Pergamon

Pharmacology Biochemistry and Behavior, Vol. 51, No. 4, pp. 901-908, 1995

0091-3057/95 $9.50 + .00

0091-3057(95)00074-7

# The NMDA Receptor and Cocaine: Evidence that MK-801 Can Induce Behavioral Sensitization Effects

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Received 10 November 1994

CAREY, R. J., H. DAI, M. KROST AND J. P. HUSTON. *The NMDA receptor and cocaine: Evidence that MK-801 can induce behavioral sensitization effects.* PHARMACOL BIOCHEM BEHAV **51**(4) 901-908, 1995.—Antagonism of the NMDA receptor with MK-801 is considered to be an effective pharmacologic manipulation to prevent the development of sensitization effects to drugs such as cocaine. The present study investigated this issue by comparing the behavioral response of separate groups of rats to three treatment cycles of either saline, 0.1 mg/kg MK-801, 10 mg/kg cocaine, or combined MK-801-cocaine (0.1/10 mg/kg). The treatments were spaced 1 week apart and were preceded by two nondrug baseline tests. In the first test cycle, the four groups had equivalent activity levels in the two nondrug tests. In the first drug test only the MK-801-cocaine group exhibited hyperactivity. By the third drug test, the MK-801-cocaine group exhibited an enhanced hyperactivity and the MK-801 group became hyperactive. Thus, behavioral drug sensitization developed but only with groups treated with MK-801. Antagonism of the NMDA receptor under some circumstances can be a highly effective treatment for the induction of behavioral sensitization effects.

Cocaine Sensitization MK-801 NMDA Psychostimulant Locomotor activity

AN EXTENSIVE animal behavior literature now exists that indicates that administration of psychostimulant dopaminergic drugs such as cocaine, amphetamine, and apomorphine induce locomotor stimulation and that this behavioral response becomes exaggerated with repeated drug administration (1,4,10,18,19,23,26,27). Because the behavioral sensitization effects of dopaminergic drugs persist long after withdrawal they are considered to represent an enduring drug induced change in the nervous system. Numerous studies have attempted to link these sensitization effects to alterations in dopamine receptors or dopamine neurotransmitter activity (16,17,20,21,29,32,34,38). As yet, however, no definitive relationships have been established.

Recent evidence from a number of reports suggests that pharmacologic antagonism of excitatory amino acid neurotransmission may be an effective manipulation to attenuate the behavioral sensitization effects associated with chronic dopaminergic drug treatment (15,25,28,33). Importantly, it is the *N*-methyl-D-Aspartate (NMDA) receptor site among the various EAA receptor subtypes (e.g., kinate, AMPA) that has been linked to long-term changes in neurons (36). Thus, the activation of NMDA receptor sites in response to dopaminergic drug stimulation seems to be critical to the development of behavioral sensitization effects to repeated dopaminergic drug treatments. Inasmuch as behavioral drug sensitization phenomena are long lasting and the NMDA receptors are considered to be critical for the development of persistent neuronal changes such as long-term potentiation (LTP), the activation of the NMDA receptor site by drugs has provided a potential mechanistic explanation for behavioral drug sensitization phenomena. In virtually all NMDA-dopaminergic drug interaction studies, the noncompetitive NMDA receptor ion channel antagonist dizocilpine (MK-801) has been used. Although MK-801 can prevent the development of behavioral sensitization to other drugs, it has also been reported that animals develop behavioral sensitization to repeated MK-801 treatments (37). Thus, it appears that antagonism at the NMDA receptor site does not block behavioral drug sensitization, per

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se, but rather that it interferes with drug sensitization effects induced by certain nonNMDA drugs (e.g., cocaine, amphetamine, morphine). The finding that pharmacologic antagonism at the NMDA receptor site induces behavioral sensitization obscures the role of the NMDA receptor site in behavioral drug sensitization effects.

The present study was undertaken to evaluate the issue of behavioral drug sensitization with respect to cocaine and the noncompetitive NMDA antagonist MK-801. Dose levels of each drug were used that initially had no reliable effects upon locomotor behavior in the behavioral test paradigm studied. With this design, possible behavioral sensitization effects related to repeated treatments or drug interactions could readily be identified. In addition, the drug treatments were spaced 1 week apart to eliminate the possible accumulation of active drug metabolites. Nondrug behavioral measures were obtained before drug tests and the behavioral analysis included tracing of actual locomotor paths. Although behavioral drug sensitization effects were observed, critically, these effects occurred only in conjunction with repeated MK-801 treatments.

## METHOD

### *Animals*

Experiments were carried out with naive male Sprague-Dawley rats from Taconic Farms (Germantown, NY), 6 mo old and approximately 400–500 g at the start of the experiments. In addition, 300–400-g Wistar rats (University of Düsseldorf/colony) were used. These latter animals were used in pilot studies to establish drug dose efficacy. Upon arrival, the animal were housed in individual 25 × 17 × 17-cm wire mesh cages in a climate-controlled room at 22 ± 2°C with a 12L : 12D cycle. During the 1st week after arrival, all animals were weighted daily for 7 days and handled extensively. All experiments occurred during the 12-h light cycle.

### *Drugs*

MK-801 was obtained from Research Biochemicals Inc. (RBI, Natick, MA) and was dissolved in sterile distilled water and injected IP 30 min before the behavioral test. Cocaine HCl (Mallinckrodt Specialty Chemical Company, St. Louis, MO, and Hoechst, Germany) was dissolved in sterile deionized distilled water and injected IP 15 min before the behavioral test. All drug solutions were of equal volume and the injection volume was 1 ml/kg.

### *Apparatus*

The test chamber was a 60 × 60 × 45-cm square box located in a red-lit illuminated room. The walls of the chamber were white and the floor was covered by white plain paper that was changed after each test session. A closed-circuit videocamera (RCA TC7011U) was mounted 50 cm above the open-field box and the signals were collected and analyzed by a video tracking system, Videomex-V (Columbus Instrument, Columbus, OH), which sent the experimental data to a PC-compatible computer by a serial cable. To enhance the subject's image from the background, the animal's head was blackened by a marker pen and the camera only tracked this feature of the rat's body. Ambient white noise (80 dB) was provided by a cassette tape player and was turned on immediately before placement of the animal in the test chamber and turned off upon the rat's removal from the test chamber. During each 10-min session, data were collected every 2.5 min for four intervals by the computer. A dot matrix printer (Epson FX-286e) was placed outside the test room and was connected to the image analyzer by a parallel cable, and the computer screen tracings of the animal's movement were printed out every 2.5 min. The complete test procedure was conducted automatically without the presence of the experimenter in the test room. In addition, a VHS VCR was also connected to the camera for the purpose of recording supplementary behavioral data and so that one could review and reinput the videotape signal to the image analyzer later in case of any possible malfunction of either the analyzer or the computer during the experiments.

### *Design and Procedures*

Initially, all 24 Sprague-Dawley rats were familiarized with the test environment with several 10-min baseline trials across 10 days 1 week before the experiment. The rats were divided into four groups ($n$ = 6), and each group had approximately the same locomotion level according to the last preexperiment familiarization trial. Every rat received saline injections on tests 1 and 2 (24 h apart), then were tested 15 min later in the chamber for 10 min. The drug test (test 3) was performed 24 h later, and the four groups of animals were injected then tested in the test chamber for 10 min. The four groups were administered either saline, cocaine (10 mg/kg, IP), MK-801 (0.1 mg/kg, IP), or MK-801 plus cocaine (0.1 plus 10 mg/kg). The MK-801 injections were administered 30 min before testing and 15 min before the cocaine injections. Saline injections were subdivided into either 30 or 15 min before testing. The same cycle of procedure was repeated twice, once in week 2 and once in week 3 (tests 4–6 and 7–9, respectively).

### *Biochemical Assay Procedures*

Immediately following completion of the behavioral testing on the last day, animals were placed in a plastic restraining cone (Braintree Products, Inc.) and decapitated. The medial prefrontal cortex, neostriatum, and limbic tissue samples were dissected, weighed, and placed in tubes containing 0.5 ml of 0.1 M perchloric acid and 4.5 μl of 10 μg/ml dihydroxybenzylamine (DHBA) as an internal standard, then homogenized and centrifuged. The resulting supernatant was filtered through 0.2-μm pore filters and the extracts were stored at −70°C until the HPLC-EC analysis, which was completed within 48–72 h. Trunk blood at sacrifice was also collected in tubes containing 200 μl of 0.5% sodium fluoride. The blood samples were centrifuged for 15 min at 14,000 rpm to obtain the plasma component. For cocaine the extraction column was a Narc2, 3 ml (125 mg) column (J.T. Baker, Phillipsburg, NJ). We used 0.5–1.0 ml of serum depending upon availability. We added 100% acetonitrile to the serum (3 : 1 acetonitrile to serum) and centrifuged it for 5 min at 2500 rpm. The supernate was decanted and added to 0.1 M sodium phosphate buffer, pH 6.1 (2 : 5 buffer to serum). Using 0.1 M HCl, the final pH of the sample was between 4 and 6. Under vacuum, the column was first conditioned with 2 ml methanol followed by 2 ml 0.1 M sodium phosphate buffer (pH 6.1). Before the column could dry the prepared sample was passed through the column, and this was immediately followed with 3 ml HPLC grade water, 3 ml 0.1 M HCl followed by 9 ml 100% methanol. Finally, the sample was eluted with 2 × 1.0 ml methylene chloride-isopropanol-ammonium hydroxide (77 : 19 : 4) and then dried under a stream of nitrogen. Mobile phase was added to the dried sample and directly injected into the HPLC column. For cocaine analyses in plasma and brain tissue, a 100 × 4.6-mm, 3μ Adsorbosphere catecholamine column (Alltech, Deerfield, IL) was used in conjunction with a 76% 0.02 M potassium phosphate, pH 3.0 buffer and 24% acetonitrile mobile phase. Column temperature was maintained at 25°C with a flow rate of 0.5 ml/min. The samples were detected with a BAS variable wavelength UV detector. The setting was 235 nm (3).

### *Statistical Analyses*

One-way analysis of variance (ANOVA) was used to determine the MK-801 effect on total locomotion during baseline-drug treatment and post hoc Duncan's tests for determining specific effects among groups. Multivariate ANOVA (MANOVA) was applied to determine the interval effect, drug effects, and their interactions. Paired *t*-tests were used to determine the locomotion differences within the same subject between different test days. *t*-Tests were employed to analyze the cocaine concentrations from biochemical studies. We used $p < 0.05$ as the criterion for statistical significance.

## RESULTS

Figure 1 presents the results for the first and third treatment cycles. In each cycle the first two tests were nondrug tests and the third day was the drug test. For cycle 1 there were no statistically significant group effects [test 1: $F(3, 60) = 0.89$, $p > 0.05$ for group differences; $F(3, 60) = 10.7$, $p < 0.001$ for interval; and $F(9, 60) = 0.4$, $p > 0.05$ for group × interval interaction; test 2: $F(3, 60) = 0.84$, $p > 0.05$ for group differences; $F(3, 60) = 11.6$, $p < 0.001$ for interval; and $F(9, 60) = 1.0$, $p > 0.05$ for group × interval interaction]. On day 3 (test 3), however, a statistically significant treatment effect was observed [$F(3, 60) = 11.4$, $p < 0.001$ for group differences; $F(3, 60) = 33.9$, $p < 0.001$ for interval; and $F(9, 60) = 0.96$, $p > 0.05$ for group × interval interaction]. Subsequent analysis of group effects of total locomotion by means of one-way ANOVA were significant [$F(3, 18) = 11.4$, $p < 0.01$] and comparisons among groups by means of Duncan's multiple range tests indicated that the combined MK-801-cocaine group had a higher locomotion level than all other groups and that the other three groups did not differ from each other. The lower half of Fig. 1 presents the results obtained for the third treatment cycle. In contrast to the first treatment cycle there were group differences in the nondrug as well as the drug tests. On the nondrug test days, there were statistically significant group differences in locomotion [test 7: $F(3, 60) = 4.5$, $p < 0.01$ for group differences; $F(3, 60) = 13.1$, $p < 0.001$ for interval; and $F(9, 60) = 0.89$, $p > 0.05$ for group × interval interaction; test 8: $F(3, 60) = 4.6$, $p < 0.01$ for group differences; $F(3, 60) = 15.4$, $p < 0.001$ for interval; and $F(9, 60) = 1.81$, $p > 0.05$ for group × interval interaction]. Subsequent statistical analysis using one-way ANOVA and Duncan's multiple range tests indicated that the MK-801 and the combined MK-801-cocaine groups had higher locomotor levels than the saline animals on both days ($p < 0.05$). The drug test results on cycle 3 differed from the drug test results in cycle 1. As can be seen in the

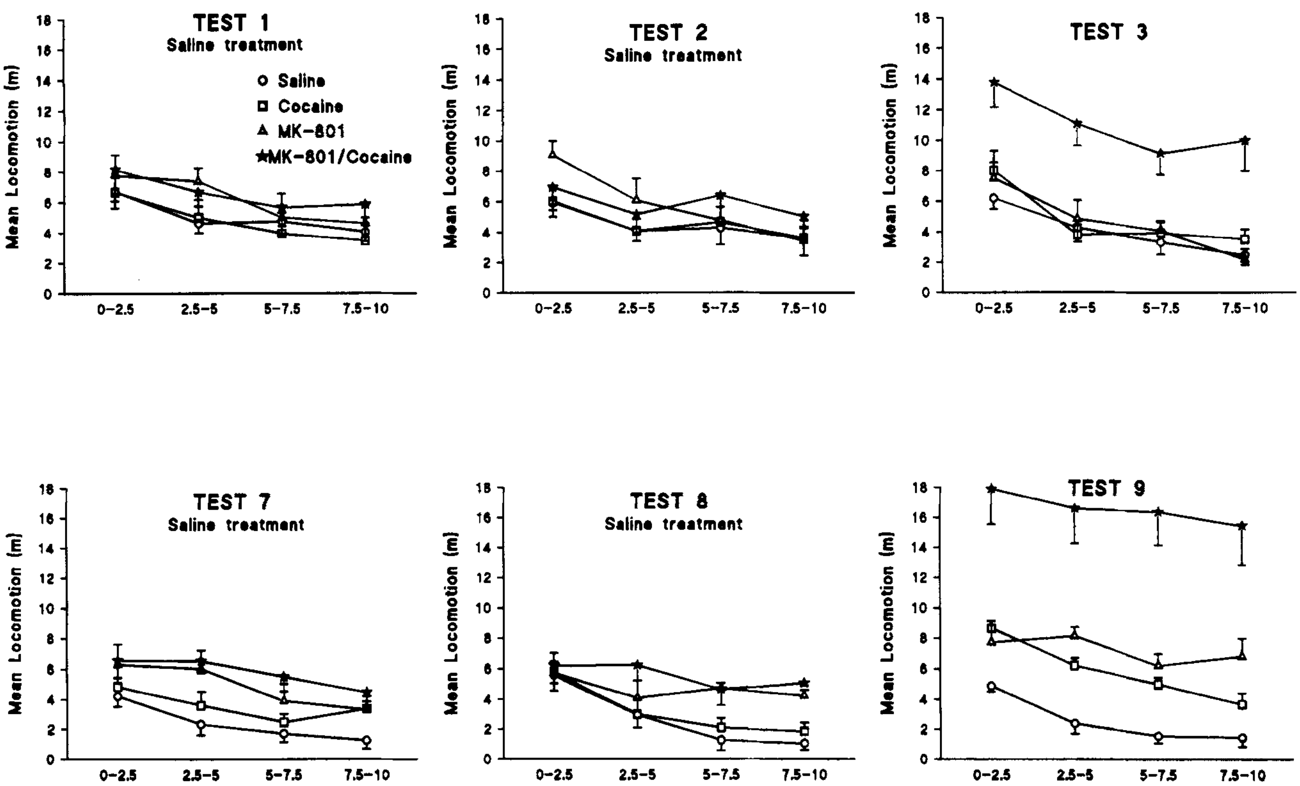


FIG. 1. Means and SEMs of locomotion by intervals (2.5 min each) for four treatment groups from tests 1-3 (upper half) and tests 7-9 (lower half). All rats were treated with saline on tests 1, 2, 7, and 8; different drug-saline treatments were given on tests 3 and 9 according to the group assignment.

lower half of Fig. 1, all drug treatment groups had higher activity levels than the saline groups. The statistical analysis of test 9 using two-way ANOVA indicated statistically significant group differences [$F(3, 57) = 23.4$, $p < 0.001$], interval effect [$F(3, 57) = 15.8$, $p < 0.001$], but not a group × interval interaction [$F(3, 57) = 1.5$, $p > 0.05$]. Subsequent analysis of the group effects by means of one-way ANOVA and Duncan's multiple range test indicated that the combined MK-801-cocaine group had a higher locomotion level than all other groups ($p < 0.05$) and that the MK-801 group also had a higher activity level than the saline group ($p < 0.05$).

To more directly evaluate the issue of sensitization, Fig. 2 shows the within-group comparison for locomotion on drug test cycle 1 (test 3) and drug test cycle 3 (test 9) for each treatment group. As can be seen in the figure, the saline group exhibited a statistically significant decrease in locomotion ($t = 4.2$, $p < 0.01$). The cocaine group had no change ($t = 1.0$, $p > 0.05$), whereas the MK-801 and combined MK-801-cocaine groups had significant increases in locomotion ($t = 3.9$, $p < 0.01$ and $t = 5.3$, $p < 0.01$, respectively).

Although the within-subject analysis presented in Fig. 2 indicates that only the two MK-801 groups had significantly elevated activity levels when the first vs. third drug treatments were compared, the extension of this analysis to the last nondrug test (test 8) vs. the last drug test (test 9) indicated that all three drug treatments increased locomotor activity levels above their respective nondrug baselines. The results are displayed in Fig. 3. The paired $t$-test comparisons were: saline group, $t = 0.44$, $p > 0.05$; cocaine group, $t = 4.95$, $p < 0.01$; MK-801 group, $t = 7.9$, $p < 0.01$; and the combined MK-801-cocaine group, $t = 5.3$, $p < 0.01$.

Inasmuch as all extant studies of behavioral drug sensitization that use locomotor activity as an index of the drug response have used indirect measures of locomotion such as photocell interruptions, the present study used video image analysis to trace the animals' movements and representative tracing of the first and fourth 2.5-min interval on test 9 for an animal from each treatment group. These animals were selected on the basis that their activity scores were the closest to the group mean. This display provides a qualitative indication of the animals' behavior patterns in response to the drug treatments. As can be seen in Fig. 4, the locomotor stimulant effects of the combined MK-801-cocaine treatment were manifested by increased locomotion throughout the test environment rather than increased stereotypical movements in a restricted spacial area of the test environment.

The biochemical results are shown in Fig. 5. As can be seen, the cocaine concentrations of cocaine alone and com-

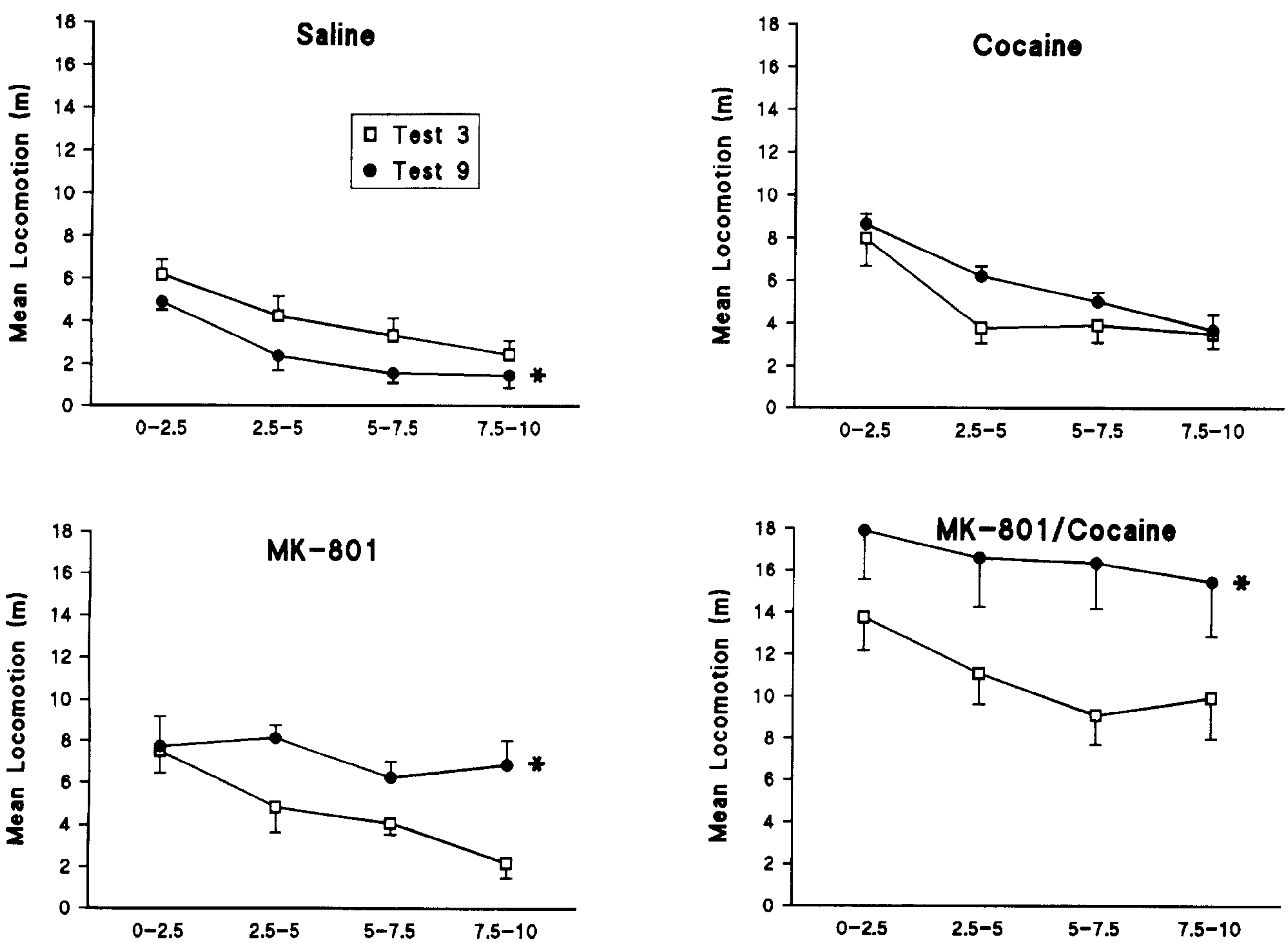


FIG. 2. Means and SEMs of locomotion by intervals (2.5 min each) for tests 3 and 9 for four treatment groups. $*p < 0.05$ between these two drug tests by paired $t$-test.

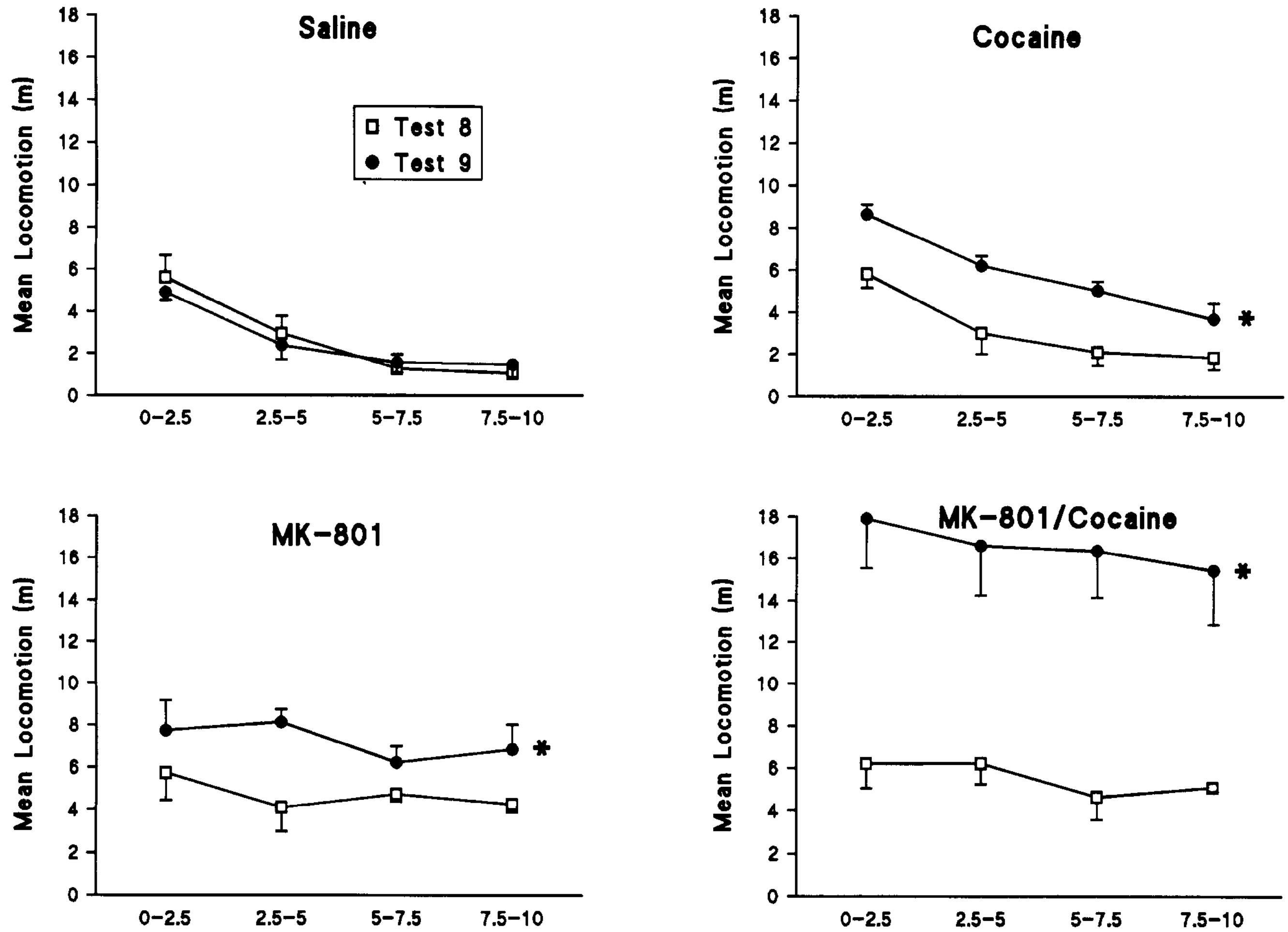


FIG. 3. Means and SEMs of locomotion by intervals (2.5 min each) for test 8 (nondrug test) and test 9 (drug test) for four treatment groups. *$p < 0.05$ by paired $t$-test.

bined MK-801-cocaine treated groups in all three brain samples were almost identical. Because of the absence of the detection of cocaine in saline- and MK-801-treated groups, $t$-tests were used for statistical determination for each brain sample and the results reflected no significant differences ($t = 0.23$, 1.62, and 1.66, respectively, for cortex, striatum, and limbic, $p > 0.05$). The results of serum cocaine concentrations was similar to the brain tissue samples. The difference between the cocaine-treated group (0.30 ± 0.135) and the combined MK-801-cocaine group (0.245 ± 0.11) was not statistically significant ($t = 0.32$, $p > 0.05$) and there was no reliable detection of cocaine in the other groups. These cocaine findings indicate that the impact of MK-801 on cocaine behavioral effect was not the result of an alteration in cocaine pharmacokinetics.

## DISCUSSION

The present findings demonstrate that nonmotoric doses of MK-801 and cocaine can interact to induce a substantial locomotor stimulant effect. Furthermore, by the third treatment this locomotor stimulant effect was enhanced. In addition, the MK-801 treatment that initially was nonmotoric became a hypermotoric treatment by the third injection. This hyperlocomotion effect was observed both in relationships to the saline group and to its own baseline drug effect in the first treatment cycle. In contrast, the cocaine treatment did not induce hyperlocomotion when evaluated in the context of all treatment groups. Furthermore, a within-group comparison indicated that the cocaine treatment group had an equivalent locomotion response in test cycles 1 and 3. On the other hand, when the locomotion level of the cocaine group was compared to its nondrug baseline or the saline group, then a cocaine-induced hyperlocomotion effect was observed in test cycle 3 (i.e., test 8 vs. test 9). Thus, when the effects of cocaine groups are considered relative to their habituated baseline there would appear to be a behavioral sensitization effect. It is critical that this difference occurred because the cocaine and saline groups exhibited a marked and statistically significant decline in activity from test cycles 1 to 3 in the nondrug tests. Thus, the locomotor stimulant effect of cocaine in the present study becomes evident in the context of habituation. In this regard we have recently shown that locomotor stimulant effects of cocaine can be observed within 5 min of the first injection if animals are extensively habituated to their environment and that the magnitude of their effect does not change with repeated treatments (11). Taken together, these results indicate that the stimulant effects of low to moderate doses of cocaine

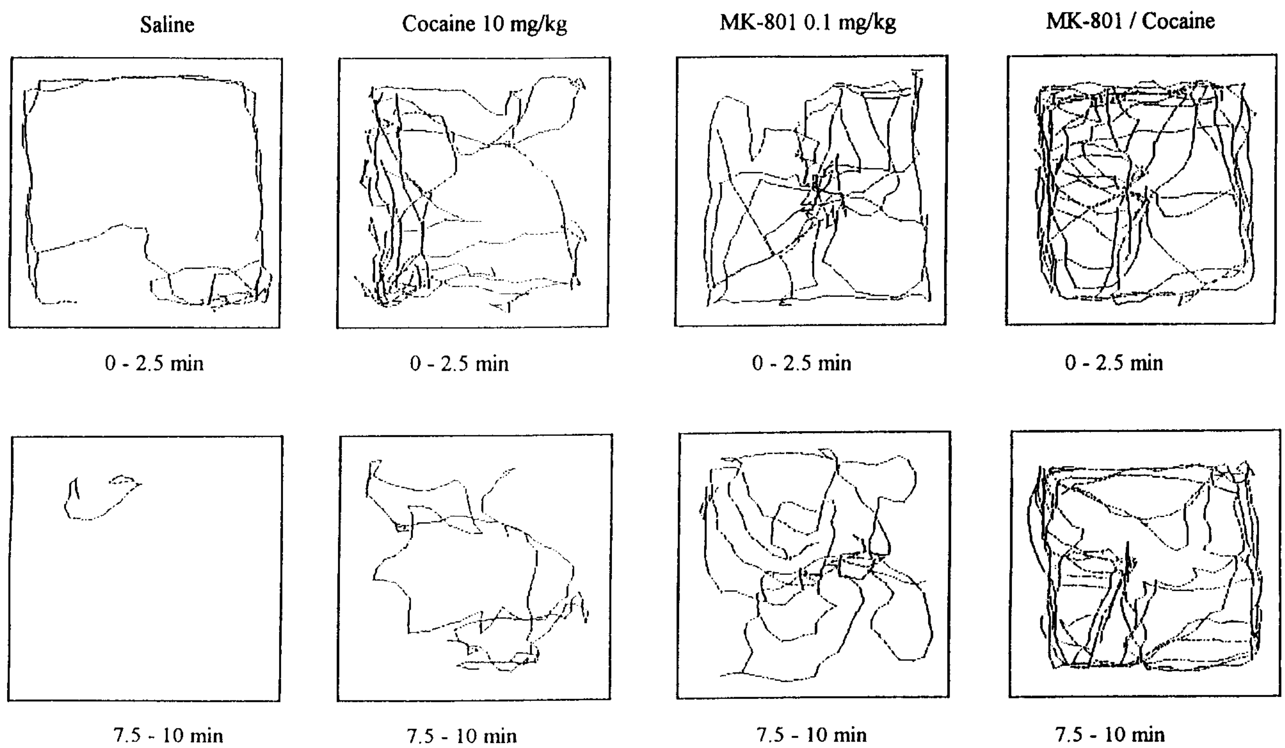


FIG. 4. Tracings of the actual routes animals traversed in the first (upper half) and fourth (lower half) 2.5-min intervals of the 10-min test sessions for four different drug–saline treatment groups on test 9.

need to be considered in the context of habituation processes, and suggest an antihabituation effect of cocaine. Such considerations are also pertinent to an assessment of the time courses of cocaine effects. In a conventional paradigm cocaine and vehicle animals are injected and then tested over several hours; typically, stimulant effects of cocaine relative to vehicle treatment are observed after 15–20 min. Because habituation occurs early in the session, the antihabituation effects become evident only after habituation has developed in the nondrug control group. Although low and modest dose effects of cocaine may be explicable in terms of antihabituation effects, higher dose effects are more complex to assess, in that behavioral stereotypy as well as preconvulsive effects can be elicited (19). Studies of high-dose cocaine effects, however, have used indices of locomotor activity (e.g., photocell interruption) that are insensitive to qualitative changes in the behavioral drug response. As a consequence, a qualitative behavioral change can be mislabeled as a quantative behavioral change and lead to a false positive identification of behavioral sensitization (10).

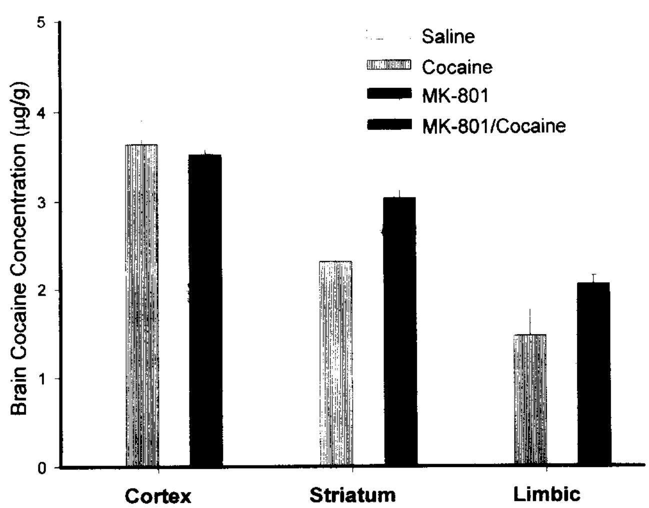


FIG. 5. Means and SEMs of cocaine concentrations of cortex, striatum, and limbic samples for each treatment group.

Another fundamental shortcoming of studies of behavioral drug sensitization is the failure to monitor the nondrug behavioral baseline. In the present study, two nondrug baseline tests preceded each drug test. These nondrug tests showed that the groups were equivalent at the start of the drug treatment phase. However, both of the groups exposed to MK-801 had become hyperactive relative to saline control animals in the nondrug tests. Critically, these were the only groups that developed behavioral sensitization to the drug effects. Thus, MK-801 treatments did not simply enhance the behavioral response elicited by MK-801 treatment; the behavioral baseline was also changed. A shift in the behavioral baseline indicates that the MK-801 treatment did something other than induce behavioral drug sensitization. Minimally, the drug enhanced behavioral responding to test environment stimuli. Whether this effect is context specific or involves a receptor status change (e.g., a change in NMDA receptor affinity) or possible neurotoxicity (e.g., damage to hippocampal cells) remains to be experimentally determined.

In understanding dopamine agonist–NMDA antagonist interactions, it is useful to consider the terminal brain area in which the dopamine agonist stimulant effects on behavior are mediated. For cocaine, there is now substantial literature indicating that cocaine blockade of the dopamine transporter in the subcortical limbic dopamine terminal area is critical for the initiation of behavioral activation effects induced by cocaine (22). Although it is the cocaine effect at subcortical limbic dopamine terminal areas that appears to be critical for the initiation of behavioral activation effects induced by cocaine, it is also the case that cocaine increases dopamine availability in all dopamine terminal areas. Of particular interest for the analysis of cocaine interactions with NMDA antagonists, such as MK-801, is the finding that increased dopamine availability in the prefrontal cortex dopamine terminal area can exert an inhibitory influence upon subcortical limbic dopamine systems by activation of the inhibitory cortical outflow neurons (5). Support for this dopamine-activated cortical inhibition is suggested by studies in which the destruction of cortical dopamine nerve terminals with the selective neurotoxin 6-OHDA induces a marked enhancement in the stimulatory effects of indirect-acting dopamine agonists such as cocaine (12,13). This cortical–subcortical relationship suggests that the effect of cocaine is related to a balance in dopaminergic activity generated at subcortical limbic vs. cortical dopamine areas. Although the dopamine receptors in the cortex are the site of initiation of possible inhibitory effects of cocaine, it appears likely that this inhibition is mediated by glutamatergic cortical outflow neurons (6). Among the subcortical receptor sites that are implicated in the transmission of cortical inhibitory influence upon subcortical structures, the NMDA receptor site is of major importance. However, if an NMDA antagonist drug (e.g., MK-801) is coadministered to animals with a dopamine agonist drug, the outcome depends on the timing of the drug treatments. When such drugs are administered simultaneously, MK-801 treatment does not appear to alter the dopaminergic stimulant effect (11,14,30). At the same time, it was also observed that for drugs such as cocaine, the dopamine agonist drug concentration in the brain peaks rapidly and the onset of motoric activation is equally rapid, showing a parallel trend (2). The peak concentration of MK-801 in brain does not develop until 30 min after an IP injection (31). Similarly, peak behavioral effects of MK-801 do not develop until 30 min postinjection (9,31,35). Possibly, the more rapid onset of the cocaine effects coupled with the slower gradual onset of disinhibitory effects of NMDA blockade may account for the absence of an interaction between MK-801 and cocaine when the drugs are administered concurrently at moderate dose levels. In contrast, if cocaine is given to an animal when NMDA receptor blockade is already in place, a pronounced exaggeration of the cocaine stimulant effect can be observed as in the present study. Functionally, NMDA blockade appears to result in effects that are analogous to those one observes with cortical dopamine terminal destruction. In both cases, the facilitation of cocaine effects occurs in the context of attenuated cocaine activation of cortical inhibition. Given an extensive 6-OHDA lesion of the cortical dopamine terminals, cocaine cannot generate dopamine in the cortical dopamine terminals and thereby activate the cortical inhibitory outflow projections to subcortical areas. Similarly, given an existing NMDA receptor blockade, the activation of cortical inhibitory neurons by cocaine is also blunted. Inasmuch as this cortical inhibitory effect of cocaine has not been experimentally investigated as a hypothesis, it is of substantial importance to address this issue in the context of cocaine behavioral effects expressed in motoric activation, sensitization, and conditioning. According to a cortical–subcortical dopamine balance hypothesis, the effects of cocaine would depend on perturbations in the relative balance in cortical–subcortical dopaminergic activation as modulated by the inhibitory tone of the NMDA receptor site. Thus, the results obtained in the present study suggest that MK-801 can enhance behavioral responses evoked by environmental or drug stimuli and in this way promote behavioral sensitization effects and place preference effects (24,37). Such effects, however, may be limited to low doses of MK-801 (i.e., <0.1 mg/kg) in that higher doses lead to behavioral disorganization, inattention, and cortical disfunction (7,8).

ACKNOWLEDGEMENTS

This research work is supported by NIDA Grant R01DA0536609, a VA Merit Review Grant, and Deutsche Forschungsgemeinschaft (Hu 306/6/4-2480).

## REFERENCES

1. Borowsky, B.; Kuhn, C. M. Chronic cocaine administration sensitizes behavioral but not neuroendocrine responses. Brain Res. 543:301–306; 1991.
2. Carey, R. J.; Damianopoulos, E. N.; DePalma, G. Differential temporal dynamics of serum and brain cocaine: Relationship to behavioral, neuroendocrine and neurochemnical cocaine induced response. Life Sci. 55:1711–1716; 1994.
3. Carey, R. J.; DePalma, G. A simple, rapid HPLC method for the concurrent measurement of cocaine and catecholamines in brain tissue samples. J. Neurosci. Methods (in press).
4. Carey, R. J.; DeVeaugh-Geiss, J. Chronic benztropine and haloperidol administration induce behaviorally equivalent pharmacological hypersensitivities separately but not in combination. Psychopharmacology (Berlin) 76:341–345; 1982.
5. Carlsson, A. Thirty years of dopamine research. Adv. Neurol. 60:1–10; 1993.
6. Carlsson, M.; Svensson, A. Interfering with glutamatergic neurotransmission by means of NMDA antagonist administration discloses the locomotor stimulatory potential of other transmitter systems. Pharmacol. Biochem. Behav. 36:45–50; 1990.
7. Dai, H.; Carey, R. J. The NMDA antagonist MK-801 can impair attention to exteroceptive stimuli. Behav. Brain Res. 62:149–156; 1994.
8. Dai, H.; Carey, R. J. Behavioral interaction between the NMDA antagonist MK-801 and the dopaminergic antagonist haloperidol: Support for a balance model. J. Psychopharmacol. 9:9–15; 1995.
9. Dai, H.; Gebhardt, K.; Carey, R. J. Time course effects of MK-801: The relationship between brain neurochemistry and behavior. Brain Res. Bull. 36:175–180; 1995.
10. Damianopoulos, E. N.; Carey, R. J. Apomorphine sensitization effects: Evidence for environmentally contingent behavioral reorganization process. Pharmacol. Biochem. Behav. 45:655–663; 1993.
11. Damianopoulos, E. N.; Carey, R. J. Evidence for NMDA receptor mediation of cocaine induced corticosterone release and cocaine conditioned stimulant effects. Behav. Brain Res. (in press).
12. Deutch, A. Y. The regulation of subcortical dopamine systems by the prefrontal cortex: Interactions of central dopamine systems and the pathogenesis of schizophrenia. J. Neural Transm. (Suppl) 36:61–89; 1992.

13. Deutch, A. Y.; Clark, W. A.; Roth, R. H. Prefrontal cortical dopamine depletion enhances the responsiveness of mesolimbic dopamine neurons to stress. Brain Res. 521:311-315; 1990.
14. Di Chiara, G.; Morelli, M. Dopamine-acetylcholine-glutamate interactions in the striatum. Adv. Neurol. 60:102-106; 1993.
15. Druhan, J. P.; Jakob, A.; Stewart, J. The development of behavioral sensitization to apomorphine is blocked by MK-801. Eur. J. Pharmacol. 243:73-77; 1993.
16. Engber, T. M.; Susel, Z.; Juncos, J. L.; Chase, T. N. Continuous and intermittent levodopa differentially affect rotation induced by $D_1$ and $D_2$ dopamine agonists. Eur. J. Pharmacol. 168:291-298; 1989.
17. Farfel, G. M.; Kleven, M. S.; Woolverton, W. L.; Seiden, L. S.; Perry, B. D. Effects of repeated injections of cocaine on catecholamine receptor binding sites, dopamine transporter binding sites and behavior in rhesus monkey. Brain Res. 578:235-243; 1992.
18. Heidbreder, C.; Goldberg, S. R.; Shippenberg, T. Inhibition of cocaine-induced sensitization by the $\alpha$-opioid receptor antagonist naltrindole. Eur. J. Pharmacol. 243:123-127; 1993.
19. Itzhak, Y.; Stein, I. Sensitization to the toxic effects of cocaine in mice is associated with the regulation of N-methyl-D-aspartate receptors in the cortex. J. Pharmacol. Exp. Ther. 262:464-470; 1992.
20. Jenner, P.; Boyce, S.; Marsden, C. D. Effect of repeated L-DOPA administration on striatal dopamine receptor function in the rat. In: Fahn, S., ed. Recent developments in Parkinson's disease. New York: Marcel Dekker; 1987.
21. Koff, J. M.; Shuster, L.; Miller, L. G. Chronic cocaine administration is associated with behavioral sensitization and time-dependent changes in striatal dopamine transporter binding. J. Pharmacol. Exp. Ther. 268:277-282; 1994.
22. Koob, G. F. Drugs of abuse: Anatomy, pharmacology and function of reward pathways [Review]. Trends Pharmacol. Sci. 13: 177-184; 1992.
23. Kuribara, H.; Asami, T.; Ida, I.; Iijima, Y.; Tadokoro, S. Effects of repeated MK-801 on ambulation in mice and in sensitization following methamphetamine. Psychopharmacology (Berlin) 108: 271-275; 1992.
24. Layer, R. T.; Kaddis, F. G.; Wallace, L. J. The NMDA receptor antagonist MK-801 elicits conditioned place preference in rats. Pharmacol. Biochem. Behav. 44:245-247; 1993.
25. Martinez Fong, D.; Rosales, M. G.; Gongora Alfaro, J. L.; Hernandez, S.; Aceves, J. NMDA receptor mediates dopamine release in the striatum of unanesthetized rats as measured by brain microdialysis. Brain Res. 595:309-315; 1992.
26. Mattingly, B. A.; Gotsick, J. E.; Marin, C. Locomotor activity and sterotypy in rats following apomorphine treatments 1-, 3- or 7-day intervals. Pharmacol. Biochem. Behav. 31:871-875; 1989.
27. Mattingly, B. A.; Gotsick, J. E.; Salamanca, K. Latent sensitization to apomorphine following repeated low doses. Behav. Neurosci. 102:553-558; 1988.
28. Morelli, M.; Di Chiara, G. Stereospecific blockade of N-methyl-D-aspartate transmission by MK 801 prevents priming of SKF 38393-induced turning. Psychopharmacology (Berlin) 101:287-288; 1990.
29. Peris, J.; Boyson, S. J.; Cass, W. A.; Curella, P.; Dwoskin, L. P.; Larson, G.; Lin, L. H.; Yasuda, R. P.; Zahniser, N. R. Persistence of neurochemical changes in dopamine systems after repeated cocaine administration. J. Pharmacol. Exp. Ther. 253: 38-44; 1990.
30. Pudiak, C. M.; Bozarth, M. A. L-NAME and MK-801 block sensitization to the locomotor-stimulanting effect of cocaine. Soc. Neurosci. Abstr. 19:1843-1843; 1993.
31. Schwartz, P. H.; Wasterlain, C. G. Determination of serum and brain concentrations of neuroprotective and nonneuroprotective doses of MK-801. J. Neurol. Sci. 115:26-31; 1993.
32. Segal, D. S.; Kuczenski, R. Repeated cocaine administration induces behavioral sensitization and corresponding decreased extracellular dopamine responses in caudate and accumbens. Brain Res. 577:351-355; 1992.
33. Tiseo, P. J.; Inturrisi, C. E. Attenuation and reversal of morphine tolerance by the competitive N-methyl-D-aspartate receptor antagonist, LY274614. J. Pharmacol. Exp. Ther. 264:1090-1096; 1993.
34. Ujike, H.; Akiyama, K.; Otsuki, S. $D_2$ but not $D_1$ dopamine agonists produce augmented behavioral response in rats after subchronic treatment with methamphetamine or cocaine. Psychopharmacology (Berlin) 102:459-464; 1990.
35. Ujike, H.; Tsuchida, H.; Kanzaki, A.; Akiyama, K.; Otsuki, S. Competitive and noncompetitive N-methyl-D-aspartate antagonists fail to prevent the induction of methamphetamine-induced sensitization. Life Sci. 50:1673-1681; 1992.
36. Watkins, J. C.; Collingridge, G. L. The NMDA receptor. London: Oxford University Press; 1989.
37. Wolf, M. E.; Khansa, M. R. Repeated administration of MK-801 produces sensitization to its own locomotor stimulant effects but blocks sensitization to amphetamine. Brain Res. 562:164-168; 1991.
38. Woolverton, W. L.; Johnson, K. M. Neurobiology of cocaine abuse [Review]. Trends Pharmacol. Sci. 13:193-200; 1992.