0 mg/kg IP injection of flupenthixol. Then on day 7 of withdrawal from the cocaine pretreatment, all rats were given a 15.0 mg/kg IP injection of cocaine. Their behavior was rated according to a modified version of the Ellinwood and Balster (6) scale for 60 min. The results indicated that flupenthixol treatment during withdrawal eliminated the tolerance normally associated with the continuous infusion of cocaine. However, this effect of flupenthixol was not dose dependent: the lowest dose had the same effect as the highest dose of flupenthixol. In the cocaine-injection subjects, flupenthixol had a slight but statistically significant reduction in the behavioral effects of cocaine. The same was true in the saline-control rats, except for the highest dose of flupenthixol, which had a significant enhancing effect on the behavioral response to cocaine. The present results suggest that the current procedures may represent an effective screening methodology for potential cocaine pharmacotherapies.

Cocaine withdrawal  Flupenthixol  Sensitization  Tolerance  Rats

ANIMAL models of drug abuse have been extensively researched over the past 20 years and include drug self-administration, drug discrimination, and conditioning procedures. They have all been used in both human and nonhuman subjects. Furthermore, these models have been extremely successful for the study of opiate abuse: they have generated effective therapeutic practices and screens for potential therapeutic drugs. However, the development of successful animal models and screening methodologies for cocaine abuse and withdrawal is still in a fledgling state. In the study of cocaine abuse there are several problems that were not as prominent as in opiate abuse. First, what is the nature of the withdrawal syndrome? Second, how do different patterns of cocaine use or abuse contribute to the withdrawal syndrome? Lastly, what are the critical symptoms that require treatment so that the individual will remain abstinent? These questions remain unanswered insofar as there is no clear clinical consensus regarding these issues.

An examination of the clinical literature indicates that compulsive cocaine abuse is characterized by a binge pattern of consumption. A binge is characterized by the readministration of the drug approximately every 30 min, depending on the route of administration. Cocaine binges last from hours to days. As the individual ends a binge, they will experience a withdrawal syndrome, which is characterized by three phases. The initial crash phase immediately follows the cessation of a binge, and is characterized by depression and agitation followed by intense hypersomnia. The next phase is the intermediate withdrawal phase, which occurs 5–12 days following a binge. This phase is characterized by symptoms that are the opposite of the effects of cocaine consumption: decreased mental and physical energy (anergia), limited interest in the

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environment, and anhedonia. During this withdrawal period, the individual is the prone to relapse, and likely to start another binge cycle. If the individual can remain abstinent for 4–6 weeks, the anhedonia and dysphoria attenuate but they may wax and wane over a 6- to 9-month period (5).

We have proposed elsewhere (12,15), that the binge pattern of use is modeled by the continuous infusion of cocaine. During a binge the cocaine plasma cocaine levels will fluctuate as a function of an oscillating pattern of self-administration. Nonetheless, the abuser is maintaining reasonably sustained plasma cocaine level over the entire binge period. The continuous infusion of cocaine produces sustained cocaine plasma levels for the entire treatment regimen. Second, binges also occur because of tolerance (5), and this dosing paradigm produces tolerance to the behavioral effects and some of the neurochemical effects of cocaine (9,12,13,16,23). Third, the anhedonia, anergia, and drug craving are thought to be the result of dopaminergic hypofunctioning (either DA depletion, autoreceptor supersensitivity, etc.). Brain slices obtained from rats exposed to the continuous infusion of cocaine exhibit decreased extracellular levels of DA when perfused with cocaine (9,15) or electrically stimulated (18). Thus, the continuous infusion of cocaine seems to produce behavioral and neurochemical effects that are consistent with the symptomatology reported by human cocaine abusers during withdrawal. This sensitization/tolerance model of compulsive cocaine abuse would be further validated if one could demonstrate that the effects of continuous or intermittent cocaine can be attenuated/eliminated by some treatment.

Treatment strategies for cocaine abuse have evaluated the efficacy of direct and indirect DA agonists, as well as DA antagonists [e.g., 5,8,11,19,25)]. We recently reported that administration of the indirect DA agonist, amantadine, on days 1–5 of the withdrawal period eliminated the tolerance associated with the continuous infusion of cocaine, and slightly suppressed the sensitization produced by daily cocaine injections (17). Another approach to the treatment of cocaine abuse involves the use of DA antagonists to block the effects of cocaine. One DA antagonist that has been examined is the neuroleptic flupenthixol. Indeed, one recent clinical report (11) indicated that low doses of the neuroleptic flupenthixol resulted in a significant increase in the number of crack abusers remaining in treatment. These authors concluded that flupenthixol may be a promising initial treatment for crack (cocaine) abuse. Furthermore, Mansbach et al. (21) have recently reported that, in rhesus monkeys, α-flupenthixol increased cocaine self-administration, suggesting a decreased reinforcing efficacy, and in squirrel monkeys, α-flupenthixol blocked the discriminative stimulus effects of cocaine. These results indicate that α-flupenthixol can block some of the acute effects of cocaine.

The present experiments examined whether the administration of flupenthixol during the withdrawal period would attenuate the behavioral deficits produced by the continuous administration of cocaine. In other words, would the administration of flupenthixol during withdrawal from either continuous or intermittent cocaine eliminate (or attenuate) the tolerance and sensitization typically found with these administration regimens. The rats were pretreated for 14 days with either continuous or intermittent daily injections of cocaine, and were then withdrawn from the pretreatment regimen for 7 days. On days 1–5 of withdrawal from the chronic cocaine pretreatment regimen, the rats received either 0.0–2.0 mg/kg IP injections of flupenthixol. On day 7 of withdrawal all rats were given a 15.0 mg/kg IP injection of cocaine, and their behavior rated according to a modified version of the Ellinwood and Balster (6) scale for 60 min.

## GENERAL METHOD

### *Animals*

Male Sprague-Dawley rats, weighing 100–125 g (Charles River Laboratories), were acclimated to the vivarium on a 12 L : 12D cycle (lights on between 0700–1900 h) for 1 week before treatment. They were housed in pairs in plastic cages with continuous access to food and water.

### *Drugs*

Cocaine HCl (received from NIDA) was dissolved in 0.9% sterile saline. Flupenthixol (RBI Inc.) was dissolved in distilled water. All doses are calculated as the base, and injection volume was based on the body weight.

### *Minipump Preparation*

Alzet Osmotic pumps (model 2ML2) from Alza Corporation (Palo Alto, CA) were filled with either 2 ml of 100 mg/ml cocaine HCl. The infusion rate was 5 μl/h, resulting in an overall average dose of 40 mg/kg/day for the cocaine pumps. The pump was primed by warming in a beaker of saline; this beaker was placed in a 37° waterbath for 4 h before surgical implantation. The minipumps have been modified by adding a microdialysis fiber to the output portal to increase the surface area over which cocaine is distributed. This modification allows for the continuous infusion of high doses of cocaine without the development of necrotic skin lesions (10).

### *Surgery*

The animals were shaved and injected locally with (0.2 cc) lidocaine (Abbott, North Chicago, IL) at the dorsal midline incision site. The animals were then anesthetized by inhalation with methoxyflurane (Metofane). A 2 cm vertical incision was made with scissors and a large SC pocket was formed with the scissors. The minipump was inserted into this pocket with the delivery portal toward the head. The opening was closed with metal surgical autoclips. On day 14, the pumps were surgically removed using the same procedure and the residual amount of cocaine measured. The amount was consistently less than 15% of the original volume, indicating that the rats approximately received the programmed daily dose.

### *Pretreatment*

Cocaine pretreatment was for a 14-day period. Table 1 presents the series of events to which the subjects were exposed in the present experiment. On day 1 of treatment animals were either: a) implanted with 2ML2 Alzet minipumps continuously infusing cocaine at a rate of 40 mg/kg/day (continuous infusion group), b) injected SC once daily with 40 mg/kg cocaine HCl (injection group), or c) injected SC with 0.9% saline (saline control group) once daily. The present experiment utilized SC cocaine injections instead of IP cocaine injections during the pretreatment phase of the present experiments. The experiment attempted to examine the effects of intermittent vs. continuous cocaine while controlling for confounding factors. Use of the IP route would have introduced several confounding factors (e.g., very different kinetic profiles, first-pass liver metabolism, possible enzyme induction, etc.), which would have circumscribed any conclusions that we could have made. Hence, the administration routes were selected to

TABLE 1

SEQUENCE OF EVENTS FOR ALL SUBJECTS IN THE PRESENT EXPERIMENT

| Pretreatment Group | Pretreatment: Days 1-14 | Withdrawal: Days 1-5 | Withdrawal: Day 7 |
|---|---|---|---|
| Saline control | Daily saline injections | Daily IP injections of 0.125-2.0 mg/kg flupenthixol | A single 15.0 mg/kg IP cocaine challenge |
| Cocaine injection | Daily 40 mg/kg SC cocaine injections | Daily IP injections of 0.125-2.0 mg/kg flupenthixol | A single 15.0 mg/kg IP cocaine challenge |
| Cocaine pump | Osmotic minipump infusing 40 mg/kg/day of cocaine | Daily IP injections of 0.125-2.0 mg/kg flupenthixol | A single 15.0 mg/kg IP cocaine challenge |

equate, as much as possible, the drug histories of the subjects. On days 1-5 of withdrawal from the pretreatment regimen, subjects received daily IP injections of 0.125, 0.25, 0.5, or 2.0 mg/kg IP injection of flupenthixol.

The data obtained from the present experiment will be compared to the data obtained from two previous experiments (13,16). The rats in those two previous experiments were exposed to the identical 14-day pretreatment regimen as the rats in the current experiment. On day 7 of withdrawal, those rats were given a 15 mg/kg cocaine injection. Thus, the rats from those experiments were exposed to exactly the same sequence of events as the rats in the present experiment. The only difference between the previous and present experiments was that the previous rats had no intervening flupenthixol treatments. The data from these subjects represent the control conditions for each cocaine pretreatment group. In other words, the subjects in these experiments are functionally equivalent to subjects receiveing 0.0 mg/kg flupenthixol during days 1-5 of withdrawal.

*Behavioral Testing*

On day 7 following pretreatment the animals were acclimated to the test room in their home cage for 30 min under normal light conditions. The test cages were standard, clear plastic laboratory animal housing cages, 28 × 18 × 12 cm, with another cage taped, upside down, in place on top. The top cage had five air holes drilled uniformly on either side. Six of these test cages were placed in a row 12 inches apart. A version of the Ellinwood and Balster Rating Scale (6) was used (Table 2). This scale has been used in several previous experiments (13,14,16,17). A rating was given to each of the animals at 5 min preinjection, and at 5-min intervals thereafter, for a total of 60 min. The observation period was for 20 s with 10 s between cages.

For the test session, each rat received a 15.0 mg/kg IP cocaine injection 5 min after receiving a baseline, no-drug behavior rating. In the present experiment, the subject types (e.g., injection, pump, saline) were randomized according to a Latin square design. The significance level was set at $p < 0.05$ for all comparisons. There were 10 rats per condition for the present experiment.

## RESULTS

Figure 1 presents the mean behavior rating for subjects from King et al. (13,16), separately for each cocaine pretreatment group. These two experiments were conducted approximately 18 months apart, and the rats were rated by the same behavior rater who was blind to the pretreatment conditions and the aims of those experiment. The same rater was used in the present experiments. Visual inspection of the figures indicates that there are no substantial differences to 15.0 mg/kg cocaine challenges between the two experiments. Mann-Whitney *U*-tests, conducted separately for each pretreatment group, comparing the two experiments that the ratings from these two experiments were not significantly different. This pattern of results indicate that the pretreatment regimen re-

TABLE 2

MODIFIED ELLINWOOD AND BALSTER (1974) RATING SCALE

| Score | | Definition |
|---|---|---|
| 1 | Asleep | Lying down, eyes closed |
| 2 | Almost asleep | Relaxed muscles, eyes partially shut |
| 3 | Dystonia | Abnormal posture, tense muscles |
| 4 | Inactive | Lying down, eyes open, infrequent sniffing |
| 5 | Inplace oral behavior | Vacuous oral movements, jaw tremor, yawning |
| 6 | Grooming | Grooming of face, body, or groin |
| 7 | Normal active movement | Investigation or sniffing of cage, rearing |
| 8 | Hyperactive | Running movement characterized by rapid changes in position (jerky) |
| 9 | Slow patterned movement | Repetitive exploration of the cage at normal levels of activity |
| 10 | Fast patterned movement | Repetitive exploration of the cage with rapid, intense, stereotyped activities |
| 11 | Stereotypy | The types of stereotypies are noted |
| 12 | Hyperreactive | The following types of behavior are described and/or counted: jerky hyperactive movements, jumping (popcorn) like movements, seizures, disjunctive movements, obstinate regression (backing up) |

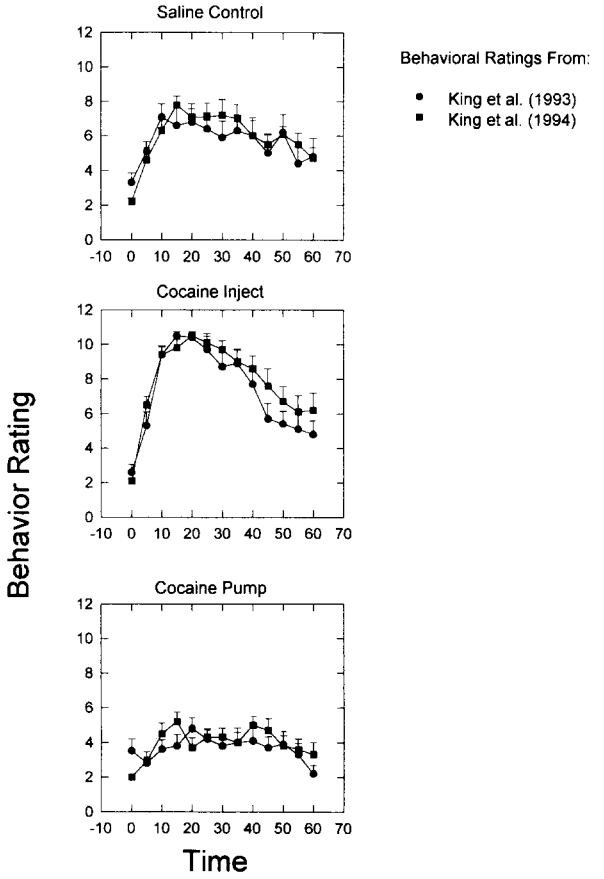


FIG. 1. Figure 1 presents the mean behavior ratings, separately for the two previous experiments. The bars represent one standard error. The open circles (○) represent the rats from King et al. (13). The solid circles (●) represent the rats from King et al. (16).

sults in stable behavioral responses to cocaine that are not highly dependent on such factors as seasonal variations, differences in rats from the supplier, etc. In other words, the effects (and magnitude of the effects) of continuous or intermittent cocaine are robust. Therefore, these data were averaged together for comparison with the results from the present experiment. These averaged data for the 15.0 mg/kg cocaine challenge in the absence of flupenthixol treatment during withdrawal are presented below as the 0.0 mg/kg flupenthixol data.

Figure 2 presents the mean behavior rating for each pretreatment group, separately for each flupenthixol pretreatment. Panel A presents the behavior ratings of subjects receiving 0.0 mg/kg flupenthixol during the withdrawal period [i.e., the averaged data from (13) and (16)]. Mann-Whitney *U*-tests comparing the saline control and cocaine injection groups indicated that the behavior ratings for the saline control subjects were significantly less than the behavior ratings of the cocaine injection subjects at 10-40 min. Mann-Whitney *U*-tests comparing the saline control and cocaine pump groups indicated that the behavior ratings for the cocaine pump subjects were significantly less than the behavior ratings of the saline subjects at 5-40 and 50-60 min. Mann-Whitney *U*-tests comparing the cocaine injection and cocaine pump groups indicated that the behavior ratings for the cocaine pump subjects were significantly less than the behavior ratings of the cocaine injection subjects at 5-60 min.

Panel B presents the behavior ratings for subjects receiving 0.125 mg/kg flupenthixol during the withdrawal period. Mann-Whitney *U*-tests comparing the saline control and cocaine injection groups indicated that the behavior ratings for the saline control subjects were significantly less than the behavior ratings of the cocaine injection subjects at 10-45 and 55 min. Mann-Whitney *U*-tests comparing the saline control and cocaine pump groups were not significantly different except at 60 min. Mann-Whitney *U*-tests comparing the cocaine injection and cocaine pump groups indicated that the behavior ratings for the cocaine pump subjects were significantly less than the behavior ratings of the cocaine injection subjects at 10-45 and 55-60 min.

Panel C presents the behavior ratings for subjects receiving 0.25 mg/kg flupenthixol during the withdrawal period. Mann-Whitney *U*-tests comparing the saline control and cocaine injection groups indicated that the behavior ratings for the saline control subjects were significantly less than the behavior ratings of the cocaine injection subjects at 15, 20, 30, 35, and 55 min. Mann-Whitney *U*-tests comparing the saline

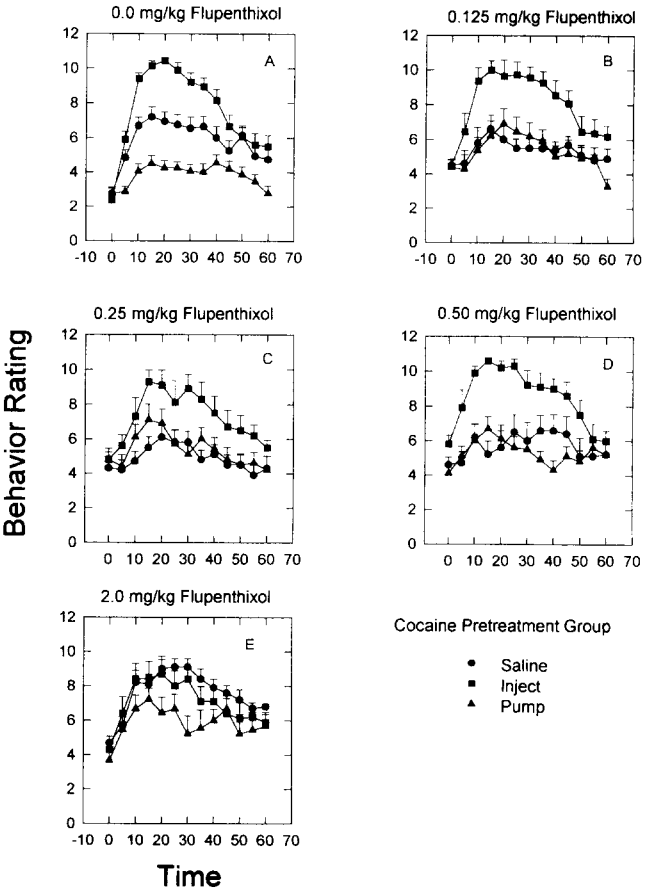


FIG. 2. Figure 2 presents the mean behavior rating for each group, separately for each flupenthixol treatment condition. The bars represent one standard error. The open circles (○) represent the saline pretreatment rats. The solid circles (●) represent the cocaine injection pretreatment rats. The open triangles (△) represent the continuous infusion pretreatment rats.

control and cocaine pump groups did not indicate any significant differences at any time point. Mann-Whitney *U*-tests comparing the cocaine injection and cocaine pump groups indicated that the behavior ratings for the cocaine pump subjects were significantly less than the behavior ratings of the cocaine injection subjects at 15, 20, 30, and 35 min.

Panel D presents the behavior ratings for subjects receiving 0.5 mg/kg flupenthixol during the withdrawal period. Mann-Whitney *U*-tests comparing the saline control and cocaine injection groups indicated that the behavior ratings for the saline control subjects were significantly less than the behavior ratings of the cocaine injection subjects at 5-40 min. Mann-Whitney *U*-tests comparing the saline control and cocaine pump groups were not significant at any time point. Mann-Whitney *U*-tests comparing the cocaine injection and cocaine pump groups indicated that the behavior ratings for the cocaine pump subjects were significantly less than the behavior ratings of the cocaine injection subjects at 0-45 min.

Panel E presents the behavior ratings for subjects receiving 2.0 mg/kg flupenthixol during the withdrawal period. Mann-Whitney *U*-tests comparing the saline control and cocaine injection groups did not indicate any significant differences at any time point. Mann-Whitney *U*-tests comparing the saline control and cocaine pump groups indicated that the behavior ratings for the cocaine pump subjects were significantly less than the behavior ratings of the saline subjects at 20-30 min. Mann-Whitney *U*-tests comparing the cocaine injection and cocaine pump groups indicated that the behavior ratings for the cocaine pump subjects were significantly less than the behavior ratings of the cocaine injection subjects at 20 and 30 min.

Because of the differential effects of cocaine pretreatment on the behavioral response to a 15.0 mg/kg cocaine injection (i.e., tolerance and sensitization), changes in the response to cocaine as a function of flupenthixol pretreatment were examined by determining the differences between no flupenthixol pretreatment [i.e., the averaged data from the experiments conducted in (13) and (16)], and the responses to 15.0 mg/kg cocaine following flupenthixol, separately for each pretreatment group. Figure 3 presents the difference scores between no flupenthixol pretreatment plus 15.0 mg/kg cocaine [i.e., the averaged data from (13) and (16)], and the data from the present experiment, separately for each cocaine pretreatment group, and flupenthixol treatment level. In this figure, the larger the difference score, the greater the effect of the particular flupenthixol pretreatment dose on cocaine-induced behavior. Positive values indicate an enhancing effect of chronic flupenthixol on cocaine-induced hyperactivity, while negative values indicate a suppressive effect of chronic flupenthixol on cocaine-induced hyperactivity.

Panel A presents the differences in behavior ratings for the 0.125 mg/kg flupenthixol pretreatment subjects, separately for each cocaine pretreatment group. Mann-Whitney *U*-tests comparing the saline control and cocaine injection groups indicated that the difference scores for the saline control subjects were significantly less than the difference scores of the cocaine injection subjects at 0, 30, 35, and 50 min. Mann-Whitney *U*-tests comparing the saline control and cocaine pump groups indicated that the difference scores for the cocaine pump subjects were significantly greater than the difference scores for the saline control rats at 20-35 and 50 min. Mann-Whitney *U*-tests comparing the cocaine injection and cocaine pump groups indicated that the difference scores for the cocaine pump subjects were significantly higher than the difference scores of the cocaine injection subjects at 20 min. The difference scores for the cocaine pump subjects were significantly less than the difference scores for the cocaine injection subjects at 0 min.

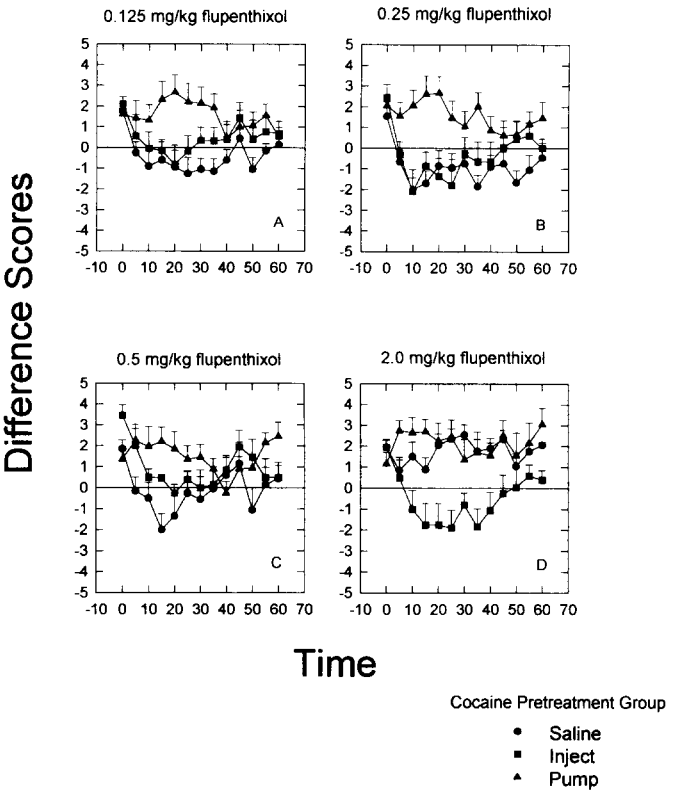


FIG. 3. Figure 3 presents the difference scores between the 0.0 mg/kg flupenthixol treatment condition plus 15.0 mg/kg cocaine and the different combinations of flupenthixol treatments and 15.0 mg/kg cocaine injection for each cocaine pretreatment group, separately for each combination of flupenthixol treatments and 15.0 mg/kg cocaine injection. The bars represent one standard error. The open circles (○) represent the saline pretreatment rats. The solid circles (●) represent the cocaine injection pretreatment rats. The open triangles (△) represent the continuous infusion pretreatment rats.

Panel B presents the differences in behavior ratings for the 0.25 mg/kg flupenthixol pretreatment subjects, separately for each cocaine pretreatment group. Mann-Whitney *U*-tests comparing the saline control and cocaine injection groups indicated that the difference scores for the saline control subjects were significantly less than the difference scores of the cocaine injection subjects at 15 and 50 min. Mann-Whitney *U*-tests comparing the saline control and cocaine pump groups indicated that the difference scores for the cocaine pump subjects were significantly greater than the difference scores for the saline control rats at 5-20, 30-35, and 50 min. Mann-Whitney *U*-tests comparing the cocaine injection and cocaine pump groups indicated that the difference scores for the cocaine pump subjects were significantly higher than the difference scores of the cocaine injection subjects at 5-20 and 35 min.

Panel C presents the differences in behavior ratings for the 0.5 mg/kg flupenthixol pretreatment subjects, separately for each cocaine pretreatment group. Mann-Whitney *U*-tests comparing the saline control and cocaine injection groups indicated that the behavior ratings for the saline control subjects were significantly less than the behavior ratings of the cocaine

injection subjects at 0, 10, 15, and 50 min. Mann-Whitney *U*-tests comparing the saline control and cocaine pump groups indicated that the difference scores for the cocaine pump subjects were significantly greater than the difference scores for the saline control rats at 5, 15, 55 min. Mann-Whitney *U*-tests comparing the cocaine injection and cocaine pump groups indicated that the difference scores for the cocaine pump subjects were significantly higher than the difference scores of the cocaine injection subjects at 15 min. The difference scores for the cocaine pump subjects were significantly less than the difference scores for the cocaine injection subjects at 0 min.

Panel D presents the differences in behavior ratings for the 2.0 mg/kg flupenthixol pretreatment subjects, separately for each cocaine pretreatment group. Mann-Whitney *U*-tests comparing the saline control and cocaine injection groups indicated that the behavior ratings for the saline control subjects were significantly higher than the difference scores for the cocaine injection subjects at 20–45 and 55–60 min. Mann-Whitney *U*-tests comparing the saline control and cocaine pump groups indicated that the difference scores for the cocaine pump subjects were significantly greater than the difference scores for the saline control rats at 5 min. Mann-Whitney *U*-tests comparing the cocaine injection and cocaine pump groups indicated that the difference scores for the cocaine pump subjects were significantly higher than the difference scores of the cocaine injection subjects at 5–25, 40, and 60 min. The difference scores for the cocaine pump subjects were significantly less than the difference scores for the cocaine injection subjects at 0 min.

## DISCUSSION

The present results extend previous findings that indicate that the effects of chronic cocaine depend on the route and temporal pattern of administration (1,7,9,12–16,20,22–24). The present experiment examined the ability of flupenthixol, a putative pharmacotherapy for cocaine abuse, to eliminate or attenuate the residual behavioral effects of the continuous infusion or daily injection of cocaine. Our results indicate that flupenthixol treatment during the first 5 days of the withdrawal period does, indeed, eliminate the tolerance, and very slightly reduce the sensitization associated with the two administration regimens.

The symptoms of cocaine withdrawal (anergia, anhedonia, and possibly drug craving) are thought to arise from dopaminergic hypofunctioning (5). Therefore, it has been proposed that one potential line of pharmacotherapies for cocaine abuse might involve DA agonists/antagonists (5,8,19,25), where the antagonists are thought to act by blocking the effects of cocaine. The present results indicate that DA antagonist treatment can eliminate/attenuate the behavioral effects associated with continuous and intermittent cocaine administration. Furthermore, this effect for the continuous infusion rats was not dose dependent: near maximal restoration of normal behavioral responsivity (i.e., elimination of the tolerance associated with the continuous infusion of cocaine) to a 15.0 mg/kg cocaine challenge was present at the lowest dose tested. This low dose effect is consistent with the report of Khalsa et al. (11), who found that the lowest doses of flupenthixol resulted in significant increases in the retention rate in a cocaine abuse treatment program.

Screening models for abuse liability have been extensively researched over the past 20 years and these models have been extremely successful in determining the abuse liability of drugs, as well as being very useful tools for examining the neurobiology of reinforcement processes. However, their use as screens for potential pharmacotherapies is conceptually constrained. One of the most common screens for potential drug treatments of cocaine abuse is to examine the ability of some drug to suppress cocaine self-administration. There are some problems with this approach. First, decreases in the rate of drug self-administration are assumed to reflect increases in the reinforcing efficacy of the drug, similar to what occurs when the unit dose of cocaine is increased (2). However, not all decreases in responding for drug self-administration can easily be interpreted as reflecting increases in the unit dose of cocaine. For example, Carroll et al. (3) have demonstrated that the presence of a second response, whose performance delivers a glucose/saccharin solution, decreases cocaine self-administration. It is unlikely that the presence of the second response increases the reinforcing efficacy of cocaine, which then reduces cocaine self-administration. Hence, the self-administration paradigm, conducted in this manner, has no a priori guide for the interpretation of changes in drug self-administration. In other words, not all decreases in drug self-administration reflect the same underlying processes, and there is no a priori way in which to determine what changes in drug self-administration mean, unless other secondary dependent variables are measured (e.g., in vivo microdialysis of extracellular DA levels).

Secondly, if the hypothesis that decreases in self-administration reflect increases in the unit dose, then drugs that decrease drug self-administration are actually making the abuse pattern more entrenched, and are, thus, contributing to cocaine abuse. Such an approach to the pharmacotherapeutic treatment of cocaine abuse is difficult to interpret because, although the rate of drug self-administration has been decreased, the strength of the abuse pattern is actually increased because the value of the reinforcer has increased. Given these considerations, additional new screens for potential pharmacotherapies are needed.

The results of our experiment would indicate that the current methods represent one potential screening methodology for drugs to treat the early initial withdrawal syndrome associated with compulsive cocaine abuse. The procedure essentially involved the examination of the ability of a drug, administered during the withdrawal period, to eliminate the residual behavioral and neurochemical consequences of our cocaine pretreatment regimens. The current methods produced consistent results in a reasonably short period of time and a minimum number of subjects. Further experiments should examine the generality of the present results as a screening procedure for pharmacotherapies for cocaine abuse. However, it must be kept in mind that the present methodology may not be appropriate for other phases of the withdrawal syndrome.

In summary, the results indicate that in the rats pretreated with the continuous infusion of cocaine, flupenthixol treatment during withdrawal eliminated the tolerance normally associated with this route of administration. In contrast, in both the saline control and cocaine injection subjects, flupenthixol treatment during withdrawal generally resulted in a slight, but statistically significant reduction in the behavioral effects of cocaine. Secondly, the present experimental procedures may represent an effective screening methodology for potential cocaine pharmacotherapies.

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## REFERENCES


1. Akimoto, K.; Hammamura, T.; Otsuki, S. Subchronic cocaine treatment enhances cocaine-induced dopamine efflux studied by in vivo intracerebral dialysis. Brain Res. 490:339–344; 1989.
2. Caine, S. B.; Koob, G. F. Modulation of cocaine self-administration in the rat through D-3 dopamine receptors. Science 260: 1814–1816; 1993.
3. Carroll, M. E.; Lac, S. T.; Nygaard, S. L. A concurretnly available nondrug reinforcer prevents the acquisiton or decreases the maintenance of cocaine-reinforced behavior. Psychopharmacology (Berlin) 97:23–29; 1989.
5. Dackis, C. A.; Gold, M. S. Pharmacological approaches to cocaine addiction. J. Subst. Abuse Treat. 2:139–145; 1985.
6. Ellinwood, E. H.; Balster, R. I. Rating the behavioral effects of amphetamine. Eur. J. Pharmacol. 28:35–41; 1974.
7. Falk, J. L.; Fang, M.; Lau C. E. Chronic oral cocaine self-administration: Pharmacokinetics and effects on spontaneous and discriminative motor functions. J. Pharmacol. Exp. Ther. 257:457–465; 1991.
8. Giannini, A. J.; Billett, W. Bromocriptine-desipramine protocol in treatment of cocaine addiction. J. Clin. Pharmacol. 27:549–554; 1987.
9. Izenwasser, S.; Cox, B. M. Inhibition of dopamine uptake by cocaine and nicotine: Tolerance to chronic treatments. Brain Res. 573:119–125; 1992.
10. Joyner, C.; King, G.; Lee, T. H.; Ellinwood, E. H., Jr. A technique for the continuous infusion of high doses of cocaine by osmotic minipump. Pharmacol. Biochem. Behav. 44:971–973; 1993.
11. Khalsa, M. E.; Brown, J.; Jatlow, P.; Gawin, F. H. Flupenthixol and desipramine markedly increase engagement in crack abuse treatment. Abstract for the annual CPDD meeting; 1993.
12. King, G. R.; Joyner, C.; Lee, T.; Kuhn, C.; Ellinwood, E. H., Jr. Intermittent and continuous cocaine administration: Residual behavioral states during withdrawal. Pharmacol. Biochem. Behav. 43:243–248; 1992.
13. King, G. R.; Joyner, C.; Lee, T. H.; Ellinwood, E. H., Jr. Withdrawal from continuous or intermittent cocaine: Effects of NAN-190 on cocaine-induced locomotion. Pharmacol. Biochem. Behav. 44:253–262; 1993.
14. King, G. R.; Joyner, C.; Ellinwood, E. H., Jr. Withdrawal from continuous or intermittent cocaine: Behavioral responsivity to 5-$HT_1$ agonists. Pharmacol. Biochem. Behav. 45:577–587; 1993.
15. King, G. R.; Kuhn, C.; Ellinwood, E. H., Jr. Dopamine efflux during withdrawal from continuous or intermittent cocaine. Psychopharmacology (Berlin) 111:179–184; 1993.
16. King, G. R.; Joyner, C.; Ellinwood, E. H., Jr. 5-$HT_3$ receptor modulation of behavior during withdrawal from continuous or intermittent cocaine. Pharmacol. Biochem. Behav. 47:339–407; 1994.
17. King, G. R.; Joyner, C.; Ellinwood, E. H., Jr. Continuous or intermittent cocaine administration: Effects of amantadine treatment during withdrawal. Pharmacol. Biochem. Behav. 47:451–457; 1994.
17. King, G. R.; Ellinwood, E. H., Jr.; Silvia, C.; Joyner, C. M.; Xue, Z.; Caron, M.; Lee, T. H. Withdrawal from continuous or intermittent cocaine: Changes in dopamine receptor function. J. Pharmacol. Exp. Ther. 269:743–749; 1994.
19. Kosten, T. R.; Schumann, B.; Wright, D. Bromocriptine treatment of cocaine abuse in patients maintained on methadone. Am. J. Psychiatry 145:381–382; 1988.
20. Lau, C. E.; Imam, A.; Fang, M.; Falk, J. L. Acute effects of cocaine on spontaneous and discriminative motor functions: Relation to route of administration and pharmacokinetics. J. Pharmacol. Exp. Ther. 257:444–456; 1991.
21. Mansbach, R. S.; Saeed, A. J.; Balster, R. L. Antagonism of cocaine's reinforcing and discriminative effects by $\alpha$-flupenthixol. Exp. Clin. Psychopharmacol. 2:3–12; 1994.
22. Post, R. M.; Contel, N. R. Human and animal studies of cocaine: Implications for development of behavioral pathology. In: Creese, I., ed. Stimulants: Neurochemical, behavioral, and clinical perspectives. New York: Raven Press; 1983:169–203.
23. Reith, M. E. A.; Benuck, M.; Lajtha, A. Cocaine disposition in the brain after continuous or intermittent treatment and locomotor stimulation in mice. J. Pharmacol. Exp. Ther. 243:281–287; 1987.
24. Stripling, J. S.; Ellinwood, E. H., Jr. Cocaine: Physiological and behavioral effects of acute and chronic administration. In: Mule, S. J., ed. Cocaine: Chemical, biological, clinical, social and treatment aspects. Cleveland: CRC Press; 1976:167–185.
25. Tennant, F. S., Jr., Sagherian, A. A. Double-blind comparison of amantadine and bromocriptine for ambulatory withdrawal from cocaine dependence. Arch. Intern. Med. 147:109–112; 1987.