Pergamon

Pharmacology Biochemistry and Behavior, Vol. 47, No. 3, pp. 451-457, 1994

0091-3057/94 $6.00 + .00

Continuous or Intermittent Cocaine Administration: Effects of Amantadine Treatment During Withdrawal

G. R. KING,[1] C. JOYNER AND E. H. ELLINWOOD, JR.

Department of Psychiatry, Duke University Medical Center, Durham, NC 27710

Received 11 March 1993

KING, G. R., C. JOYNER AND E. H. ELLINWOOD, JR. *Continuous or intermittent cocaine administration: Effects of amantadine treatment during withdrawal.* PHARMACOL BIOCHEM BEHAV **47**(3) 451-457, 1994.--Research indicates that daily cocaine injections produce sensitization to, while the continuous infusion of cocaine produces tolerance to, its behavioral and neurochemical effects. The effects of the continuous infusion of cocaine are consistent with the withdrawal syndrome reported by human cocaine abusers. The present experiment examined whether amantadine administrations during withdrawal from continuous or intermittent cocaine attenuate and/or 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The rats were pretreated for 14 days with either continuous or intermittent daily injections of cocaine, and were then withdrawn from the pretreatment regimen for 7 days.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, half the subjects received a 5.0 mg/kg IP injection of amantadine, and the other half received a 20.0 mg/kg IP injection of amantadine. 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 the modified Ellinwood and Balster (6) scale for 60 min. The results indicated that amantadine treatment during withdrawal eliminated the tolerance normally associated with the continuous infusion of cocaine. In contrast, in both the saline control and daily injection subjects amantadine treatment during withdrawal resulted in a slight, but statistically significant, reduction in the behavioral effects of cocaine. The present results therefore indicate that low doses of amantadine should be considered as a potential pharmacotherapy for the early stages of cocaine withdrawal. Furthermore, the present experimental procedures may represent an effective screening methodology for potential cocaine pharmacotherapies.

Cocaine withdrawal Amantadine treatment 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

[1] Requests for reprints should be addressed to G. R. King, Ph.D., Box 3870, Duke University Medical Center, Durham, NC 27710.

environment, and anhedonia. During this withdrawal period, the individual is 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 (11,14) that the binge pattern of use is modeled by the continuous infusion of cocaine. During a binge, the 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 and some of the neurochemcial effects of cocaine (9,11,12,15,20). 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 (14). 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.

Amantadine is a drug that has been commonly used to treat Parkinson's disease. Amantadine's mode of action is generally attributed to its ability to augment the release of neuronal dopamine, and to delay the normal reuptake of dopamine from the synaptic cleft (4). Amantadine would seem to be an excellent candidate for use in the treatment of cocaine abuse because its dopaminergic activity would mimic some of the effects of cocaine. Furthermore, amantadine seems to have a low abuse liability because it is not self-administered by baboons (21). It has been proposed that drug craving and/or anhedonia and anergia are due to dopaminergic hypofunctioning. Hence, amantadine has been tried as a pharmacotherapy for cocaine abuse. Some reports have indeed indicated that amantadine may be an effective anticraving agent (5,24).

The present experiment examined whether the administration of amantadine during the withdrawal period would attenuate the behavioral deficits produced by the continuous administration of cocaine. In other words, would the administration of amantadine 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, the rats received either a 5.0 or a 20.0 mg/kg IP injection of amantadine. On day 7 of withdrawal, all rats were given a 15.0 mg/kg IP injection of cocaine, and their behavior was rated according to the Ellinwood and Balster (6) scale for 60 min.

METHOD

Animals

Male Sprague-Dawley rats, weighing 100 to 125 g (Charles River Laboratories), were acclimated to the vivarium on a 12 L : 12 D cycle (light between 0700 and 1900) 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. Amantadine HCl (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 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°C waterbath for 4 h before surgical implantation. The minipumps were 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

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 amantadine injections (5 or 20 mg/kg)	A single 15.0 mg/kg IP cocaine challenge
Cocaine injection	Daily 40 mg/kg SC cocaine injections	Daily IP amantadine injections (5 or 20 mg/kg)	A single 15.0 mg/kg IP cocaine challenge
Cocaine pump	Osmotic minipump infusing 40 mg/kg/day of cocaine	Daily IP amantadine injections (5 or 20 mg/kg)	A single 15.0 mg/kg IP cocaine challenge

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 one 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 equate, as much as possible, the drug histories of the subjects. On days 1-5 of withdrawal from the pretreatment regimen, all subjects received daily IP injections of amantadine. Half of the subjects in each pretreatment group received a 5 mg/kg amantadine injection and the remaining subjects received a 20 mg/kg amantadine injection.

The data obtained from the present experiment will be compared to the data obtained from two previous experiments (12,15). 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 amantadine treatments.

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 in. apart. A modified version of the Ellinwood and Balster Rating Scale (6) was used (Table 2). 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. (12) and King et al. (15), 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 the experiments. 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 indicated that the ratings from these two experiments were not significantly different. This pattern of results indicates that the pretreatment regimen results in stable behavioral responses to

TABLE 2

MODIFIED ELLINWOOD AND BALSTER (1974) RATING SCALE USED IN ALL EXPERIMENTS

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)

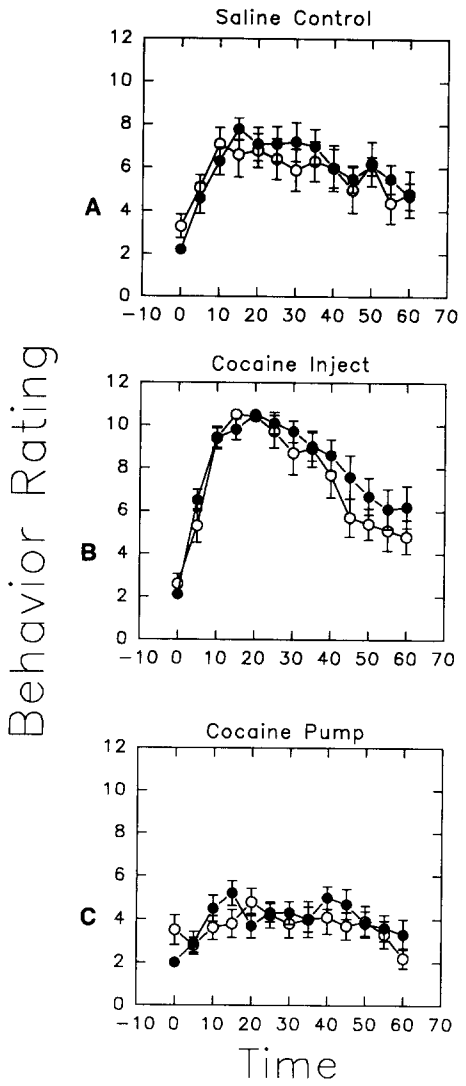

FIG. 1. The mean behavior ratings, separately for the two previous experiments. The bars represent 1 SE. The open circles (○) represent the rats from King et al. (12). The solid circles (●) represent the rats from King et al. (15).

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 amantadine treatment during withdrawal are presented below.

Figure 2 presents the mean behavior rating for each pretreatment group, separately for each amantadine pretreatment. Panel A presents the behavior ratings of subjects receiving 0.0 mg/kg amantadine during the withdrawal period [i.e., the averaged data from (12) and (15)]. 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 5.0 mg/kg amantadine 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 15–25 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 *higher* than the behavior ratings of the saline subjects at 10, 20–30, and 45 min.

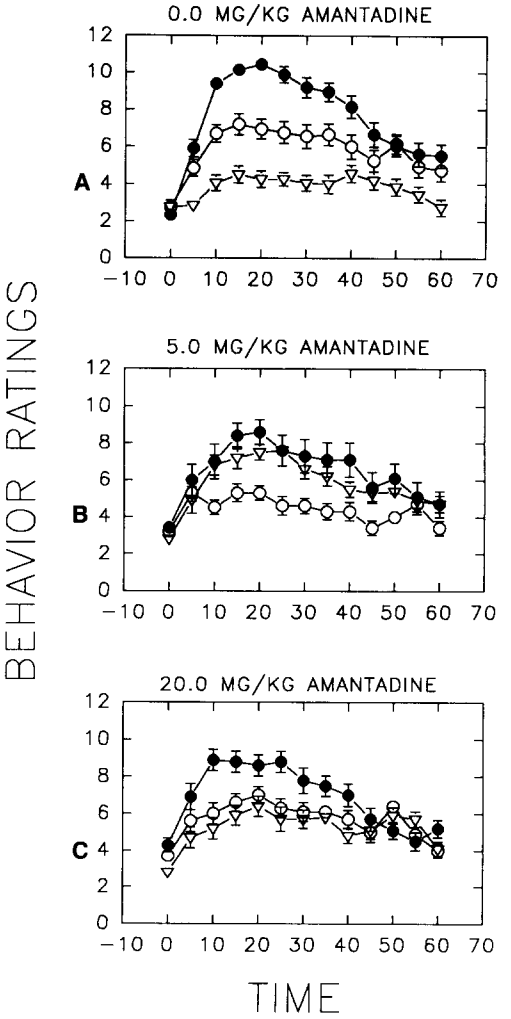

FIG. 2. The mean behavior rating for each amantadine treatment condition, separately for each amantadine dose during withdrawal. The bars represent 1 SE. The open circles (○) represent the saline control subjects. The solid circles (●) represent the cocaine injection subjects. The open triangles (△) represent the cocaine pump subjects.

Mann-Whitney *U*-tests comparing the cocaine injection and cocaine pump groups indicated that the behavior ratings for the cocaine pump and the cocaine injection are not significantly different at any time point.

Panel C presents the behavior ratings for subjects receiving 20.0 mg/kg amantadine 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, 15, and 25 min. Mann-Whitney *U*-tests comparing the saline control and cocaine pump groups indicated that the behavior ratings for the cocaine pump and the saline subjects were not significantly different 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, 10–25, and 40 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 amantadine pretreatment were examined by determining the differences between no amantadine pretreatment and the responses to 15.0 mg/kg cocaine following amantadine, separately for each pretreatment group. Figure 3 presents the difference scores between no amantadine pretreatment plus 15.0 mg/kg cocaine [i.e., the averaged data from (12) and (15)] and the data from the present experiment, separately for each cocaine pretreatment group, and amantadine treatment level. In this figure, the larger the difference score, the greater the effect of the particular amantadine pretreatment dose on cocaine-induced behavior. Positive values indicate an *enhancing* effect of chronic amantadine on cocaine-induced hyperactivity, while negative values indicate a *suppressive* effect of chronic amantadine on cocaine-induced hyperactivity.

Panel A presents the differences in behavior ratings for the 5.0 mg/kg amantadine 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 behavior ratings of the cocaine injection subjects at 0 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 10–50, and 60 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 10–35, 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.

Panel B presents the differences in behavior ratings for the 20.0 mg/kg amantadine 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 min, and significantly higher than the difference scores for the cocaine injection subjects at 20 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 35, and 50–60 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, 20, 30, 35, 50, and 55 min. The difference scores for the cocaine pump subjects were significantly less than the difference scores for the cocaine injection subjects at 0 min.

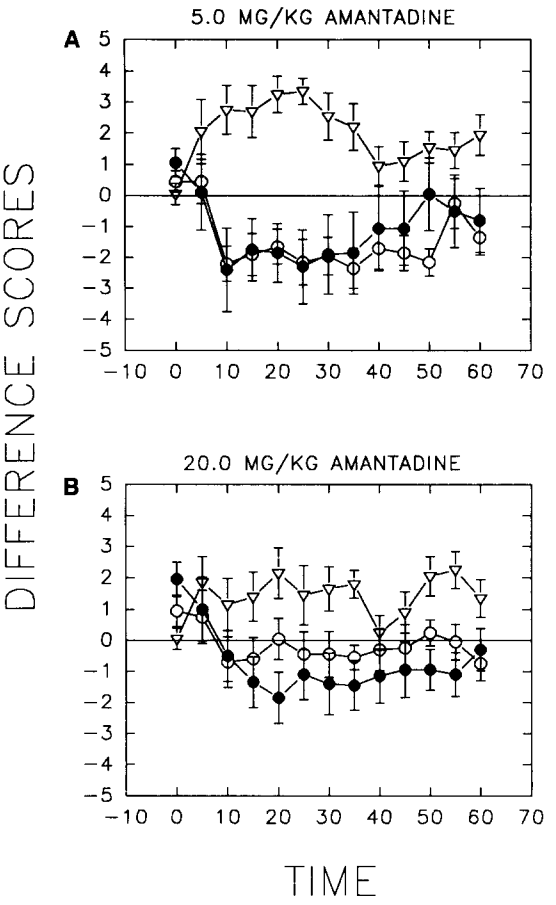

FIG. 3. The difference scores between the 0.0 mg/kg amantadine treatment condition plus 15.0 mg/kg cocaine and the different combinations of amantadine treatments and 15.0 mg/kg cocaine injection for each cocaine pretreatment group, separately for each combination of amantadine treatments and 15.0 mg/kg cocaine injection. The bars represent 1 SE. 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.

DISCUSSION

The present results extend previous findings, which indicate that the effects of chronic cocaine depend on the route and temporal pattern of administration (1,7,9,11–15,18–20,23). The present experiment examined the ability of amantadine, a putative pharmacotherapy for cocaine withdrawal, to eliminate or attenuate the residual behavioral effects of the continuous infusion or daily injection of cocaine. Our results indicate that amantadine treatment during the first 5 days of the withdrawal period does indeed eliminate the tolerance,

and 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 mimetics, or compounds that increase or restore dopaminergic functioning (5,6,17,24). The present results indicate that an indirect dopamine agonist treatment can eliminate the tolerance associated with the continuous infusion of cocaine. For example, either 5.0 or 20.0 mg/kg of amantadine during the first 5 days of withdrawal resulted in an enhanced response to a 15.0 mg/kg injection of cocaine. Thus, the present results indicate that treatment with a low dose of amantadine provides a candidate treatment for the early stages of cocaine withdrawal and for compulsive binge type cocaine abuse.

Intermittent administration of indirect dopamine agonists can induce sensitization [e.g., (1,7,19,23)]. The increase in the behavioral response to a cocaine challenge in the continuous infusion subjects could simply be the result of the induction of sensitization; this is not likely. If the effects of amantadine in the cocaine pump subjects were the result of inducing sensitization, then one would expect the saline control rats to also exhibit sensitization, which was not the case. Mechanisms other than sensitization must be considered. One possible candidate is the NMDA receptor. Amantadine is a noncompetitive NMDA receptor antagonist (21), and has been shown to block the *N*-methyl-D-aspartic acid-evoked release of acetylcholine from the rat neostriatum, while perfusion of striatal slices with 30 μM of amantadine had no significant effect on DA release (22). Hence, the effects of amantadine may be partially mediated by alterations in NMDA receptor regulation of neurotransmitter release. There is one caveat to be kept in mind, the effects of DA agonists during withdrawal may be different if a direct DA agonist is used; this type of result would potentially indicate that there are multiple DA mechanisms involved in the cocaine withdrawal syndrome. Future research should examine this possibility.

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 used as 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 unit dose of cocaine (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 unit dose 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.

Secondly, if the hypothesis that decreases in self-administration reflect increases in the unit dose [and hence increases the reinforcing value of cocaine (increases in unit dose are thought to be similar to the effects of increasing reinforcer magnitude)], 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 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.

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

ACKNOWLEDGEMENTS

This research was supported by NIDA grant SRCD-5P5D-DA05303, E. H. Ellinwood, Jr. principal investigator. The authors wish to thank Z. Xue for help in performing the surgeries and in analyzing the data.

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 concurrently available nondrug reinforcer prevents the acquisiton or decreases the maintenance of cocaine-reinforced behavior. Psychopharmacology (Berlin) 97:23–29; 1989.
4. Cedarbaum, J. M.; Schleifer, L. S. Drugs for Parkinson's disease, pasticity, and acute muscle spasms. In: Gilman, A.; Rall, T. W.; Nies, A. S.; Taylor, P., eds. The pharmacological basis of therapeutics. New York: Pergamon Press; 1990:463–484.

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.
11. 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.
12. 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.
13. 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.
14. King, G. R.; Kuhn, C.; Ellinwood, E. H., Jr. Dopamine efflux during withdrawal from continuous or intermittent cocaine. Psychopharmacology (Berlin) 111:179–184; 1993.
15. 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. 47:399–407; 1994.
16. Kornhuber, J.; Bormann, J.; Hubers, M.; Rusche, K.; Riederer, P. Effects of the 1-amino-adamantanes at the MK-801 binding site of the NMDA-receptor-gated ion channel: A human post-mortem brain study. Eur. J. Pharmacol. 206:297; 1991.
17. Kosten, T. R.; Schumann, B.; Wright, D. Bromocriptine treatment of cocaine abuse in patients maintained on methadone. Am. J. Psychiatry 145:381–382; 1988.
18. 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.
19. 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.
20. 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.
21. Sannerud, C. A.; Griffiths, R. R. Amantadine: Evaluation of reinforcing properties and effect on cocaine self-injection in baboons. Drug Alcohol Depend. 21:195–202; 1988.
22. Stoof, J. C.; Booji, J.; Drukarch, B.; Wolters, E. Ch. The anti-parkinson drug amantadine inhibits the N-methyl-D-aspartic acid-evoked release of acetylcholine from rat neostriatum in a non-competitive way. Eur. J. Pharmacol. 213:439–443; 1992.
23. 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.
24. 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.