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Interactions Between *N*-Methyl-D-Aspartate Receptor Antagonists and the Discriminative Stimulus Effects of Morphine in Rats

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BESPALOV, A. Y., P. M. BEARDSLEY AND R. L. BALSTER. *Interactions between* N*-methyl-D-aspartate receptor antagonists and the discriminative stimulus effects of morphine in rats.* PHARMACOL BIOCHEM BEHAV **60**(2) 507–517, 1998.—NMDA receptor antagonists have previously been reported to alter some pharmacological and behavioral effects of acute and chronic opioid administration. The present study assessed the interactions of NMDA antagonists with the discriminative stimulus properties of morphine. Adult male Long–Evans rats were trained to discriminate 3.2 mg/kg of SC morphine from water under a two-lever fixed-ratio 10 schedule of food reinforcement. During test sessions, IP injections of the noncompetitive NMDA receptor antagonist dizocilpine (0.03–0.2 mg/kg), the competitive antagonists NPC 17742 (1–16 mg/kg), and SDZ 220-581 (0.1–3 mg/kg), the polyamine site antagonist eliprodil (3–17.3 mg/kg), the glycine-site partial agonist (+)-HA-966 (3–56 mg/kg), and the nonselective glutamate antagonist kynurenic acid (30–150 mg/kg) were coadministered with SC morphine (1–3.2 mg/kg; interaction tests) or water (generalization tests). In generalization tests, none of the compounds completely substituted for morphine. Concurrent administration of morphine and NMDA antagonists did not greatly alter the discriminative stimulus properties of morphine. Various doses of NPC 17742, SDZ 220-581, or (+)-HA-966 somewhat increased levels of morphine-appropriate lever selection, whereas some attenuation of morphine-lever selection was obtained when morphine was coadministered with eliprodil. These results show that NMDA antagonists have minimal interactions with the discriminative stimulus effects of morphine. © 1998 Elsevier Science Inc.

Morphine NMDA antagonists NPC17742 Dizocilpine SDZ220-581 Eliprodil HA-966 Kynurenic acid Drug discrimination

RECENT findings suggest that pharmacological activity of opiates can be modulated by drugs affecting *N*-methyl-D-aspartate (NMDA) receptor-based neurotransmission. For example, combined intrathecal administration of morphine and NMDA receptor antagonists results in augmentation of morphine' s analgesic potency (11) and inhibition of morphine-induced clonic seizure-like excitatory effects (38). Intracerebral and systemic administration of NMDA receptor antagonists was also reported to significantly affect morphine analgesia (1,30,35,37,56). Recently, NMDA receptor antagonists were shown to block morphine-induced conditioned place preference in rats (62). The nonselective endogenous antagonist of excitatory amino acid (EAA) receptors kynurenic acid has also been shown to modulate morphine's effects in conditioned place preference and electrical brain stimulation paradigms (6) and impaired the acquisition of intravenous morphine self-administration in rats (7). Combined administration of morphine and NMDA antagonists has been reported to prevent the development of tolerance to the analgesic effects of morphine (26,41,59,61), sensitization to its psychostimulant properties (29), and physical dependence upon it (57,61) while potentiating morphine-induced catalepsy and lethality (60). Moreover, there was an observation of acute interactive effects of the noncompetitive NMDA receptor antagonist dizocilpine and morphine on cortical EEG and EEG power spectra in rats (24).

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In this article we will be describing a study of the interactions between NMDA antagonists and the discriminative stimulus effects of morphine. Because of the ability of NMDA antagonists to enhance opioid analgesia and attenuate tolerance development, there is clinical interest in combining these classes of drugs for treatment of chronic pain (1,11). For this reason it is important to know if the subjective effects of opiates, as modeled by morphine discrimination, are also enhanced.

There have been several reports on the discriminative stimulus effects of PCP-like NMDA receptor antagonists in morphine- and fentanyl-trained rats and pigeons. These studies have found that PCP and PCP-like drugs such as dizocilpine and ketamine partially generalized from morphine or fentanyl (25,31,33,46). However, these intermediate levels of drug lever selection were attributed to the performance deficits resulting from the NMDA antagonist administration (33). Studies of the morphine-like discriminative stimulus effects of other subtypes of NMDA antagonists have not been reported. There has also been a report that PCP-type drugs decreased drug-lever selection produced by the training dose of fentanyl (33). In the present report we describe an assessment of the ability of a wider range of NMDA antagonists to produce morphine-like discriminative stimulus effects or to alter morphine's stimulus effects.

The NMDA receptor is the best characterized of the EAA receptor subtypes found in the mammalian central nervous system (42). Direct agonists and competitive antagonists bind directly to a transmitter-recognition site on the receptor complex. There are additional pharmacologically distinct sites at which activity produces alterations in NMDA neurotransmission, including (a) a channel site for the noncompetitive PCP-like antagonists; (b) a strychnine-insensitive glycine coactivator site; and (c) a polyamine binding site. For the present study, NMDA antagonists that interact at these sites were tested along with a nonselective glutamate antagonist kynurenic acid (KYNA). The competitive antagonists tested were NPC 17742 (19) and SDZ 220-581 (43,63), selected because they are among the most potent, systemically active compounds available of this type. Dizocilpine was selected as a representative PCP-like noncompetitive antagonist (69) that was repeatedly demonstrated to block the development of tolerance to morphine analgesia (26). (+)-HA-966, a glycine site agonist/antagonist, and eliprodil, a possible polyamine-site antagonist, whose behavioral effects differ substantially from the competitive and the PCP-site noncompetitive antagonists (2,54,55), were also tested.

METHOD

Subjects

Thirty-eight adult, experimentally naive, male, Long–Evans hooded rats (Harlan, Dublin, VA) were used. Animals were housed individually in suspended wire cages with water available ad lib. Food (Purina Rodent Chow) consumption was restricted to 10–12 g/day given after behavioral testing and on weekends to maintain a constant body weight (300–360 g). All experiments were conducted during the light period of a 12 L:12 D cycle (0800–2000 h). Experiments were approved by the Institutional Animal Care and Use Committee of Virginia Commonwealth University and were performed in accordance with the recommendations and policies of the U.S. National Institutes of Health Guidelines for the Use of Animals.

Apparatus

Twelve standard two-lever operant conditioning chambers (BRS/LVE, Beltsville, MD) were connected to a microcomputer through an interface and controlled by MED-PC software (MED Associates, Inc., East Fairfield, VT). Each chamber was equipped with a white house light centered above the levers and a food dispenser that delivered 45-mg food pellets (Noyes Formula A, P. J. Noyes Company, Inc., Lancaster, NH).

Procedure

Initial training. Rats were initially trained to lever press for food pellet delivery according to a fixed ratio 1 (FR1) schedule of reinforcement using the lever that eventually would become the water-designated lever. All training and subsequent acquisition sessions were conducted daily (Monday–Friday). After rats had acquired the lever-press response (1–4 days), the FR value was gradually increased to 10. Then the active lever was switched to the opposite side and the FR value was reduced to FR1. As soon as rats showed evidence of responding on this lever, the FR value was rapidly increased to FR10.

Discrimination training. All drug discrimination training sessions were divided into two or three consecutive discrete trials, each consisting of a 30-min timeout (TO) period during which injections could be given followed by a 5-min food reinforcement component during which lever pressing was reinforced under the FR10 schedule of pellet delivery. At the start of each trial, rats were administered a sham injection (i.e., standard injection procedure that did not result in needle puncture and fluid delivery) or injected subcutaneously with either 3.2 mg/kg of morphine or sterile water, returned to their home cages after the injection, and then 30 min later were placed into the operant chambers for 5 min. The house light was illuminated at the start of each trial and extinguished at the end of the trial. Training sessions varied in the sequence of the trials: type A, sham–water–morphine; type B, sham–morphine; type C, water–morphine. Animals experienced all three types of sessions in an alternating sequence predetermined for each 2-month block of training and testing. Half of the rats were trained to press the right lever for food reinforcement after receiving morphine and the left lever following water or sham injection; the reverse pairing was used with the remaining rats. Incorrect responses reset the FR requirement on the correct lever.

Acquisition training proceeded until the following criteria were met on at least 8 out of 10 consecutive training sessions: 1) the first completed FR (FFR) had to occur on the correct lever; and 2) the percentage of all lever presses emitted on the correct lever was more than 90% during these sessions. After the criteria were met, the rats were given test days. Tests (single trial, both levers active) were conducted on Tuesdays and Fridays provided that the following criteria were met: 1) during the most recent training session of each type (A, B, and C) the FFR was correct for all trials; 2) overall 90% or greater correct-lever responding on each of these sessions; and 3) overall response rate was greater than 0.4 lever presses per second. During test sessions 10 consecutive responses on either lever produced a pellet delivery.

Each rat was repeatedly tested with either water or the training dose of morphine (3.2 mg/kg) until four consecutive test sessions were completed that satisfied criteria #2 and #3 described above.

Morphine dose–response determination and naltrexone antagonism. Morphine dose–response functions were initially obtained when morphine (0, 1.0, 1.7, and 3.2 mg/kg) was in-

jected by itself and subsequently were reobtained when morphine was coadministered with the vehicles (IP) for various NMDA receptor antagonists. These tests were conducted in a random order within the period of drug combination testing (see below). As a control, 11 randomly selected rats were tested with the combination of the training dose of morphine and 0.3 mg/kg of naltrexone (SC, 15 min preinjection time) to estimate reversibility and to affirm the opiate-receptor mediation of the stimulus control exerted by morphine.

Stimulus generalization testing. Stimulus generalization tests were conducted with the following drugs: NPC 17742 (vehicle, 2–16 mg/kg; preinjection time 60 min), SDZ 220-581 (vehicle, 0.1–3 mg/kg; preinjection time 60 min), dizocilpine (vehicle, 0.03–0.2 mg/kg; preinjection time 15 min), eliprodil (vehicle, 3–17.3 mg/kg; preinjection time 30 min), (+)-HA-966 (vehicle, 3–56 mg/kg; preinjection time 30 min), and kynurenic acid (vehicle, 30–150 mg/kg; preinjection time 20 min). During each test there were two injections given; one SC with sterile water (preinjection time 30 min) and one IP with the test drug or its vehicle (preinjection time as described above). Test sessions consisted of a single 5-min trial. Control tests with the training dose of morphine and with sterile water were conducted at intervals throughout the study; these tests consisted of two trials, with IP vehicle as the second injection. Each subject was tested with no more than three different NMDA antagonists.

Drug combination testing. Each of the drugs tested alone were also tested in combination with each of three doses of morphine. Test sessions consisted of a single trial. During each test two injections were given, one SC with morphine (1, 1.7, or 3.2 mg/kg; 30-min preinjection time), and one IP with the test drug or its vehicle (drugs, vehicles, and preinjection times are listed above). Three to four doses of each test drug were evaluated (see figures). Drugs and doses were tested in random order.

Data Analysis

The percentage of responses on the morphine-designated lever (MLR) and response rate (responses/s; RR) were calculated for each test session, with means calculated for the group data. Data from rats emitting less than 0.03 responses/s were omitted from calculations of group % morphine lever responses but were included in group response rate determinations. The morphine doses estimated to produce 50% morphine-lever responding (ED_{50}) for morphine alone and in combination with each dose of the NMDA antagonists were calculated based upon the log-linear analysis of the dose–response curves (SAS-STAT, release 6.11, SAS Institute, Cary, NC). The lever on which the first FR was completed was also recorded and used to compare individual subject results.

Drug discrimination results (percentage morphine-lever responding) were subjected to a two-way analysis of variance (ANOVA) with repeated measures on both factors (dose of morphine and dose of NMDA antagonist). Analysis of the descriptive statistics produced by the SAS-STAT UNIVARIATE procedure demonstrated that some of the data were not distributed normally (Wilks-Shapiro's test). The distribution-free two-factorial analysis of variance (ANOVA) was conducted using a combination of the RANK and General Linear Model (GLM) procedures. Briefly, data were ranked and the ranks were later subjected to ANOVA (GLM procedure for unbalanced design with unequal group sizes). Because each subject was measured under all levels of morphine (0, 1.0, 1.7, and 3.2 mg/kg) and NMDA antagonist doses, the present experiment was treated as a subject by morphine dose by NMDA antagonist dose factorial design. Group comparisons were performed using a post hoc Wilcoxon's rank-sum test (only where ANOVA revealed significant effects). Null hypothesis was rejected at the $p < 0.05$ level.

Drugs

The drugs used were as follows: morphine sulfate and naltrexone hydrochloride (National Institute on Drug Abuse, Rockville, MD); NPC 17742 ((2R,4R,5S)-2-amino-4,5-(1,2-cyclohexyl)-7-phosphonoheptanoic acid, Nova Pharmaceuticals Corporation, Baltimore, MD); and SDZ 220-581 (α-amino-2′-chloro-5-(phosphonomethyl) (1,1′-biphenyl)-3-propanoic acid, Sandoz, Basel, Switzerland); dizocilpine maleate (MK-801) and (+)-HA-966 (R(+)-3-amino-1-hydroxy-2-pyrrolidone, both from Research Biochemicals International, Natick, MA); eliprodil (Synthelabo Recherche, Bagneaux, France); and kynurenic acid (Sigma Chemical Company, St. Louis, MO). Morphine and (+)-HA-966 were prepared in sterile water, dizocilpine, and naltrexone in physiological saline, eliprodil in 0.1% Tween-80 in saline, NPC 17742 and SDZ 220-581 in equimolar NaOH in saline, and kynurenic

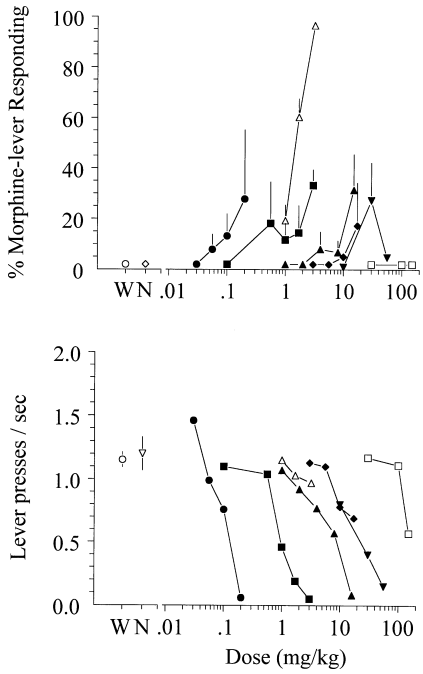

FIG. 1. Mean percentage (S.E.M.) of morphine-lever responding (upper panel) and mean response rates (lower panel) following morphine (1–3.2 mg/kg; △), NPC 17742 (1–16 mg/kg; ▲), SDZ 220–581 (0.1–3 mg/kg; ■), dizocilpine (0.03–0.2 mg/kg; ●), (+)-HA-966 (3–56 mg/kg; ▼), eliprodil (3–17.3 mg/kg; ◆), and KYNA (30–150 mg/kg; □) administration in rats trained to discriminate 3.2 mg/kg of morphine from water ('W'). Points above 'N' represent tests performed after combined administration of training dose of morphine and 0.3 mg/kg of naltrexone ($n = 11$). Each point is based on observations made in 8 (NPC 17742; $n = 5$ for 1 mg/kg and $n = 6$ for 16 mg/kg for both MLR and RR data; $n = 4$ for 16 mg/kg for MLR), 6 (SDZ 220–581; $n = 9$ for 1 mg/kg, $n = 5$ for 3 mg/kg for RR, $n = 3$ for 3 mg/kg for MLR), 7 ((+)-HA-966; $n = 5$ for 56 mg/kg for MLR), 7 (dizocilpine; $n = 6$ for 0.1 mg/kg and $n = 2$ for 0.2 mg/kg), 6 (eliprodil; $n = 7$ for 17.3 mg/kg), or 5 (KYNA) rats. For the sake of clarity standard errors are not shown for all data points.

acid in 10% Tween-80 in saline. Morphine and its vehicle were injected subcutaneously while all other drugs and their vehicles were administered intraperitoneally. All injections were delivered in a volume of 1 ml/kg. Dosages are based upon the forms of the drugs listed above.

RESULTS

Acquisition Results

All 38 rats acquired the morphine–water discrimination in 27 days (or 68 trials). Control tests with the training dose of morphine and water produced group averages of more than 95% correct lever responding on every occasion on which the subjects were tested.

Morphine Dose–Response Testing

Morphine administration resulted in a dose-dependent increase in morphine-lever selection (Fig. 1) with an ED_{50} of 1.5 mg/kg (CI: 1.2–1.9 mg/kg). Dose-dependent decreases in response rate were obtained at doses above the 3.2 mg/kg training dose. The morphine dose–effect function was also evaluated when morphine (1–3.2 mg/kg) was coadministered with vehicles for the various NMDA antagonists (Figs. 2–7). These tests yielded morphine dose-related increases in percentages of morphine-lever responding with ED_{50}s shown in Table 1.

The stimulus effects of the training dose of morphine were completely blocked in all experimental subjects by pretreatment with 0.3 mg/kg of naltrexone (Fig. 1). Administration of naltrexone alone did not produce morphine-like responding and did not affect response rate (data not shown).

Stimulus Generalization Testing

None of the NMDA antagonists produced >50% levels of morphine-lever responding. Dose–effect curves for each test drug are depicted in Fig. 1. Results of stimulus generalization testing can also be seen in Figs. 2–7 (data points above "W" in each figure). Dose-dependent increases in morphine-lever selection were produced by all drugs except for kynurenic acid (zero-levels of morphine-lever responding) and (+)-HA-966 (absence of dose dependency). Even after administration of the NMDA antagonist dose that produced the highest average level of morphine-lever responding, the first FR was usually completed on the water-designated lever: two out of two rats at 16 mg/kg of NPC 17742, two out of two rats at 3.0 mg/kg of SDZ 220-581, six out seven rats at 30 mg/kg of (+)-HA-966, one out of two rats at 17.3 mg/kg of eliprodil, six out of seven rats at 0.2 mg/kg of dizocilpine, five out of five rats at 30 mg/kg of KYNA (the actual group size was higher for each of the doses mentioned but not all rats completed 10 consecutive lever presses on either lever). Rates of responding were dose dependently decreased by all tested drugs (Fig. 1).

Drug Combination Testing

When morphine was tested in combination with each of the NMDA antagonists and their vehicles morphine dose continued to be a significant determinant of morphine-lever selection in all treatment groups: NPC 17742, $F(3, 172) = 18.3$; SDZ 220-581, $F(3, 145) = 24.5$; (+)-HA-966, $F(3, 141) = 41.9$; eliprodil, $F(3, 140) = 15.7$; dizocilpine, $F(3, 112) = 47.2$; kynurenic acid, $F(3, 82) = 169.3$ ($p < 0.05$ for each drug). Although some of the NMDA antagonists slightly altered the discriminative stimulus and response rate effects of morphine, the more general conclusion is that these interactive effects were modest and differed in direction and magnitude among the individual test drugs.

NPC 17742 and SDZ 220-581. Administration of these two competitive NMDA antagonists in combination with morphine resulted in a slight enhancement of morphine-lever selection (Figs. 2 and 3, upper panels). Both drugs tended to shift the morphine dose–effect curve to the left when tested in combination with the lower doses of morphine (1 and 1.7 mg/kg) that did not produce full substitution when tested alone. For NPC 17742, this enhancement of morphine occurred with

TABLE 1

POTENCY OF MORPHINE FOR DISCRIMINATIVE STIMULUS EFFECTS IN RATS TREATED WITH COMBINATIONS OF MORPHINE AND NMDA RECEPTOR ANTAGONISTS

NPC 17742	Dose (mg/kg)	Vehicle	1	2	4	8	16
	ED_{50}	1.5	1.7	0.6	0.9	0.9	1.0
	CL*	0.9–2.5	0.8–3.8	0.02–11.2	0.2–4.4	0.2–5.1	0.02–9.9
SDZ 220-581	Dose (mg/kg)	Vehicle	0.1	0.56	1		
	ED_{50}	1.5	1.0	0.7	0.9		
	CL*	0.9–2.4	0.3–3.5	0.06–8.9	0.1–8.3		
(+)-HA-966	Dose (mg/kg)	Vehicle	3	10	30	56	
	ED_{50}	1.8	1.6	0.9	1.0	NS†	
	CL*	1.4–2.2	0.9–2.6	0.2–4.1	0.2–5.7		
Dizocilpine	Dose (mg/kg)	Vehicle	0.03	0.056	0.1		
	ED_{50}	1.6	1.8	1.7	1.9		
	CL*	1.2–2.1	1.4–2.3	1.0–3.0	0.8–4.6		
Eliprodil	Dose (mg/kg)	Vehicle	3	5.6	10	17.3	
	ED_{50}	1.5	2.1	1.8	2.2	2.9	
	CL*	1.0–2.3	0.5–8.8	0.9–3.3	1.1–4.2	1.5–5.6	
Kynurenic acid	Dose (mg/kg)	Vehicle	30	100	150		
	ED_{50}	1.8	1.9	2.1	2.6		
	CL*	1.4–2.5	1.5–2.5	1.8–2.5	1.6–4.1		

*95% confidence limits.

†ED_{50} value is not significant (Student's *t*-test, $p > 0.05$).

the doses that produced little of no morphine-lever responding when given alone. There was some tendency for the highest dose of NPC 17742 to lower the level of morphine-lever responding produced by 3.2 mg/kg morphine, but this occurred at a dose of NPC 17742 that markedly decreased rates of responding as well. Similarly, with SDZ 220-581 some enhancement of morphine's discriminative stimulus effects occurred at doses of SDZ 220-581 that had minimal morphine-like effects by themselves. However, both NPC 17742 and SDZ 220-581 were found to lower, nonsignificantly, morphine's ED50 values (Table 1).

Support for the enhancement of morphine's discriminative stimulus effects by the competitive NMDA antagonists comes from the analysis of variance results. NPC 17742 and SDZ 220-581 both significantly increased morphine-lever selection, $F(5, 172) = 3.17$, $p = 0.017$; $F(5, 145) = 2.78$, $p = 0.034$, respectively. On the other hand, analysis of shifts of individual curves (fixed dose of NPC 17742 or SDZ 220-581 vs. vehicle) did not show significant effects of any fixed dose of NPC

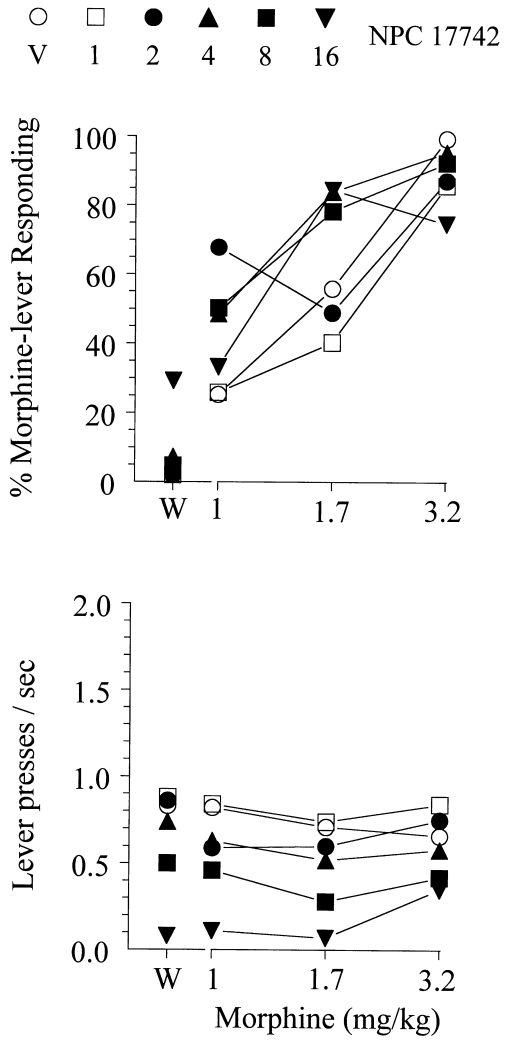

FIG. 2. Mean percentage of morphine-lever responding (upper panel) and response rates (lower panel) following the administration of NPC 17742 alone (vehicle and 1–16 mg/kg) and in combination with morphine (1.0–3.2 mg/kg) in rats trained to discriminate 3.2 mg/kg of morphine from water (W). Points above W represent tests performed after combined administration of water and the NPC 17742 doses. Each point is based on observations made in 8 rats (1.0 mg/kg of morphine: $n = 3$ for 16 mg/kg of NPC 17742 for MLR; 1.7 mg/kg of morphine: $n = 6$ for 8 mg/kg and $n = 4$ for 16 mg/kg of NPC 17742 for MLR; 3.2 mg/kg of morphine: $n = 7$ for 16 mg/kg of NPC 17742 for MLR).

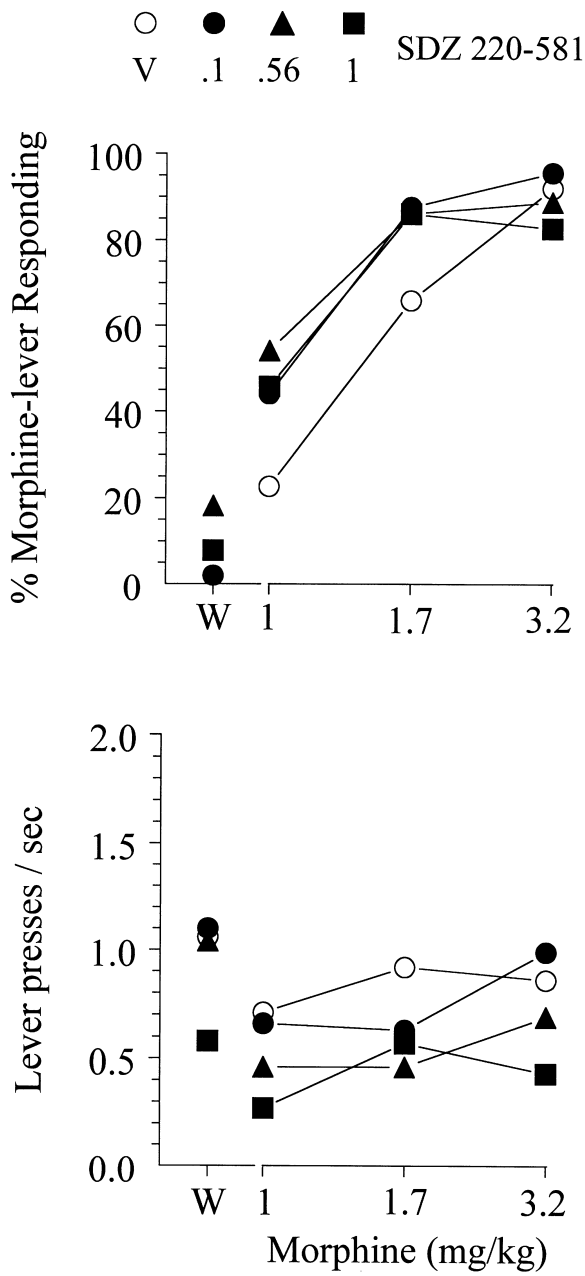

FIG. 3. Mean percentage of morphine-lever responding (upper panel) and response rates (lower panel) following the administration of SDZ 220–581 alone (vehicle and 0.1–1 mg/kg) and in combination with morphine (1.0–3.2 mg/kg) in rats trained to discriminate 3.2 mg/kg of morphine from water (W). Points above W represent tests performed after combined administration of water and the SDZ 220–581 doses. Each point is based on observations made in 9 rats (1.7 and 3.2 mg/kg of morphine: = 8 for 1 mg/kg of SDZ 220–581 for MLR).

17742. In the case of SDZ 220-581, pretreatment with 0.56 mg/kg of SDZ 220-581 was found to significantly elevate morphine-lever responding, $F(1, 57) = 6.41$, $p = 0.03$)

The doses of morphine tested in combination with NPC 17742 and SDZ 220-581 did not alter rates of responding when given in combination with the vehicles for these test drugs (Figs. 2 and 3, lower panels). The response rates after combination treatments with morphine and the competitive antagonists were lower than for morphine plus vehicle [NPC 17742: $F(5, 232) = 30.43$, $p = 0.0001$; SDZ 220-581: $F(5, 188) = 31.55$, $p = 0.0001$], but were not greatly different from the response rates produced by the antagonists alone. Stated another way, the dose-dependent decreases in rates of responding produced by NPC 17742 and SDZ 220-581 were neither antagonized nor enhanced by morphine.

(+)-HA-966. Similar to NPC 17742 and SDZ 220-581, treatment with the glycine-site partial agonist (+)-HA-966 also shifted the morphine dose–effect functions somewhat to the left (Fig. 4, upper panel). As with the competitive antagonists, this enhancement was only seen with the doses of morphine that did not produce full substitution. At 3.2 mg/kg morphine, which produced 100% morphine-lever responding when tested alone, (+)-HA-966 produced a dose-dependent decrease in morphine-lever responding associated with response rate decreases. The enhancement of morphine's discriminative stimulus effects occurred at doses of (+)-HA-966 that did not produce morphine-lever responding when tested alone, showing that the enhancement was not from additive effects. The ability of (+)-HA-966 to reliably modify the discriminative stimulus effects is supported by the ANOVA results that found a significant main effect of (+)-HA-966 dose, $F(4, 141) = 3.67$, $p = 0.016$, and interaction between the (+)-HA-966 dose and morphine dose factors, $F(12, 141) = 2.22$, $p = 0.02$. The significant interaction effect is the result of the enhancement at low doses of morphine and the attenuation at the high dose. Morphine-lever responding in rats treated with 30 mg/kg of (+)-HA-966 (filled squares; Fig. 4) was significantly higher than morphine tested in combination with vehicle [open circles; Fig. 4; $F(1, 52) = 7.14$, $p = 0.014$].

(+)-HA-966 in combination with morphine did not produce effects on rates of responding that were different from what was observed when (+)-HA-966 was given alone. There was some tendency for the highest dose of morphine to further decrease the rates of responding already lowered by 30 and 56 mg/kg (+)-HA-966.

Eliprodil. In contrast to the results with NPC 17742, SDZ 220-581, and (+)-HA-966, eliprodil (3-17.3 mg/kg) produced dose-related rightward shifts in morphine dose–effect functions (Fig. 5, upper panel). Although the overall ANOVA did not reveal a statistically significant effect of antagonist dose in subjects treated concurrently with morphine and eliprodil, $F(4, 140) = 1.46$, $p = 0.241$, a significant interaction between eliprodil dose and morphine dose factors was observed, $F(12, 140) = 1.98$, $p = 0.049$, reflecting that the already low levels of morphine-lever responding after 1 mg/kg morphine were not further reduced by eliprodil. Eliprodil decreased the moderate to high levels of morphine-lever selection produced by the two higher doses of morphine when given in combination with vehicle. This decrease induced by eliprodil was statistically significant at the 1.7 mg/kg dose of morphine, $F(4, 34) = 3.17$, $p = 0.0316$. The highest dose of eliprodil (17.3 mg/kg) was the only individual dose producing significant alterations in morphine-lever responding, $F(1, 60) = 5.42$, $p = 0.049$.

Inspection of individual subject data also provides evidence that eliprodil altered morphine-lever selection in rats cotreated with 1.7 and 3.2 mg/kg of morphine plus eliprodil. Thus, four out of seven rats completed their first FR on the morphine-appropriate lever after being treated with 1.7 mg/kg of morphine combined with vehicle, while only one out of seven rats selected the morphine lever when morphine was combined with an eliprodil dose of 10 or 17.3 mg/kg. Morphine lever selection occurred

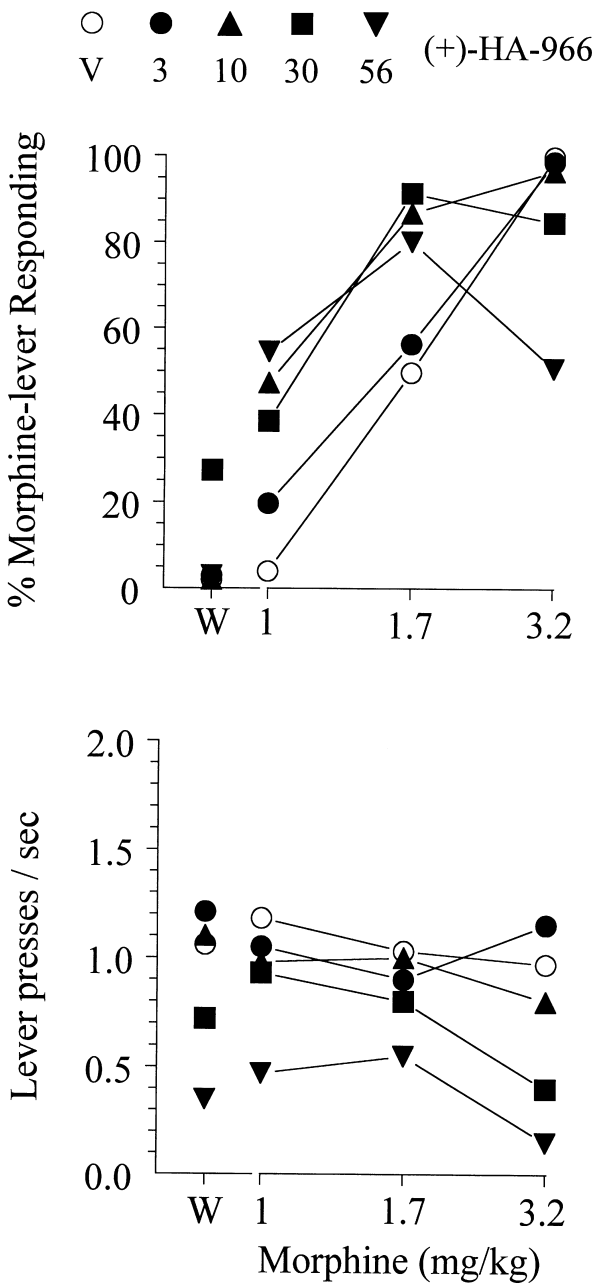

FIG. 4. Mean percentage of morphine-lever responding (upper panel) and response rates (lower panel) following the administration of (+)-HA-966 alone (vehicle and 3–56 mg/kg) and in combination with morphine (1.0–3.2 mg/kg) in rats trained to discriminate 3.2 mg/kg of morphine from water (W). Points above W represent tests performed after combined administration of water and the (+)-HA-966 doses. Each point is based on observations made in 8 rats (1.0 and 1.7 mg/kg of morphine; $n = 7$ for 56 mg/kg of (+)-HA-966 for MLR), 7 (3.2 mg/kg of morphine; $n = 3$ for 56 mg/kg of (+)-HA-966 for MLR).

after the administration of the training dose of morphine (3.2 mg/kg) in all (n = 8) subjects when it was combined with eliprodil's vehicle, while only three out five rats completed the first FR on the morphine lever when treated with a combination of 3.2 mg/kg of morphine and 17.3 mg/kg of eliprodil. Response rates were minimally altered by morphine and eliprodil and by any of the combinations (Fig. 5, lower panel). The two highest doses of eliprodil (10 and 17.3 mg/kg) when given alone produced modest response rate decreases that were neither antagonized nor enhanced by morphine.

Dizocilpine and kynurenic acid. Both dizocilpine and kynurenic acid produced minimal shifts in the morphine dose–

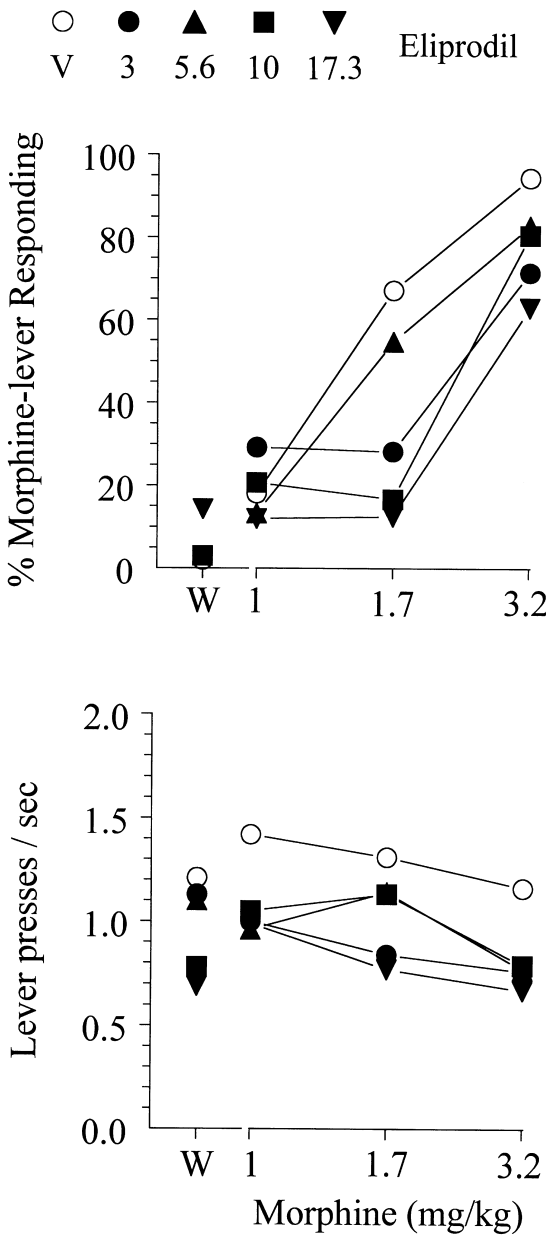

FIG. 5. Mean percentage of morphine-lever responding (upper panel) and response rates (lower panel) following the administration of eliprodil alone (vehicle and 3–17.3 mg/kg) and in combination with morphine (1.0–3.2 mg/kg) in rats trained to discriminate 3.2 mg/kg of morphine from water (W). Points above W represent tests performed after combined administration of water and the eliprodil doses. Each point is based on observations made in 6 rats (3.2 mg/kg of morphine; n = 7 for 17.3 mg/kg of eliprodil), 8 (1.0 mg/kg of morphine; n = 7 for 5.6 mg/kg of eliprodil for morphine-lever responding), 7 (1.7 mg/kg of morphine).

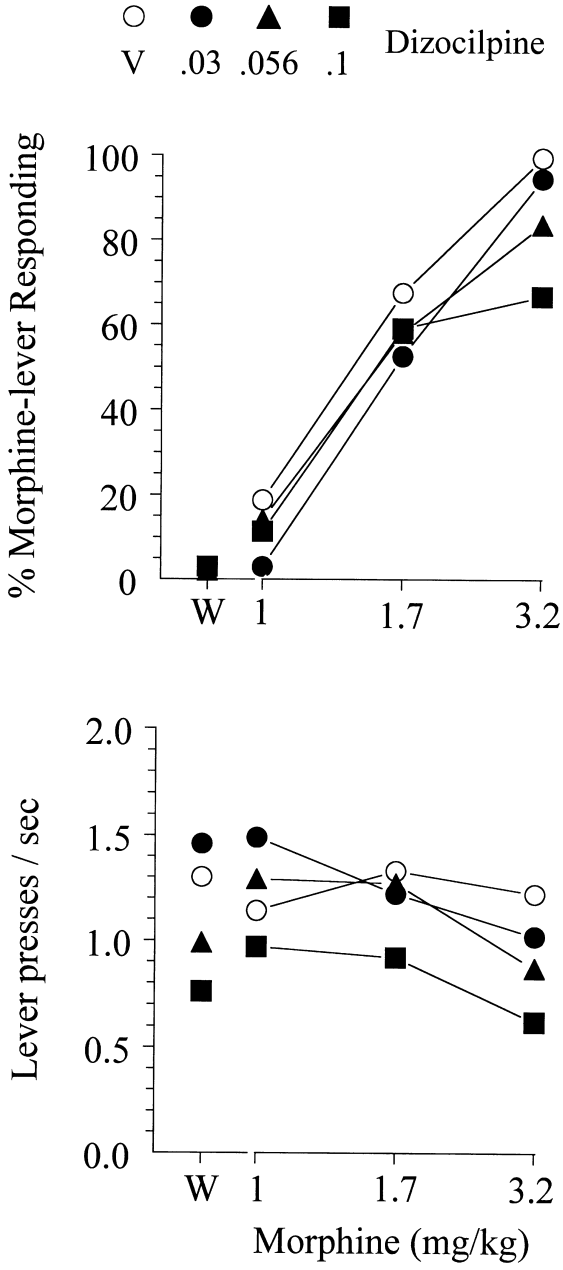

FIG. 6. Mean percentage of morphine-lever responding (upper panel) and response rates (lower panel) following the administration of dizocilpine alone (vehicle and 0.03–0.1 mg/kg) and in combination with morphine (1.0–3.2 mg/kg) in rats trained to discriminate 3.2 mg/kg of morphine from water (W). Points above W represent tests performed after combined administration of water and the dizocilpine doses. Each point is based on observations made in 7 rats (1.0 mg/kg of morphine), 8 (1.7 mg/kg of morphine; n = 7 for 0.03 mg/kg and 0.1 mg/kg of dizocilpine for MLR), 7 (3.2 mg/kg of morphine; n = 5 for 0.1 mg/kg of dizocilpine for MLR).

effect curves (Figs. 6 and 7, upper panels). The effects of either drug did not reach statistical significance at any morphine dose nor did the overall analysis of variance yield a significant effect of antagonist treatment for morphine combined with dizocilpine or kynurenic acid, $F(3, 112) = 0.36$, $p = 0.782$, $F(3, 82) = 1.23$, $p = 0.329$, respectively. Data are not shown for the results at 0.2 mg/kg of dizocilpine due to profound response rate suppression and behavioral toxicity (e.g., ataxia, motor discoordination) exerted by this dose alone. Interactions were not observed between the response rate effects of morphine and either dizocilpine or kynurenic acid. The response rate decreases associated with both of these antagonists were neither antagonized nor enhanced by morphine.

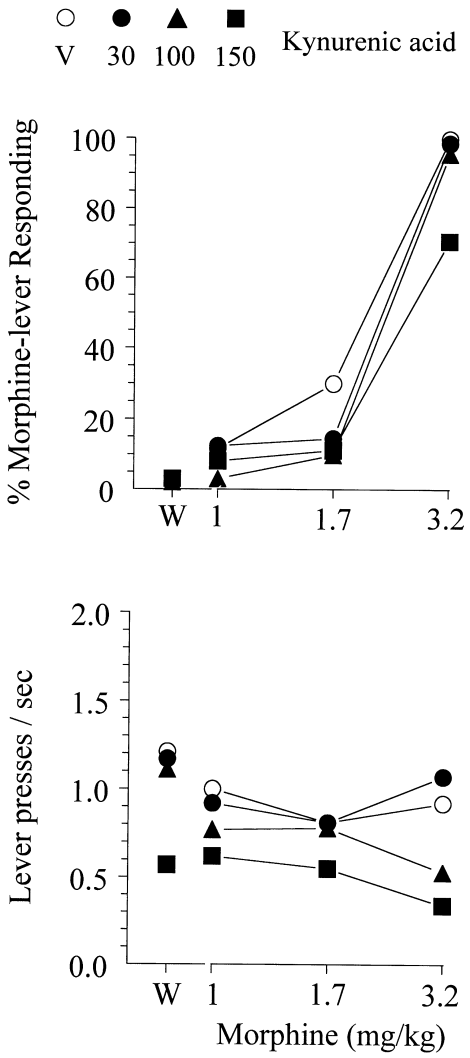

FIG. 7. Mean percentage of morphine-lever responding (upper panel) and response rates (lower panel) following the administration of kynurenic acid alone (vehicle and 30–150 mg/kg) and in combination with morphine (1.0–3.2 mg/kg) in rats trained to discriminate 3.2 mg/kg of morphine from water (W). Points above W represent tests performed after combined administration of water and the KYNA doses. Each point is based on observations made in 5 rats (1.0 and 1.7 mg/kg of morphine), 5 (3.2 mg/kg of morphine; $n = 4$ for 150 mg/kg of KYNA for MLR).

DISCUSSION

There were two major findings in the present studies. First, none of the tested NMDA receptor antagonists produced significant levels of morphine-lever responding in rats trained to discriminate 3.2 mg/kg of morphine from water. Second, NMDA receptor antagonists only modestly altered morphine's discriminative stimulus and response rate effects and differed in their effects on stimulus control by morphine, causing enhancement, attenuation, or no effects on morphine discrimination, depending on the drug studied.

Previous studies of the discriminative stimulus effects of PCP-like NMDA receptor antagonists in morphine-trained rats and pigeons have found that PCP and PCP-like drugs such as dizocilpine and ketamine produced intermediate (in rats, maximums of 58, 36, and 54%) levels of morphine-lever selection (31,46). It was reported that the morphine-like discriminative stimulus effects of PCP-like drugs in rats and squirrel monkeys were not antagonized by naltrexone, suggesting that the partial morphine-lever responding produced by these drugs is not mediated by direct actions on opiate receptors (27,33). The potency order of the PCP-type drugs to produce drug-lever selection was in agreement with their relative affinities for PCP receptors, but not for morphine receptors (33). Moreover, morphine by itself did not produce appreciable levels of drug-lever responding in rats trained to discriminate a competitive NMDA receptor antagonist NPC 12626 from saline (8) or in rats discriminating PCP from saline (51). Morphine did not substitute for NMDA as the training drug either (22).

Intermediate levels of drug-lever responding have been seen in other drug discrimination studies where NMDA antagonists have been tested for substitution, regardless of the training drug. This list includes NMDA (32,66), pentylenetetrazol (18), dopamine D_1 and D_2 receptors agonists (12), pentobarbital (44,67), and Δ^9-tetrahydrocannabinol (9). Results from our laboratory indicate that competitive NMDA receptor antagonists are also able to produce intermediate drug-lever responding in rats discriminating morphine (this study) or cocaine (unpublished observations). Therefore, it appears that this effect is rather characteristic for NMDA receptor antagonists, although mechanisms underlying this phenomenon are not completely understood. One possibility that has been suggested (33) is that NMDA antagonists may interfere with the discrimination task, possibly by a state-dependent mechanism. In this regard it should be noted that PCP-like NMDA antagonists have been shown to impair attention to exteroceptive stimuli in a modified open-field procedure (15), disrupt prepulse inhibition of the acoustic startle response (39,64), and have selective effects on the learning components of repeated acquisition tasks (58). NMDA antagonists disrupt a wide variety of other learning and memory tasks as well (13,14,16).

The fact that maximal levels of morphine-lever responding produced by NMDA antagonists in the present study were generally produced at doses that decreased overall rates of responding is consistent with this hypothesis that disruption of the discriminative task may have occurred. Partial morphine-like discriminative stimulus effects of PCP-like drugs were also associated with increases in the latency to complete the first FR and total number of responses before the delivery of first reinforcer in an earlier study as well (33). Similar results were obtained in our study where partial substitution was accompanied by responses occurring on both levers before the first reinforcer was delivered (data not shown). It is worth

noting that responding on both levers was not normally observed in subjects tested under training (training drug or vehicle) conditions. If disruption of the discrimination was the basis for the partial substitution seen with some of the NMDA antagonists, our results suggest that there are differences between them with regard to their ability to induce this effect. Eliprodil and kynurenic acid were the only antagonists that did not produce intermediate levels of responding. Eliprodil has also been reported to lack the amnestic and memory-impairing effects typically seen with other types of NMDA antagonists (45,50). For NPC 17742, SDZ 220-581, and dizocilpine, intermediate levels of drug-lever selection were induced in a dose-dependent manner and maximum effects occurred when response rates were suppressed by 90% or more. Although (+)-HA-966 was also capable of occasioning some morphine-lever responding, this effect was not dose related and did not correlate with the rate of responding.

Other studies have shown differences in the behavioral effects of NMDA receptor antagonists acting at different sites of the NMDA receptor complex (4). For example, the competitive NMDA antagonist CGP 37849 decreased the amplitude of the acoustic startle response, whereas the noncompetitive antagonist dizocilpine enhanced the amplitude of the acoustic startle response (64). Competitive antagonists (NPC 12626, CGS 19755, CGP 37849) failed to disrupt prepulse inhibition of acoustic startle as normally observed with PCP-like drugs, suggesting that actions at the PCP binding site, and not NMDA antagonism per se, are responsible for the disruption of prepulse inhibition by phencyclidine-like drugs (39,64). Although there is some overlap in the discriminative stimulus properties of competitive and noncompetitive NMDA antagonists, competitive antagonists have been shown to substitute only partially for PCP-like drugs (40,65), while noncompetitive NMDA antagonists fail to produce drug-lever responding in NPC 12626-trained rats (8,21,68). There is no everlap in the discriminative stimulus effects of PCP and those of eliprodil (2) and many glycine-site NMDA antagonists (3,54).

The second major finding of the present study was that drug-lever responding and response rate effects of morphine were only modestly altered when tested in combination with NMDA antagonists, with differences among NMDA antagonists in the magnitude and direction of interactive effects seen here as well. Morphine's discriminative stimulus effects were somewhat enhanced by NPC 17742, SDZ 220-581, and (+)-HA-966. Previous reports do not clarify the neuropharmacological mechanisms of such interactions. For example, systemic administration of competitive NMDA antagonists block morphine-conditioned place preference [CGP 37849: (62)] but does not affect morphine-induced stimulation of A10 dopamine neurons (±)-CPP, CGS19755: (20)). Analgesic effects of morphine are not influenced by several competitive NMDA antagonists [NPC 17742: (34); LY274614: (17)]. Microinjections of competitive NMDA antagonist APV into the nucleus accumbens reportedly reduce heroin-induced locomotion (47) but do not affect intravenous heroin self-administration (48).

Similarly, existing reports provide little information on the interactions between the morphine and glycine-site NMDA receptor antagonists. For example, 7-chlorkynurenic acid markedly potentiates morphine's analgesic effect after intrathecal administration (11). Systemic administration of kynurenic acid (a nonselective antagonist at the glycine site) also appears to augment opiate analgesia [(41); Bespalov and Zvartau, unpublished observations]. However, another glycine site antagonist, ACEA-1011, was reported to inhibit excitatory effects of intrathecal morphine (38). Moreover, in the present experiments, the effects of kynurenic acid did not resemble those of (+)-HA-966, thus creating a possibility that agonist properties of (+)-HA-966 are, at least in part, responsible for potentiation of morphine discrimination. Previously, *d*-serine, a selective agonist for the glycine site associated with the NMDA receptor, was shown to potentiate the antinociception produced by morphine using the formalin test in rats (28).

In contrast to the results with the competitive antagonists and (+)-HA-966, eliprodil decreased levels of responding on the morphine-appropriate lever when given in combination with morphine. In the only other relevant study, another polyamine NMDA receptor antagonist, ifenprodil, was shown to enhance the analgesic effects of morphine in mice (5). Further studies with NMDA antagonists of this type in combination with opioid are needed.

Dizocilpine had minimal effects on morphine discrimination. This lack of effect is not due to testing an insufficient dose range of dizocilpine because the highest dose tested almost completely eliminated responding and produced observable behavioral toxicity. In previous studies of PCP-like NMDA antagonists, both attenuation and enhancement of the effects of opiates have been observed. In some studies, PCP-like NMDA antagonists were able to attenuate the effects of opiates [conditioned place preference in rats: (62); hot plate analgesia in mice: (35); morphine-induced immediate early genes expression: (36,53)]. In others, dizocilpine was demonstrated to potentiate opiate activity (antinociception (tail-flick test) induced by a low dose of morphine in rats (30); antinociceptive effects of spinal morphine in rats (23,71); morphine-induced facilitation of brain stimulation reward in rats (10); morphine-induced catalepsy and lethality in rats (60).

Although earlier results indicated that kynurenic acid is able to attenuate the effects of morphine in conditioned place preference and electrical brain stimulation paradigms (6), present data suggest that kynurenic acid is able to selectively alter these effects of morphine rewarding properties of opiates while leaving its discriminative stimulus properties unaffected.

In summary, a diverse selection of site-selective NMDA antagonists did not produce morphine-like discriminative stimulus effects, consistent with their lack of known interactions with mu-opioid receptors that are known to mediate morphine discrimination (49,52,70). Some of them produced partial substitution, but these results can be explained by their disruption of the morphine discrimination. Although NMDA antagonists have been reported in other studies to significantly alter pharmacological and behavioral effects of opioids, they appear to have only modest and inconsistent effects on the discriminative stimulus and response rate effects of morphine. Combinations of opiates and NMDA antagonists have been suggested for treatment of pain and opiate tolerance. These results suggest that these combinations are not likely to result in a significant enhancement of the subjective effects of opiates that would limit their usefulness and enhance their abuse potential.

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REFERENCES

1. Advokat, C.; Rhein, F. Q.: Potentiation of morphine-induced antinociception in acute spinal rats by the NMDA antagonist dextrorphan. Brain Res. 699: 157–160; 1995.
2. Balster, R. L.; Nicholson, K. L.; Sanger, D. J.: Evaluation of the reinforcing effects of eliprodil in rhesus monkeys and its discriminative stimulus effects in rats. Drug Alcohol Depend. 35:211–216; 1994.
3. Balster, R. L.; Mansbach, R. S.; Shelton, K. L.; Nicholson, K. L.; Grech, D. M.; Wiley, J. L.; Li, H.; Weber, E.: Behavioral pharmacology of two novel substituted quinoxalinedione glutamate antagonists. Behav. Pharmacol. 6:577–589; 1995.
4. Balster, R. L.; Willetts, J.: Phencyclidine: A drug of abuse and a tool for neuroscience research. In: Schuster, C. R.; Kuhar, M. J., eds. Pharmacological aspects of drug dependence: Towards an integrated neurobehavioral approach. Handbook of experimental pharmacology, vol. 118. Berlin: Springer Verlag; 1996:233–262.
5. Bernardi, M.; Bertolini, A.; Szczawinska, K.; Genedani, S.: Blockade of the polyamine site of NMDA receptors produces antinociception and enhances the effect of morphine, in mice. Eur. J. Pharmacol. 298:51–55; 1996.
6. Bespalov, A. Y.; Dumpis, M. A.; Piotrovsky, L. B.; Zvartau, E. E.: Excitatory amino acid receptors antagonist kynurenic acid attenuates rewarding potential of morphine. Eur. J. Pharmacol. 264:233–239; 1994.
7. Bespalov, A. Y.; Zvartau, E. E.: Influence of kynurenic acid on the acquisition of intravenous morphine self-administration in rats. Bull. Exp. Biol. Med.; (in press).
8. Bobelis, D. J.; Balster, R. L.: Pharmacological specificity of the discriminative stimulus properties of 2-amino-4,5-(1,2-cyclohexyl)-7-phosphonoheptanoic acid (NPC 12626), a competitive *N*-methyl-D-aspartate receptor antagonist. J. Pharmacol. Exp. Ther. 264:845–853; 1993.
9. Browne, R. G.; Weissman, A.: Discriminative stimulus properties of delta-9-tetrahydrocannabinol: Mechanistic studies. J. Clin. Pharmacol. 21:227S–234S; 1981.
10. Carlezon, W. A., Jr.; Wise, R. A.: Morphine-induced potentiation of brain stimulation reward is enhanced by MK-801. Brain Res. 620:339–342; 1993.
11. Chapman, V.; Dickenson, A. H.: The combination of NMDA antagonism and morphine produces profound antinociception in the rat dorsal horn. Brain Res. 573:321–323; 1992.
12. Cory-Slechta, D. A.; Widzowski, D. V.: Low level lead exposure increases sensitivity to the stimulus properties of D_1 and D_2 agonists. Brain Res. 553:65–74; 1991.
13. Cox, J.; Guthrie, R.; Macrae, M.; Kehoe, E. J.: MK-801 impairs acquisition and expression of conditioned responses in the rabbit nictitating membrane preparation. Psychobiology 22:156–166; 1994.
14. Cross, A. J.; Murray, T. K.; Snape, M. F.: Characterization of learning and memory deficits following NMDA receptor antagonism. Amino Acids 8:79–87; 1995.
15. Dai, H.; Carey, R. J.: The NMDA receptor antagonist MK-801 can impair attention to exteroceptive stimuli. Behav. Brain Res. 62:149–156; 1994.
16. Danysz, W.; Zajaczkowski, W.; Parsons, C. G.: Modulation of learning processes by ionotropic glutamate receptor ligands. Behav. Pharmacol. 6:455–474; 1995.
17. Elliott, K.; Minami, N.; Kolesnikov, Y.; Pasternak, G.; Inturrisi, C.: The NMDA receptor antagonists, LY274614 and MK-801, and the nitric oxide synthase inhibitor, Ngnitro-*l*-arginine, attenuate analgesic tolerance to the μ-opioid morphine but not to κ-opioids. Pain 56:69–75; 1994.
18. Emmett-Oglesby, M. W.; Herz, A.: Opioid modulation of the discriminative stimulus produced by pentylenetetrazol. Psychopharmacology (Berlin) 92:313–319; 1987.
19. Ferkany, J. W.; Hamilton, G. S.; Patch, R. J.; Huang, Z.; Borosky, S. A.; Bednar, D. L.; Jones, B. E.; Zubrowski, R.; Willetts, J.; Karbon, E. W.: Pharmacological profile of NPC 17742 (2R,4R,5S-(2-amino-4,5-(1,2-cyclohexyl)-7-phosphonoheptanoic acid), a potent, selective and competitive *N*-methyl-D-aspartate receptor antagonist. J. Pharmacol. Exp. Ther. 264:256–264; 1993.
20. French, E. D.: Competitive NMDA receptor antagonists attenuate phencyclidine-induced excitations of A10 dopamine neurons. Eur. J. Pharmacol. 217:1–7; 1992.
21. Gold, L. H.; Balster, R. L.: Effects of NMDA receptor antagonists in squirrel monkeys trained to discriminate the competitive NMDA receptor antagonist NPC 12626 from saline. Eur. J. Pharmacol. 230:285–292; 1993.
22. Grech, D. M.; Willetts, J.; Balster, R. L.: Pharmacological specificity of *N*-methyl-D-aspartate discrimination in rats. Neuropharmacology 32:349–354; 1993.
23. Gutstein, H. B.; Trujillo, K. A.: MK-801 inhibits the development of morphine tolerance at spinal sites. Brain Res. 626:332–334; 1993.
24. Haberny, K. A.; Young, G. A.: Acute interactive effects of MK-801 and morphine on cortical EEG and EEG power spectra in rats. Brain Res. Bull. 36:325–331; 1995.
25. Herling, S.; Coale, E. H.; Valentino, R. J.; Hein, D. W.; Woods, J. H.: Narcotic discrimination in pigeons. J. Pharmacol. Exp. Ther. 214:139–146; 1980.
26. Herman, B. H.; Vocci, F.; Bridge, P.: The effects of NMDA receptor antagonists and nitric oxide synthase inhibitors on opioid tolerance and withdrawal. Neuropsychopharmacology 13: 269–293; 1995.
27. Holtzman, S. G.: Phencyclidine-like discriminative stimulus properties of opioids in the squirrel monkeys. Psychopharmacology (Berlin) 77:295–300; 1982.
28. Hunter, J. C.; Atwal, P.; Woodruff, G. N.; Singh, L.: Differential modulation of kappa and mu opioid antinociception by the glycine/NMDA receptor agonist D-serine. Br. J. Pharmacol. 112: 1002–1003; 1994.
29. Jeziorski, M.; White, F. J.; Wolf, M. E.: MK-801 prevents the development of behavioral sensitization during repeated morphine administration. Synapse 16:137–147; 1994.
30. Kest, B.; Marek, P.; Liebeskind, J. C.: The specific *N*-methyl-D-aspartate (NMDA) receptor antagonist MK-801 blocks U-50,488, but not morphine antinociception. Brain Res. 589:139–142; 1992.
31. Koek, W.; Woods, J. H.: Partial generalization in pigeons trained to discriminate morphine from saline: Applications of receptor theory. Drug Dev. Res. 16:169–181; 1989.
32. Koek, W.; Woods, J. H.; Colpaert, F. C.: *N*-methyl-D-aspartate antagonism and phencyclidine-like activity: A drug discrimination analysis. J. Pharmacol. Exp. Ther. 253:1017–1025; 1990.
33. Koek, W.; Colpaert, F. C.; Vignon, J.: Effects of phencyclidine-type drugs in rats discriminating fentanyl from saline: Pharmacological and behavioral characterization of intermediate levels of drug lever selection. J. Pharmacol. Exp. Ther. 264:746–756; 1993.
34. Kolesnikov, Y. A.; Ferkany, J.; Pasternak, G. W.: Blockade of μ- and κ1 opioid analgesic tolerance by NPC17742, a novel NMDA antagonist. Life Sci. 53:1489–1494; 1993.
35. Lipa, S. M.; Kavaliers, M.: Sex differences in the inhibitory effects of the NMDA antagonist, MK-801, on morphine and stress-induced analgesia. Brain Res. Bull. 24:627–630; 1990.
36. Liu, J.; Nickolenko, J.; Sharp, F. R.: Morphine induces c-*fos* and *jun*B in striatum and nucleus accumbens via D_1 and *N*-methyl-D-aspartate receptors. Proc. Natl. Acad. Sci. USA 91:8537–8541; 1994.
37. Lutfy, K.; Hurlbut, D. E.; Weber, E.: Blockade of morphine-induced analgesia and tolerance in mice by MK-801. Brain Res. 616:83–88; 1993.
38. Lutfy, K.; Woodward, R. M.; Keana, J. F.; Weber, E.: Inhibition of clonic seizure-like excitatory effects induced by intrathecal morphine using two NMDA receptor antagonists: MK-801 and ACEA-1011. Eur. J. Pharmacol. 252:261–266; 1994.
39. Mansbach, R. S.: Effects of NMDA receptor ligands on sensorimotor gating in the rat. Eur. J. Pharmacol. 202:61–66; 1991.
40. Mansbach, R. S.; Balster, R. L.: Pharmacological specificity of the phencyclidine discriminative stimulus in rats. Pharmacol. Biochem. Behav. 39:971–975; 1991.
41. Marek, P.; Ben-Eliyahu, S.; Gold, M.; Liebeskind, J. C.: Excitatory amino acid antagonists (kynurenic acid and MK-801) attenu-

ate the development of morphine tolerance in the rat. Brain Res. 547:77–81; 1991.
42. Monaghan, D. T.; Bridges, R. J.; Cotman, C. W.: The excitatory amino acid receptors: Their classes, pharmacology, and distinct properties in the function of the central nervous system. Annu. Rev. Pharmacol. Toxicol. 29:365–402; 1989.
43. Müller, W.; Kipfer, P.; Lowe, D. A.; Urwyler, S.: Syntheses of biphenyl analogues of AP7, a new class of competitive *N*-Methyl-D-aspartate (NMDA) receptor antagonists. Helv. Chim. Acta 78:2026–2035; 1995.
44. Overton, D. A.: A comparison of the discriminable CNS effects of ketamine, phencyclidine and pentobarbital. Arch. Int. Pharmacodyn. 215:180–189; 1975.
45. Patat, A.; Molinier, P.; Hergueta, T.; Brohier, S.; Zieleniuk, I.; Danjou, Ph.; Warot, D.; Puech, A.: Lack of amnestic, psychotomimetic or impairing effect on psychomotor performance of eliprodil, a new NMDA antagonist. Int. Clin. Psychopharmacol. 9:155–162; 1994.
46. Picker, M. J.; Doty, P.; Negus, S. S.; Mattox, S. R.; Dykstra, L. A.: Discriminative stimulus properties of U50,488 and morphine: Effects of training dose on stimulus substitution patterns produced by mu and kappa opioid agonists. J. Pharmacol. Exp. Ther. 254:13–22; 1990.
47. Pulvirenti, L.; Swerdlow, N. R.; Koob, G. F.: Nucleus accumbens NMDA antagonist decreases locomotor activity produced by cocaine, heroin or accumbens dopamine, but not caffeine. Pharmacol. Biochem. Behav. 40:841–845; 1991.
48. Pulvirenti, L.; Maldonado-Lopez, R.; Koob, G. F.: NMDA receptors in the nucleus accumbens modulate intravenous cocaine but not heroin self-administration in the rat. Brain Res. 594:327–334; 1992.
49. Rosecrans, J. A.; Goodloe, M. H.; Bennett, G. J.; Hirschhorn, I. D.: Morphine as a discriminative cue: Effects of amine depletors and naloxone. Eur. J. Pharmacol. 21:252–256; 1973.
50. Sanger, D. L.; Joly, D.: The effects of NMDA receptor antagonists and sigma ligands on the acquisition of conditioned fear in mice. Psychopharmacology (Berlin) 104:27–34; 1991.
51. Shannon, H. E.: Evaluation of phencyclidine analogs on the basis of their discriminative stimulus properties in the rat. J. Pharmacol. Exp. Ther. 216:543–551; 1981.
52. Shannon, H. E.; Holtzman, S. G.: Blockade of the discriminative effects of morphine in the rat by naltrexone and naloxone. Psychopharmacology (Berlin) 50:119–124; 1976.
53. Sharp, F. R.; Liu, J.; Nickolenko, J.; Bontempi, B.: NMDA and D1 receptors mediate induction of c-*fos* and *jun*B genes in striatum following morphine administration: Implications for studies of memory. Behav. Brain Res. 66:225–230; 1995.
54. Singh, L.; Menzies, R.; Tricklebank, M. D.: The discriminative stimulus properties of (+)-HA-966, an antagonist at the glycine/*N*-methyl-D-aspartate receptor. Eur. J. Pharmacol. 186:129–132; 1990.
55. Singh, L.; Donald, A. E.; Foster, A. C.; Hutson, P. H.; Iversen, L. L.; Iversen, S. D.; Kemp, J. A.; Leeson, P. D.; Marshall, G. R.; Oles, R. J.; Priestley, T.; Thorn, L.; Tricklebank, M. D.; Vass, C. A.; Williams, B. J.: Enantiomers of HA-966 (3-amino-1-hydroxypyrrolid-2-one) exhibit distinct central nervous system effects: (+)-HA966 is a selective glycine/*N*-methyl-D-aspartate receptor antagonist but (−)-HA966 is a potent (δ-butyrolactone-like sedative. Proc. Natl. Acad. Sci. USA 87:347–351; 1990.
56. Suh, H. W.; Song, D. K.; Kim, Y. H.; Yoo, J. S.; Tseng, L. F.: Differential antagonism by MK-801 against antinociception induced by opioid receptor agonists administered supraspinally in mice. Eur. J. Pharmacol. 263:217–221; 1994.
57. Tanganelli, S.; Antonelli, T.; Morari, M.; Bianchi, C.; Beani, L.: Glutamate antagonists prevent morphine withdrawal in mice and guinea pigs. Neurosci. Lett. 122:270–272; 1991.
58. Thompson, D. M.; Mastropaolo, J.; Winsauer, P. J.; Moerschbaecher, J. M.: Repeated acquisition and delayed performance as a baseline to assess drug effects on retention in monkeys. Pharmacol. Biochem. Behav. 25:201–207; 1986.
59. Tiseo, P. J.; Cheng, J.; Pasternak, G. W.; Inturrisi, C. E.: Modulation of morphine tolerance by the competitive *N*-methyl-D-aspartate receptor antagonist LY274614: Assessment of opioid receptor changes. J. Pharmacol. Exp. Ther. 268:195–201; 1994.
60. Trujillo, K. A.; Akil, H.: The NMDA receptor antagonist MK-801 increases morphine catalepsy and lethality. Pharmacol. Biochem. Behav. 38:673–675; 1991.
61. Trujillo, K. A.; Akil, H.: Inhibition of morphine tolerance and dependence by the NMDA receptor antagonist MK-801. Science 251:85–87; 1991.
62. Tzschentke, T. M.; Schmidt, W. J.: *N*-Methyl-D-aspartic acid-receptor antagonists block morphine-induced conditioned place preference in rats. Neurosci. Lett. 193:37–40; 1995.
63. Urwyler, S.; Lowe, D.; Meier, C.; Mhller, W.: Biphenyl-AP7-derivatives, a new class of competitive *N*-methyl-D-aspartate receptor antagonists: In vitro pharmacology. J. Neurochem. (Suppl.) 65:S12C; 1995.
64. Wedzony, K.; Golembiowska, K.; Zazula, M.: Differential effects of CGP 37849 and MK-801, competitive and noncompetitive NMDA antagonists, with respect to the modulation of sensorimotor gating and dopamine outflow in the prefrontal cortex of rats. Naunyn Schmiedebergs Arch. Pharmacol. 350:555–562; 1994.
65. Willetts, J.; Balster, R. L.: The discriminative stimulus effects of *N*-methyl-D-aspartate antagonists in phencyclidine-trained rats. Neuropharmacology 27:1249–1256; 1988.
66. Willetts, J.; Balster, R. L.: Effects of competitive and noncompetitive *N*-methyl-D-aspartate (NMDA) antagonists in rats trained to discriminate NMDA from saline. J. Pharmacol. Exp. Ther. 251:627–633; 1989.
67. Willetts, J.; Balster, R. L.: Pentobarbital-like discriminative stimulus effects of *N*-methyl-D-aspartate antagonists. J. Pharmacol. Exp. Ther. 249:438–443; 1989.
68. Willetts, J.; Bobelis, D. J.; Balster, R. L.: Drug discrimination based on the competitive *N*-methyl-D-aspartate antagonist, NPC 12626. Psychopharmacology (Berlin) 99:458–462; 1989.
69. Wong, E. H.; Kemp, J. A.; Priestly, T.; Knight, A. R.; Woodruff, G. N.; Iversen, L. L.: The anticonvulsant MK-801 is a potent *N*-methyl-D-aspartate antagonist. Proc. Natl. Acad. Sci. USA 83: 7104–7108; 1986.
70. Woods, J. H.; Bertalmio, A. J.; Young, A. M.; Essman, W. D.; Winger, G.: Receptor mechanisms of opioid drug discrimination. In: Colpaert, F. C.; Balster, R. L., eds. Transduction mechanisms of drug stimuli. Berlin: Springer Verlag; 1988:95–106.
71. Yamamoto, T.; Yaksh, T. L.: Studies on the spinal interaction of morphine and the NMDA antagonist MK-801 on the hyperesthesia observed in a rat model of sciatic mononeuropathy. Neurosci. Lett. 135:67–70; 1992.