Pergamon

Pharmacology Biochemistry and Behavior, Vol. 47, No. 4, pp. 907–912, 1994

0091-3057/94 $6.00 + .00

The Noncompetitive NMDA Antagonist MK-801 Fails to Block Amphetamine-Induced Place Conditioning in Rats

DIANE C. HOFFMAN

Neurogen Corporation, 35 Northeast Industrial Road, Branford, CT 06405

Received 26 July 1993

HOFFMAN, D. C. *The noncompetitive NMDA antagonist MK-801 fails to block amphetamine-induced place conditioning in rats.* PHARMACOL BIOCHEM BEHAV 47(4) 907–912, 1994.—The noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist MK-801 prevents the development of sensitization to the locomotor-activating effects of amphetamine. In the present study, the possibility that the NMDA receptor might also play a role in the rewarding effects of amphetamine (as measured in the conditioned place preference paradigm) was investigated. Male Sprague–Dawley rats received amphetamine (2.0 mg/kg IP) paired with one side of a two-compartment box and saline paired with the other side. During these pairings locomotor activity was measured. On the test day, the amount of time drug-free rats spent in each compartment was determined. Rats trained with amphetamine alone showed a significant increase in time spent on the drug-paired side from pre- to postconditioning, indicating a place preference. When rats were injected with MK-801 (0.03, 0.1, or 0.3 mg/kg SC) prior to amphetamine, no significant effects on amphetamine place conditioning were observed. Rats treated with MK-801 alone showed significant place conditioning, but only at the intermediate dose. On conditioning days, MK-801 produced a dose-dependent enhancement of amphetamine-induced locomotor activity; however, MK-801 alone caused a similar increase in activity. The preferential D_2 dopamine receptor antagonist eticlopride (0.01, 0.05, or 0.1 mg/kg SC) significantly reduced amphetamine locomotor activity, and the highest dose blocked place conditioning. These data suggest that the NMDA receptor is not involved in either the rewarding or locomotor-activating effects of amphetamine.

MK-801 Amphetamine Eticlopride Place preference Locomotor activity Glutamate Dopamine NMDA receptors Rats

ANATOMICAL and pharmacological studies have illustrated a synaptic interaction between dopamine and the excitatory amino acid glutamate within the striatum (1,2,6,19,30) and the nucleus accumbens (29). Recent behavioral studies have supported a functional interaction between these two neurotransmitters. Blockade of specific glutamate receptor subtypes antagonizes at least some of the acute and chronic behavioral effects of the dopamine agonists cocaine and amphetamine.

In acute studies, competitive and noncompetitive *N*-methyl-D-aspartate (NMDA) antagonists block cocaine-induced stereotypy in mice and rats (12), and the quisqualate receptor antagonist L-glutamic acid diethyl ester (GDEE) blocks the locomotor-activating effects of amphetamine (5). A possible site of action for these interactions may be the nucleus accumbens, since intra-accumbens administration of GDEE blocks the locomotor-activating effects of amphetamine and cocaine (25) and microinjections of the selective NMDA receptor antagonist 2-amino-5-phosphonopentanoic acid (AP5) into the nucleus accumbens dose-dependently decrease the heightened locomotor activity and enhanced responding for a conditioned reward resulting from intra-accumbens amphetamine infusions (16).

In addition to the acute behavioral effects of amphetamine and cocaine, glutamate appears to play a significant role in the development of behavioral sensitization following chronic administration of stimulants. Sensitization refers to the progressively larger increases in locomotor activity or stereotypy with successive injections of amphetamine or cocaine. Karler and colleagues (13,15) were the first to report that pretreatment with the noncompetitive NMDA antagonists MK-801 or ketamine blocks the development of sensitization to the locomotor-activating effects of either amphetamine or cocaine in mice. The competitive NMDA antagonist 3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP) as well as the kainate antagonist 6,7-dinitroquinoxaline (DNQX) were also

effective (14). The importance of glutamate in stimulant-induced behavioral sensitization was subsequently confirmed by Wolf and Khansa (33) and Stewart and Druhan (28), who independently demonstrated that MK-801 blocks amphetamine-induced behavioral sensitization in rats. Each group also showed that MK-801 blocks the development of conditioned locomotion in response to a saline injection in the same environment in which the rats were previously treated with amphetamine.

In addition to the locomotor-activating effects of psychomotor stimulants, these drugs are well-known for their rewarding properties, as demonstrated in the self-administration and place conditioning paradigms. Although dopaminergic release in the nucleus accumbens is primarily responsible for these effects (8,17,32), a glutamatergic influence is possible given the close anatomical and functional relationship between dopamine and glutamate. This possibility was addressed in the present study. In particular, the possibility that NMDA receptors play a role in the rewarding effects of amphetamine, as measured in the conditioned place preference paradigm (8), was investigated. In this paradigm, rats receive several pairings of amphetamine with a distinctive environment, and later, in the absence of the drug, the rats demonstrate a relative increase in the amount of time spent in this environment compared to an equally distinctive alternative environment. This relative increase in time on the drug-paired side presumably reflects the rewarding properties of the drug. Several doses of the noncompetitive NMDA antagonist MK-801 were administered prior to the amphetamine pairings, and the effects on place conditioning were examined. Since dopamine receptor antagonists are known to block amphetamine place conditioning (8), the effects of MK-801 were compared to those of the preferential D_2-like (D_2, D_3, and D_4) dopamine receptor antagonist eticlopride (11).

METHOD

Animals

One hundred and twelve male Sprague-Dawley rats (SASCO, St. Louis) weighing 275–350 g served as subjects. The rats were housed in groups of two per cage in a temperature-controlled (21 ± 1°C) colony room on a 12-h light/dark (0700–1900) cycle. The rats had free access to food and water. Each rat was experimentally naive. Testing occurred during the light phase of the light/dark cycle.

Apparatus

Four similar rectangular chambers were constructed of wooden sides with Plexiglas covers. Each chamber consisted of two compartments (36 × 27 × 38 cm) joined by a small tunnel (9.5 × 6.5 × 8 cm); entrance to the tunnel could be blocked by inserting wooden guillotine doors. The compartments differed in brightness, pattern on the walls, and floor texture; in two chambers, one compartment was painted brown and had a mesh (1.3-cm squares) floor and the other was painted in vertical black and white stripes (1.2 cm wide underneath a Plexiglas surface) with a rod (1.5 cm between rods) floor. In the remaining two chambers, the striped compartment had a mesh floor and the brown compartment had a rod floor. Each compartment was equipped with two sets of photocell emitters and detectors (at a height of 5 cm) which divided the length of each compartment into three equal areas. The tunnel also contained two sets of photocell emitters and detectors. The photocells were connected to a single-board computer that recorded the number of beam interruptions as well as the amount of time spent in each compartment during the preexposure and test sessions. The single-board computers communicated with a Macintosh SE using Red Ryder 10.3 software.

Drugs

(+)-MK-801 hydrogen maleate [(5*R*,10*S*)-(+)-5-methyl-10,11-dihydroxy-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine hydrogen maleate] (Research Biochemicals International, Natick, MA) and *d*-amphetamine sulfate (Sigma Chemical Co., St. Louis) were dissolved in physiological saline (0.9%). Eticlopride hydrochloride (Research Biochemicals International) was dissolved in 0.98 ml 1% lactic acid, buffered with 0.02 ml 0.1 N NaOH and made up to the appropriate volume with distilled water (final pH 2.5–3.0). MK-801 and eticlopride were administered SC in the neck region 15 min prior to an IP injection of amphetamine. This pretreatment time was chosen because following a 15-min time interval MK-801 produces immediate and long-lasting behavioral activation (locomotion and stereotypy) (9).

Procedure

The experimental design consisted of three phases: preexposure, conditioning, and test. The preexposure phase involved adapting the rats to the experimental chambers and obtaining a baseline measure of the amount of time spent in each compartment. With the guillotine doors removed, the rats were placed in the "start" compartment (opposite to the one that would eventually be paired with drug) with access to the entire chamber for 15 min. The choice of the start compartment was counterbalanced across rats. The amount of time the rat spent in each compartment was measured.

Following the preexposure session, rats were returned to their home cage; at least 2 h later, the conditioning phase of the experiment was initiated. This phase involved four 30-min sessions which occurred over four consecutive days. On days 1 and 3, eight groups of rats (n = 8–12 each) were pretreated with MK-801 (0, 0.03, 0.1, or 0.3 mg/kg SC); 15 min later, they received saline or 2.0 mg/kg amphetamine IP and were confined to the drug-paired compartment for 30 min. On days 2 and 4, the rats were pretreated with saline 15 min prior to another saline injection; the rats were then confined to the alternative compartment for 30 min. In an additional four groups of rats (n = 8 each), eticlopride (0, 0.01, 0.05, or 0.1 mg/kg SC) was administered 15 min prior to 2.0 mg/kg amphetamine on days 1 and 3, and the vehicle was injected 15 min prior to saline on days 2 and 4. The effects of eticlopride alone at the highest dose were also tested. On days 1 and 3, this group of rats (n = 8) was treated with 0.1 mg/kg eticlopride followed 15 min later by a saline injection; on days 2 and 4, the vehicle was administered 15 min prior to saline. Locomotor activity was measured during each 30-min session.

The test phase occurred on the fifth day. Drug-free rats were placed in the start compartment and were given access to the entire chamber for 15 min. The amount of time spent in each compartment was measured.

RESULTS

Place Conditioning

To analyse for place conditioning, the amount of time spent on the drug-paired side during the preexposure and test

sessions was compared (Figs. 1 and 2). A significant increase or decrease in time spent on the drug-paired side from preexposure to test suggests the establishment of a conditioned place preference or aversion, respectively. A two-way analysis of variance (ANOVA) with one repeated measure (phase) was conducted on the groups treated with amphetamine and pretreated with either saline or MK-801 (Fig. 1A); the phase effect was highly significant, $F(1, 32) = 46.02, p < 0.001$, while the group effect and Phase × Group interaction were not significant. These results suggest that amphetamine produced a significant place preference that was generally unaffected by pretreatment with MK-801. As further confirmation, planned tests of simple main effects were conducted on the phase variable (preexposure vs. test) of each group; a significant ($p < 0.025$) increase in the amount of time spent on the drug-paired side from preexposure to test was observed for each group, indicating a place preference (Fig. 1A).

Although the groups treated with the higher doses of MK-801 (0.1 and 0.3 mg/kg) showed significant place conditioning, the effects appeared to be slightly attenuated relative to the saline control group (Fig. 1A). To determine if place conditioning was significantly reduced at these higher doses the data were expressed as the difference between time in the drug-paired environment during the test and preexposure for each of the four groups (data not shown), and a one-way ANOVA was conducted. The main effect of group was not significant

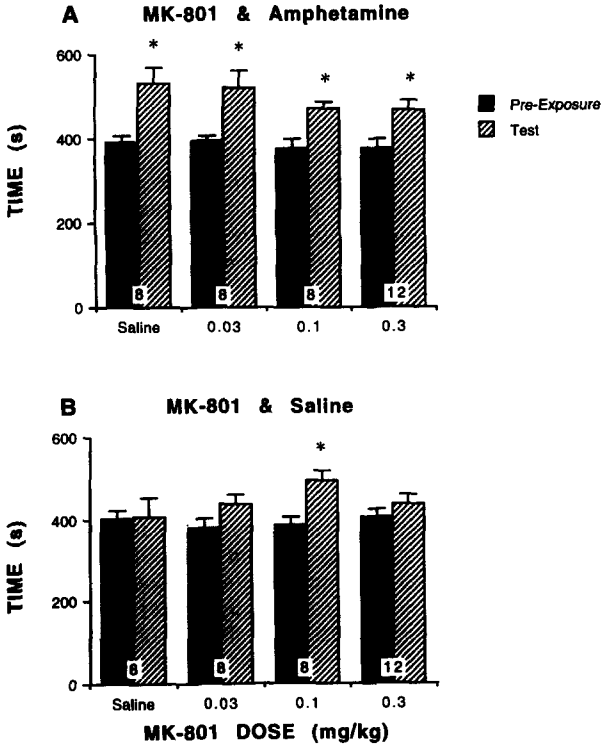

FIG. 1. Mean (± SEM) time spent on the drug-paired side during the preexposure and test sessions. (A) Rats treated with MK-801 (0, 0.03, 0.1, or 0.3 mg/kg SC) 15 min prior to amphetamine (2.0 mg/kg IP). (B) Rats treated with MK-801 (0, 0.03, 0.1, or 0.3 mg/kg SC) 15 min prior to saline (IP). Figures in the columns represent the number of rats in each group. *$p < 0.025$, differs significantly from preexposure (F test).

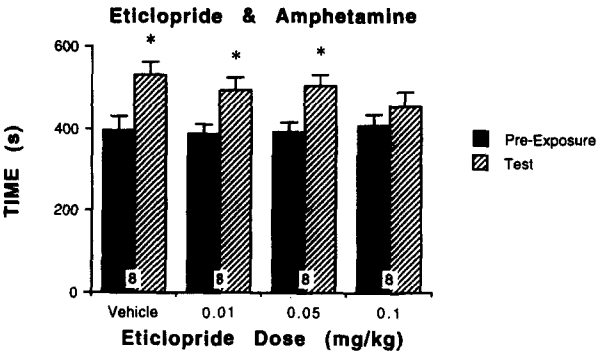

FIG. 2. Mean (± SEM) time spent on the drug-paired side during the preexposure and test sessions in rats pretreated with eticlopride (0, 0.01, 0.05, or 0.1 mg/kg SC) 15 min prior to amphetamine (2.0 mg/kg IP). Figures in the columns represent the number of rats in each group. *$p < 0.005$, differs significantly from preexposure (F test).

($p > 0.05$), and post hoc comparisons (Tukey) revealed no significant differences between groups.

The amount of time spent on the drug-paired side by rats treated with saline (instead of amphetamine) and pretreated with saline or MK-801 is shown in Fig. 1B. A two-way ANOVA with one repeated measure (phase) revealed a significant phase effect, $F(1, 32) = 8.15, p < 0.01$. The group effect and the Phase × Group interaction were not significant. Despite the nonsignificant interaction, planned tests of simple main effects revealed a significant phase effect only in the group pretreated with 0.1 mg/kg MK-801 ($p < 0.01$). The phase effect associated with the lowest dose of MK-801 approached significance ($P = 0.08$). Thus, only the intermediate dose of MK-801 resulted in significant place conditioning. However, when the data were expressed as the difference between time in the drug-paired environment during the test and preexposure, there were no significant differences between groups (Tukey, $p > 0.05$).

The effects of eticlopride on amphetamine-induced place conditioning are presented in Fig. 2; only the highest dose appeared to block the amphetamine place preference. A two-way ANOVA with one repeated measure (phase) revealed a significant phase effect, $F(1, 28) = 34, p < 0.001$. The group effect and the Phase × Group interaction were not significant. Following planned tests of simple main effects, all groups, with the exception of the 0.1 mg/kg eticlopride group, demonstrated a significant phase effect ($p < 0.01$). When the highest dose of eticlopride was tested alone (data not shown), neither a place preference nor aversion was observed (the mean amounts of time on the drug-paired side during the preexposure and test were 412 and 466 s, respectively). The phase effect was not significant following a one-way ANOVA ($p > 0.05$).

Locomotor Activity

During conditioning, MK-801 dose-dependently increased locomotor activity in both saline- and amphetamine-treated rats (Table 1). A two-way ANOVA (MK-801 Pretreatment × Amphetamine Treatment) was conducted on the activity scores for each conditioning day (days 1 and 3) separately. Only the main effect of MK-801 pretreatment was significant, $F(3, 64) = 22.45, p < 0.001$, and $F(3, 64) = 53.10, p < 0.001$, day 1 and day 3, respectively. Within either the saline

TABLE 1

THE EFFECTS OF MK-801 ON LOCOMOTOR ACTIVITY (±SEM) IN SALINE- OR AMPHETAMINE-TREATED RATS

	Day 1		Day 3	
	Saline	Amphetamine	Saline	Amphetamine
MK-801 (mg/kg) Pretreatment				
0	210 (18)	355 (33)*	224 (19)	419 (55)*
0.03	220 (15)	333 (25)*	213 (15)	416 (52)*
0.1	530 (72)	409 (56)	507 (132)	538 (59)
0.3	891 (173)†	1107 (133)†	1253 (136)†	1290 (96)†

*$p < 0.05$ (F test), within the same dose of MK-801, amphetamine-treated rats showed significantly greater activity than the saline-treated rats. †$p < 0.05$ (Tukey test), MK-801 significantly increased activity compared to vehicle (0 mg/kg) within either the saline- or amphetamine-treated rats.

or the amphetamine condition the highest dose of MK-801 caused a significant increase in activity compared to vehicle controls on day 1 and day 3 (Tukey, $p < 0.05$, Table 1). A significant amphetamine effect in the overall analysis was not obtained; however, individual planned comparisons (F test) conducted at each dose of MK-801 revealed a significant amphetamine-induced increase in activity in groups pretreated with 0 or 0.03 mg/kg MK-801 ($p < 0.005$) on either day 1 or day 3. On conditioning days 2 and 4, when rats received two saline injections, the activity scores between groups did not differ significantly (data not shown).

Eticlopride markedly reduced the heightened locomotor activity associated with amphetamine (Table 2). On each conditioning day, the main effect of eticlopride pretreatment was significant, $F(3, 28) = 17$, $p < 0.001$, and $F(3, 28) = 22$, $p < 0.001$, day 1 and day 3, respectively, and each dose of eticlopride differed significantly from the vehicle group (Tukey, Table 2).

DISCUSSION

In the present experiment, amphetamine produced a conditioned place preference that was not significantly altered by the noncompetitive NMDA antagonist MK-801. MK-801 alone produced marked increases in locomotor activity and a significant place preference at one dose, although this effect was not dose-related. This latter finding is consistent with a previous study (18) demonstrating a significant place conditioning effect with the same dose of MK-801; unfortunately, higher doses were not tested. It is also consistent with the rewarding properties of MK-801 demonstrated in behavioral paradigms other than place conditioning (3,7). In contrast to the effects of MK-801, the D_2 dopamine receptor antagonist eticlopride reduced amphetamine locomotor activity and blocked place conditioning at a dose that by itself did not result in a significant place preference or aversion. This is consistent with the well-known role of dopamine in amphetamine place conditioning (8,10).

TABLE 2

THE EFFECTS OF ETICLOPRIDE ON AMPHETAMINE-INDUCED LOCOMOTOR ACTIVITY (±SEM)

	Day 1	Day 3
Eticlopride (mg/kg) Pretreatment		
0	363 (51)	392 (52)
0.01	218 (14)*	250 (32)*
0.05	82 (11)†	91 (17)†
0.1	103 (32)†	53 (18)†

*$p < 0.05$, †$p < 0.01$ (Tukey test), significantly different from vehicle.

The failure of MK-801 to influence the rewarding properties of amphetamine is in agreement with previous studies showing no effect of NMDA antagonists on the acute locomotor-activating effects (including stereotypy) of amphetamine (5,14). These latter studies are difficult to interpret, however, since MK-801 itself produces dose-related increases in stereotyped sniffing and locomotion (9). In the present study, substantially larger increases in activity were observed with MK-801 relative to amphetamine. When these compounds were administered together there did not appear to be an additive effect on locomotion, but perhaps the amphetamine response was simply too small to detect beyond the larger stimulant effect of MK-801. Wolf and Khansa (33) also failed to show an additive effect of MK-801 and amphetamine despite similar increases in locomotor activity produced by each drug alone. It is possible, as they suggested, that the lack of additivity reflects either a common mechanism for increasing activity or a reduction of the amphetamine locomotor response by MK-801.

The place conditioning paradigm offers a distinct advantage over locomotor activity measures when assessing the interaction between amphetamine and MK-801: the rats are tested drug-free, and consequently, the confounds associated with drug-induced locomotor stimulant effects are minimized. Using this technique, no effect of MK-801 on amphetamine place conditioning was observed. One could argue that since MK-801 itself possesses rewarding properties, this may have obscured its ability to block the rewarding effects of amphetamine. This is an unlikely explanation for the present findings because MK-801 alone produced a significant place preference at only one intermediate dose; a higher dose of MK-801 that was ineffective in producing place conditioning was also ineffective in disrupting the amphetamine-induced place preference.

The failure of MK-801 to block the rewarding properties

of amphetamine is contrasted with the marked effects of MK-801 on the development of amphetamine-induced sensitization. Several studies have now shown that MK-801 and other NMDA antagonists potently block the development of sensitization to the locomotor-activating effects of amphetamine or cocaine (13,15,28,33). In addition, Schenk et al. (26) recently demonstrated that MK-801 prevents the development of sensitization to cocaine's reinforcing effects produced by amphetamine preexposure. These findings, in conjunction with the present results, suggest that the NMDA glutamate receptor plays a specific role in the long-lasting behavioral plasticity associated with chronic amphetamine treatment and does not play a role in the acute locomotor-activating or rewarding properties of amphetamine. The possibility, however, that other glutamate receptor subtypes are involved in the rewarding properties of amphetamine remains to be tested, especially since the quisqualate receptor antagonist GDEE microinjected into the nucleus accumbens decreased amphetamine-induced locomotor activity (25).

NMDA receptors have been shown to play a critical role in the acquisition of a number of learned behaviors. Blockade of NMDA receptors with both competitive and noncompetitive antagonists produces deficits in the acquisition and extinction of conditioned fear (4,21) as well as the acquisition of olfactory discrimination (27) and spatial learning (20,22,23). Also, the food preference that rats develop when a novel food is placed on the mouth region of an anesthetized conspecific is eliminated when rats are pretreated with low doses of MK-801 (24). It is somewhat surprising, therefore, that MK-801 failed to affect amphetamine place conditioning, a paradigm that involves learning and memory processes (31). However, as demonstrated by others, the NMDA receptor is not involved in all forms of learning. For example, intraventricular administration of AP5 fails to affect the acquisition of a visual discrimination task (23), and MK-801 fails to block experience-dependent facilitation of maternal responding; for example, dams that previously received one hour experience with pups demonstrate facilitated maternal responding relative to inexperienced dams, and this learning is not affected by MK-801 (20). It would seem, therefore, that the acquisition of amphetamine-induced place conditioning represents another learning paradigm apparently unaffected by MK-801 treatment.

ACKNOWLEDGEMENTS

Thanks are extended to Hilary Donovan for her excellent technical assistance and to Dr. J. V. Cassella for his helpful comments on an earlier draft of the manuscript.

REFERENCES

1. Bouyer, J. J.; Park, D. H.; Joh, T. H.; Pickel, V. M. Chemical and structural analysis of the relation between cortical inputs and tyrosine hydroxylase-containing terminals in the rat neostriatum. Brain Res. 302:267–276; 1984.
2. Clow, D. W.; Jhamandas, K. Characterization of L-glutamate action on the release of endogenous dopamine from the rat caudate-putamen. J. Pharmacol. Exp. Ther. 248:722–728; 1989.
3. Corbett, D. Possible abuse potential of the NMDA antagonist MK-801. Behav. Brain Res. 34:239–246; 1989.
4. Falls, W. A.; Miserendino, M. J. D.; Davis, M. Extinction of fear-potentiated startle: Blockade by infusion of an NMDA antagonist into the amygdala. J. Neurosci. 12:854–863; 1992.
5. Freed, W. J.; Cannon-Spoor, H. E. A possible role of AA2 excitatory amino acid receptors in the expression of stimulant drug effects. Psychopharmacology 101:456–464; 1990.
6. Freund, T. F.; Powell, J. F.; Smith, A. D. Tyrosine hydroxylase-immunoreactive boutons in synaptic contact with identified striatonigral neurons, with particular reference to dendritic spines. Neuroscience 13:1189–1216; 1984.
7. Herberg, L. J.; Rose, I. C. The effects of MK-801 and other antagonists of NMDA-type glutamate receptors on brain-stimulation reward. Psychopharmacology 99:87–90; 1989.
8. Hoffman, D. C. The use of place conditioning in studying the neuropharmacology of drug reinforcement. Brain Res. Bull. 23: 373–387; 1989.
9. Hoffman, D. C. Typical and atypical neuroleptics antagonize MK-801-induced locomotion and stereotypy in rats. J. Neural Transm. Gen. Sect. 89:1–10; 1992.
10. Hoffman, D. C.; Beninger, R. J. The effects of selective dopamine D_1 or D_2 receptor antagonists on the establishment of agonist-induced place conditioning in rats. Pharmacol. Biochem. Behav. 33:273–279; 1989.
11. Hogberg, T.; Ramsby, S.; Ogren, S. O.; Norinder, U. New selective dopamine D-2 antagonists as antipsychotic agents. Acta Pharmacol. Suec. 24:289–328; 1987.
12. Karler, R.; Calder, L. D. Excitatory amino acids and the actions of cocaine. Brain Res. 582:143–146; 1992.
13. Karler, R.; Calder, L. D.; Chaudhry, I. A.; Turkanis, S. A. Blockade of "reverse tolerance" to cocaine and amphetamine by MK-801. Life Sci. 45:599–606; 1989.
14. Karler, R.; Calder, L. D.; Turkanis, S. A. DNQX blockade of amphetamine behavioral sensitization. Brain Res. 552:295–300; 1991.
15. Karler, R.; Chaudhry, I. A.; Calder, L. D.; Turkanis, S. A. Amphetamine behavioral sensitization and the excitatory amino acids. Brain Res. 537:76–82; 1990.
16. Kelley, A. E.; Throne, L. C. NMDA receptors mediate the behavioral effects of amphetamine infused into the nucleus accumbens. Brain Res. Bull. 29:247–254; 1992.
17. Koob, G. F.; Goeders, N. E. Neuroanatomical substrates of drug self-administration. In: Liebman, J. M.; Cooper, S. J., eds. The neuropharmacological basis of reward. Oxford, UK: Oxford University Press; 1989:106–163.
18. 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.
19. Leviel, V.; Gobert, A.; Guibert, B. The glutamate-mediated release of dopamine in the rat striatum: Further characterization of the dual excitatory-inhibitory function. Neuroscience 39:305–312; 1990.
20. Malenfant, S. A.; O'Hearn, S.; Fleming, A. S. MK801, an NMDA antagonist, blocks acquisition of a spatial task but does not block maternal experience effects. Physiol. Behav. 49:1129–1137; 1991.
21. Miserendino, M. J. D.; Sananes, C. B.; Melia, K. R.; Davis, M. Blocking of acquisition but not expression of conditioned fear-potentiated startle by NMDA antagonists in the amygdala. Nature 345:716–718; 1990.
22. Morris, R. G. M. Synaptic plasticity and learning: Selective impairment of learning in rats and blockade of long-term potentiation in vivo by the N-methyl-D-aspartate receptor antagonist, AP5. J. Neurosci. 9:3040–3057; 1989.
23. Morris, R. G. M.; Anderson, E.; Lynch, G. S.; Baudry, M. Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP5. Nature 319:774–776; 1986.
24. Myhal, N.; Fleming, A. S. MK-801 effects on a learned food preference depends on dosage: Is it disruption of learning or a conditioned aversion? Psychobiology 18:428–434; 1990.
25. Pulvirenti, L.; Swerdlow, N. R.; Koob, G. F. Microinjection of

a glutamate antagonist into the nucleus accumbens reduces psychostimulant locomotion in rats. Neurosci. Lett. 103:213–218; 1989.
26. Schenk, S.; Valadez, A., McNamara, C.; House, D. T.; Higley, D.; Bankson, M. G.; Gibbs, S.; Horger, B. A. Development and expression of sensitization to cocaine's reinforcing properties: Role of NMDA receptors. Psychopharmacology 111:332–338; 1993.
27. Staubli, U.; Olivier, T.; DiLorenzo, M.; Lynch, G. Antagonism of NMDA receptors impairs acquisition but not retention of olfactory memory. Behav. Neurosci. 103:54–60; 1989.
28. Stewart, J.; Druhan, J. P. Development of both conditioning and sensitization of the behavioral activating effects of amphetamine is blocked by the noncompetitive NMDA receptor antagonist, MK-801. Psychopharmacology 110:125–132; 1993.
29. Totterdell, S.; Smith, A. D. Convergence of hippocampal and DA-ergic input onto identified neurons in the nucleus accumbens of the rat. J. Chem. Neuroanat. 2:285–298; 1989.
30. Werling, L. L.; Jacocks, H.M., III; McMahon, P. N. Regulation of [^{3}H] dopamine release from guinea pig striatum by NMDA receptor/channel activators and inhibitors. J. Pharmacol. Exp. Ther. 255:40–45; 1990.
31. White, N. M.; Carr, G. D. The conditioned place preference is affected by two independent reinforcement processes. Pharmacol. Biochem. Behav. 23:37–42; 1985.
32. Wise, R. A.; Hoffman, D. C. Localization of drug reward mechanisms by intracranial injections. Synapse 10:247–263; 1992.
33. 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.