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Pharmacology Biochemistry and Behavior, Vol. 53, No. 4, pp. 791–797, 1996

0091-3057/96 $15.00 + .00

SSDI 0091-3057(95)02163-9

The NMDA Antagonist Memantine Blocks the Expression and Maintenance of Morphine Dependence

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Received 14 June 1995; Accepted 10 October 1995

POPIK, P. AND P. SKOLNICK. *The NMDA antagonist memantine blocks the expression and maintenance of morphine dependence.* PHARMACOL BIOCHEM BEHAV 53(4) 791–797, 1996. – The ability of memantine (1-amino-3,5-dimethyl-adamantane) to block the expression and maintenance of morphine dependence was examined in mice. When administered to morphine-dependent mice 45 min prior to naloxone challenge, memantine (7.5–30 mg/kg IP) in a dose-dependent manner reduced jumping behavior (a manifestation of the expression of dependence). The ability of memantine to attenuate naloxone-precipitated jumping was reversed by administration of glycine, an observation consistent with electrophysiological studies indicating that memantine is a use-dependent (uncompetitive) *N*-methyl-D-aspartate (NMDA) antagonist. In an independent series of experiments, the effect of memantine on a preestablished morphine dependence was investigated. A residual dependence to morphine was present 3 days after cessation of morphine administration. Repeated administration of memantine (10 mg/kg, IP) or the competitive NMDA antagonist NPC 17742 [2R,4R,5S-(2-amino-4,5-(1,2-cyclohexyl)-7-phosphonoheptanoic acid)] (6 mg/kg, IP) during this 3-day period abolished subsequent naloxone-precipitated jumping. In contrast, when administered concurrently with morphine after dependence had already been well established, memantine (10 and 20 mg/kg, IP) did not affect the maintenance of morphine dependence. Based on these findings, NMDA antagonists appear to inhibit the maintenance of opioid dependence, an action distinct from their acute inhibitory effects on the expression of dependence. Nonetheless, these regimen-dependent effects of memantine indicate that the most efficacious use of NMDA antagonists would be in detoxified subjects, rather than in individuals with an established dependence who are currently abusing opioids.

NMDA receptor antagonists Morphine Dependence Addiction Withdrawal Memantine NPC 17742 Glycine

CONVERGING lines of evidence indicate that *N*-methyl-D-aspartate (NMDA) antagonists can affect opiate tolerance and dependence. In studies addressing the effects of NMDA antagonists on the *expression* of ongoing morphine dependence, NMDA antagonists block or attenuate behaviors associated with precipitated morphine withdrawal when administered prior to naloxone challenge (3,6,33,35,46,49,55). In addition to diminishing the physical signs of withdrawal in laboratory rodents, the use-dependent channel blocker MK-801 (dizocilpine) has recently been shown to attenuate the motivational aspects of morphine withdrawal. Thus, Higgins et al. (18) have demonstrated that during morphine withdrawal in a specific location, rats acquire a subsequent aversion to that location, while MK-801 pretreated animals do not exhibit such an aversion.

Co-administration of NMDA antagonists with morphine has also been shown to block the *development* of dependence. For example, Trujillo and Akil (55) demonstrated that naive rats administered combined treatment with morphine and MK-801 did not display signs of morphine dependence as measured by naloxone-precipitated withdrawal. However, to our knowledge, the potential usefulness of NMDA antagonists in

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attenuating preexisting morphine dependence (i.e., *maintenance* of dependence) has not been examined in a readily quantifiable animal model. Examination of this aspect of dependence is particularly relevant, since it more closely mirrors the clinical situation in which an addicted individual is already opiate-dependent.

The objective of the present experiments was to determine whether an NMDA antagonist could affect the maintenance as well as expression of opiate dependence. The present studies were performed with memantine, since it is a use-dependent NMDA antagonist (K_i ~ 450 nM) in electrophysiological and neurochemical assays (4,7,26) and is in current clinical use for the treatment of Parkinson's disease and senile dementia (10,15,16). To examine the specificity of memantine's action at NMDA receptors, parallel experiments were performed with NPC 17742, a competitive NMDA antagonist (13).

MATERIALS AND METHODS

Animals

Male Swiss NIH mice, 29–32 g of body weight (HSD, Veterinary Resources Branch, NIH, Bethesda, MD) were housed in plastic cages (8/cage) under standard laboratory conditions (lights on at 0600 h, lights off 1800 h; room temperature 23 ± 1°C) with chow and tap water available ad lib.

Drugs

Morphine base was dissolved in 1 N HCl and the pH adjusted to 7 with NaOH and phosphate-buffered saline (PBS). Other drugs (naloxone HCl, memantine, NPC 17742 [2R, 4R,5S-(2-amino-4,5-(1,2-cyclohexyl)-7-phosphonoheptanoic acid)] and glycine) were dissolved in PBS, which was also used for placebo injections. The doses of memantine used in this study were based on previous reports demonstrating activity in several behavioral measures (e.g., [5,30,39]). The glycine regimen employed was based on a previous report demonstrating that it significantly (~70%) elevated brain glycine levels (56) and could reduce the dissociative anesthetic properties of MK-801 (12). Naloxone and morphine were obtained from Dr. K. Rice, NIDDK, NIH, Bethesda, MD, and NPC 17742 (a product of Nova Pharmaceuticals) was kindly donated by Dr. J. Witkin, NIDA, Baltimore, MD. Memantine was a gift from Merz & Co. GmbH, Germany. Glycine was purchased from Sigma Chemical Corp. (St. Louis, MO). All injections (0.2 ml) were administered intraperitoneally.

Experimental Design

Effects of memantine on the expression of morphine dependence. Mice were injected with morphine (30 mg/kg, twice daily, at 0930 h and 1730 h) for 3 days, with an additional, last dose administered on the morning of the test (fourth) day (this regimen will be referred to as Treatment #1 in subsequent sections). Two h after the last dose of morphine, mice (n = 7–13 per treatment) were injected with placebo or glycine (800 mg/kg). Fifteen min later, they received either placebo or memantine. The second injection of placebo or glycine (800 mg/kg) was given fifteen min later. Mice were challenged with naloxone (4 mg/kg) 30 min later and individually placed in the transparent plastic cylinders (42 cm high, 19 cm diameter). The number of jumps was recorded during a 10 min test period (36,46). All animals were used only once. The final dose of morphine that was given was necessary to produce a robust naloxone-precipitated morphine withdrawal, as the severity of this phenomenon depends on the rapidity with which opioids are removed from their receptors (e.g., [20]). The regimen employed to produce morphine dependence was empirically determined to produce a readily quantifiable and reproducible number of jumps, as well as more realistically model the regimen of a drug abuser (i.e., discrete, multiple injections of a constant dose as opposed to steadily increasing doses or continuous release from a pellet).

Effects of memantine on the maintenance of morphine dependence. Naloxone (4 mg/kg) precipitated withdrawal (Test 1) was produced following the morphine regimen (Treatment #1) as described in the preceding section. Twenty four h after naloxone challenge, mice were divided into three groups and received either memantine (10 mg/kg, n = 11), NPC 17742 (6 mg/kg, n = 11) or placebo (n = 20) twice daily for three days (Treatment #2). Twenty h after the last injections and 3 h after a morning dose of morphine, the severity of naloxone-precipitated withdrawal was measured again (Test 2). This treatment schedule is referred to as the *detoxified mouse regimen*. In a variation of this experiment, mice were injected with a drug regimen identical to that described above except that in Treatment #2, memantine (10 [n = 11] or 20 mg/kg [n = 7], twice daily) or placebo (n = 19) were administered 15–30 min preceding morphine (30 mg/kg, twice daily) injections. This treatment is referred to as the *continuous morphine regimen*.

Locomotor activity. Mice were transferred to the testing facility and left undisturbed for at least one h. Animals (n = 7–8 per treatment) received a placebo injection and 15 min later were injected with either placebo or memantine (5 or 15 mg/kg). Locomotor activity (distance traveled) was recorded for 120 min immediately after injection. Locomotor activity was analyzed by a PC computer, using the EYE (J. Długopolski, Kraków, Poland) and TRACK-ANALYZER programs (57). Activity was monitored under dim light by placing a mouse in a 42 × 42 × 23 cm square arena constructed of black lucite. Four arenas were monitored simultaneously. All treatments and observations were counterbalanced throughout the experiment. Animals were used only once.

Statistical analysis. The mean number of jumps was calculated for each group of mice. One-way analysis of variance was used for calculating differences among data from the experiments aimed at measuring effects of drugs on the expression of morphine withdrawal. In experiments investigating effects of drugs on the maintenance of morphine dependence, preliminary studies indicated that there was no correlation (r = 0.04) between the number of naloxone-precipitated jumps on the first and second withdrawal tests. Based on these observations, data were analyzed using a one-way between subjects analysis of variance with post hoc Student-Newman-Keuls test. Statistical significance was assumed when $p < 0.05$.

RESULTS

Administration of memantine to morphine-dependent mice 45 min prior to naloxone challenge attenuated jumping behavior, an expression of morphine dependence. These effects were dose-dependent (7.5–30 mg/kg), with the first statistically significant reduction in naloxone-precipitated jumping manifested at a dose of 10 mg/kg (Fig. 1). The dose that inhibited 50% of jumps (ED_{50}) was 6.9 mg/kg (CI: 6.7–7.1 mg/kg). In pilot studies, mice (n = 10) pretreated with placebo for 3 days and challenged with naloxone (4 mg/kg) demonstrated no jumps during the 10 min observation period.

Parenterally administered glycine (2 × 800 mg/kg) re-

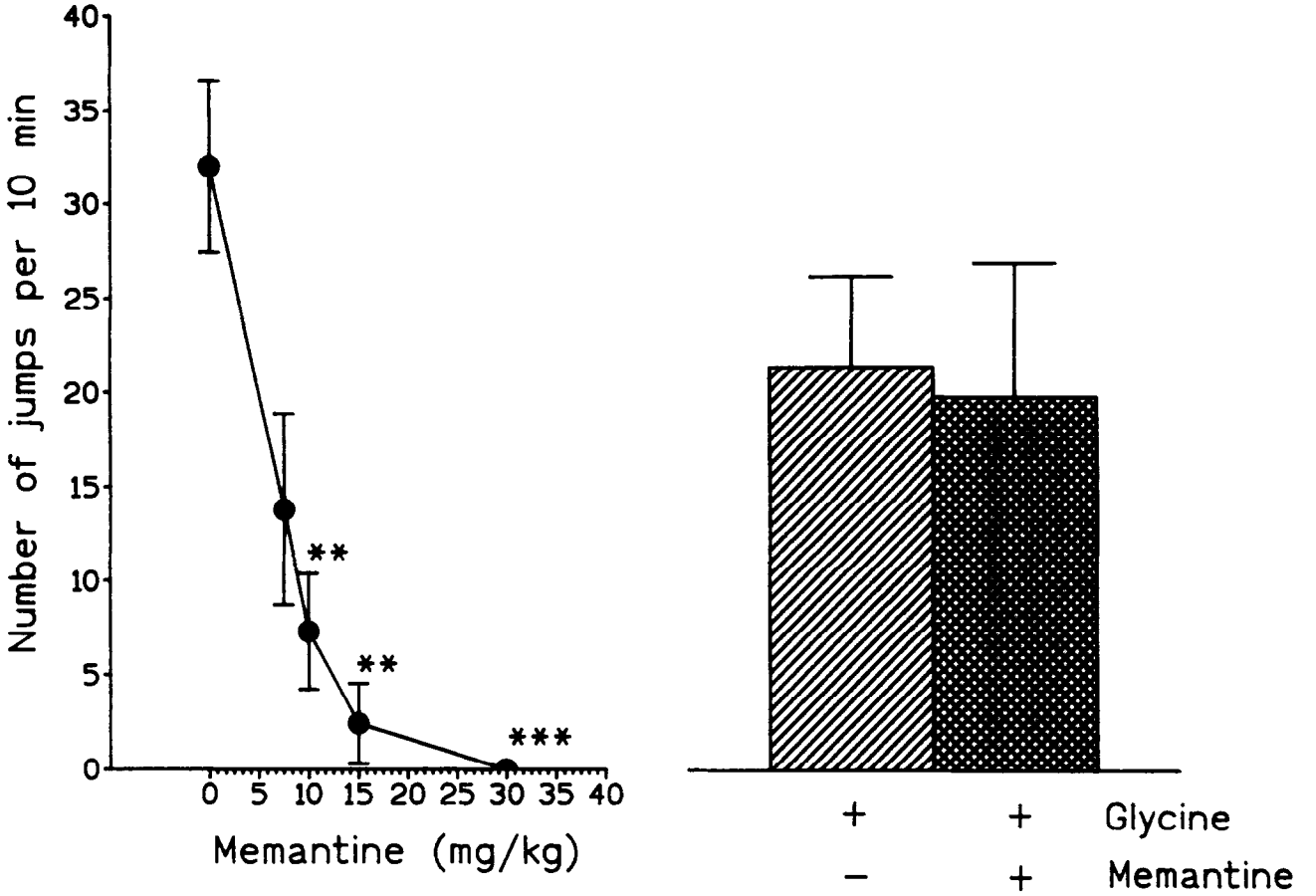

FIG. 1. Effects of memantine on the expression of morphine dependence. Values represent the mean ± SEM number of jumps by morphine-dependent mice following naloxone challenge. Mice received morphine (30 mg/kg, IP) twice daily for 3 days. On the morning of the fourth (test) day, mice received an additional morphine injection. Two hours later, mice were injected with placebo or glycine (800 mg/kg, IP). Fifteen minutes later, they received placebo or memantine. A second injection of placebo or glycine was given 15 min later. Mice were challenged with naloxone (4 mg/kg, IP) 30 min after the last injection, and observed for jumping behavior during the subsequent 10 min as described in Methods. The hatched bar represents the number of jumps in mice that received glycine, placebo, glycine, and naloxone. The cross-hatched bar represents the number of jumps of mice administered glycine, memantine (10 mg/kg, IP), glycine, and naloxone. ANOVA: $F(6, 52) = 5.27$, $p < 0.001$. Symbols: $^{**}p < 0.01$; $^{***}p < 0.001$, vs. naloxone-challenged mice administered 3 pretreatment placebo injections (Student-Newman-Keuls test). The number of jumps in glycine treated animals (in the presence or absence of memantine; hatched and cross-hatched bars) did not significantly differ from controls (i.e., placebo-pretreated, naloxone-challenged mice). Each group consisted of 7–13 mice.

versed the effect of memantine (10 mg/kg) to reduce naloxone-precipitated jumping (Fig. 1). Thus, combined treatment with glycine and memantine (Fig. 1., cross-hatched bar) increased the number of naloxone-precipitated jumps to values that were not significantly different from placebo pretreated, naloxone challenged, morphine-dependent animals. Glycine did not significantly affect naloxone-precipitated withdrawal in the absence of memantine (Fig. 1, hatched bar). Concomitant with jumping, mice exhibited penile licking and diarrhea. These latter behaviors were not quantitated. No ataxia or measurable gross motor disturbances were noted at doses of 7.5–15 mg/kg of memantine during naloxone-precipitated morphine withdrawal test.

In order to examine the effects of memantine on the maintenance of morphine dependence, mice were rendered dependent by administering morphine for 3 days followed by naloxone-precipitated withdrawal on day 4. This cohort was divided into three groups, with subjects receiving either placebo, memantine (10 mg/kg), or NPC 17742 (6 mg/kg) during days 5–7 (detoxified mouse regimen). On day 8, morphine dependence was measured again by administration of morphine and 3 h thereafter, naloxone. Table 1 (upper panel) demonstrates that mice treated with memantine or NPC 17742 exhibited almost no jumps compared to placebo treated animals. In the continuous morphine regimen, morphine dependent mice were administered an additional 3 days of either [placebo + morphine] or [memantine (10 or 20 mg/kg) + morphine] treatment. Under these conditions, memantine did not diminish the severity of the naloxone-precipitated withdrawal (Table 1, lower panel). The comparison of these two treatment regimens also revealed that when morphine was omitted during days 5–7, mice remained morphine-dependent, albeit to a lesser extent than mice treated continuously with morphine.

Doses of memantine which attenuated the expression of morphine dependence increased locomotor activity (Table 2). At 15 mg/kg, memantine significantly increased distance travelled during a 120 min test period. Analysis of locomotor activity data revealed that memantine-induced hypermotility

TABLE 1

EFFECTS OF MEMANTINE ON THE MAINTENANCE OF MORPHINE DEPENDENCE

Days 1-3 Treatment	Day 4 Jumps	Days 5-7 Treatment	Day 8 Jumps
Detoxified mouse regimen*			
		Placebo	8.0† ± 1.8 [20]
Morphine	15.1 ± 1.6 [44]	Memantine (10)	1.9‡§ ± 1.0 [11]
		NPC 17742 (6)	0.9‡¶ ± 0.6 [11]
			$F(3, 82) = 12.97, p < 0.0001$
Continuous morphine regimen#			
		Placebo + Morphine	21.5 ± 5.8 [19]
Morphine	21.7 ± 3.3 [42]	Memantine (10) + Morphine	18.7 ± 4.7 [11]
		Memantine (20) + Morphine	20.0 ± 4.6 [7]
			$F(3, 75) < 1, p > 0.05$

*Mice were injected with morphine (30 mg/kg, IP, twice daily for 3 days) and received an additional morphine injection on Day 4 (0930 h). Three hours later, withdrawal was precipitated by naloxone. These animals were divided into 3 groups and treated for the next 3 days with either memantine, NPC 17742, or placebo at the doses indicated in parentheses. Twenty hours after the last drug administration and 3 h after a dose of morphine (30 mg/kg, IP; 0930 h), the severity of naloxone-precipitated withdrawal was measured again (Day 8). Symbols: †$p < 0.01$; ‡$p < 0.001$ vs. score on Jump 1 test (Student-Newman-Keuls test). §$p < 0.05$; ¶$p < 0.01$ vs. placebo on Jump 2 test (t-test).

#In this experiment, mice were treated as described above, except that morphine (30 mg/kg, IP, twice daily for 3 days) was injected after placebo or memantine on Days 5-7. On Day 8, naloxone-precipitated morphine withdrawal was measured exactly as described above. The doses of memantine are given in parentheses and the number of mice is indicated in brackets.

was manifested in each of the 10 min intervals of the test period (data not shown).

DISCUSSION

Jumping behavior is a prominent feature of naloxone-precipitated morphine withdrawal in mice (36). Naloxone-precipitated morphine withdrawal bears a pharmacological resemblance to the abstinence syndrome in humans, and is often employed as a measure of opioid dependence. Following acute administration, several classes of NMDA antagonists have been reported to block the expression (that is, reduce the severity of naloxone-precipitated behaviors) of opioid dependence (3,6,33,35,46,49,55). Moreover, co-administration of morphine and an NMDA antagonist has also been shown to block the development of opioid dependence in animals as measured by a reduction in naloxone-precipitated behaviors (55).

While preclinical evidence suggests that NMDA antagonists may be useful in the treatment of opioid withdrawal and dependence, the side effect profiles of competitive NMDA antagonists (e.g., D-CPP-ene) and use-dependent channel blockers (e.g., CNS 1102) in early stage clinical trials (31,45) would likely preclude their use in this therapeutic context. Electrophysiological (4) and neurochemical (25,26) properties indicate that memantine is a use-dependent NMDA antagonist that is ≥2 orders of magnitude less potent than the prototypical use-dependent channel blocker, MK-801. In addition, memantine substitutes for phencyclidine as a discriminative stimulus, and this action can be attributable to its NMDA antagonist properties rather than to a blockade of dopamine reuptake (39).

Memantine is currently prescribed for the treatment of Parkinson's disease and senile dementia (10,15,16). Based on its use in humans, memantine does not appear to have the same side effect profile as higher affinity NMDA antagonists (e.g., PCP, MK-801, see, [31,45]). Nonetheless, in one study with four elderly Parkinsonian patients, Riederer et al. (34) reported psychotic-like symptoms in two subjects. Since memantine is structurally related to the dopamine agonist adamantine, it is unclear if these side effects were due to an action at NMDA receptors or via a direct stimulation of DA receptors. In view of the overall clinical experience with this compound, we selected memantine to examine the potential of NMDA antagonists to block both the expression and maintenance of opioid dependence.

Like other NMDA antagonists (3,6,33,35,46,49,55), pretreatment with memantine dose-dependently attenuated expression of naloxone-precipitated morphine withdrawal. While it could be argued that this attenuation of jumping behavior is attributable to physical impairment (e.g., ataxia) produced by use-dependent channel blockers (e.g., [8,12,14, 19]), we observed no evidence of gross motor impairment in memantine treated animals at these doses. Moreover, doses of memantine that were effective in reducing the expression of

TABLE 2

THE EFFECTS OF MEMANTINE ON LOCOMOTOR ACTIVITY IN MICE

Memantine Dose	Locomotor Activity Score
0	15,623 ± 1,770 [8]
5	19,406 ± 2,416 [7]
15	34,849* ± 2,479 [8]

Data (in arbitrary path units) were collected during a 120-min observation period and are presented as the mean ± SEM. Doses are expressed in mg/kg, IP Memantine was injected immediately before placing a mouse in the apparatus. ANOVA: $F(2, 20) = 21.5$, $p < 0.0001$. Symbol: *$p < 0.001$ vs. placebo (Student-Newman-Keuls test). The number of mice is indicated in brackets.

morphine dependence (ED_{50} 6.9 mg/kg) were equal or lower than that needed to increase locomotor activity (Table 2). In addition, hypermotility cannot explain the effects of memantine on maintenance of morphine dependence since NPC 17742 inhibits locomotor activity (14) but produces a similar attenuation of the maintenance of morphine dependence (Table 1).

Administration of glycine reversed memantine-induced reductions in naloxone-precipitated jumping (Fig. 1). This observation is consistent with the hypothesis that the ability of memantine to reduce the expression of morphine dependence is effected through its action as a use-dependent channel blocker, since glycine and other agonists at strychnine-insensitive glycine receptors (e.g., D-serine) can reduce or abolish a variety of the behaviors induced by other use-dependent channel blockers (e.g., MK-801 and phencyclidine, see, [8,12,51,52]). The ability of agonists acting at strychnine-insensitive glycine receptors to attenuate the behavioral actions of use-dependent channel blockers may be explained by a number of mechanisms. Since glycine is required for the activation of NMDA receptors (23), increasing the concentration of glycine or a glycine-mimetic can increase the probability at which NMDA receptors are activated if glycine concentrations in situ are subsaturating (37,47). Increased activation of NMDA receptors increases the likelihood of membrane depolarization, which would facilitate the dissociation of use-dependent blockers (2,21,32).

Previous studies have demonstrated that co-administration of morphine and an NMDA antagonist will prevent the development of opiate dependence (55). However, this regimen may not adequately model clinical situations of individuals with a previously established opioid dependence. To our knowledge, the present findings are the first which demonstrate that administration of an NMDA antagonists can affect the *maintenance* of morphine dependence. Thus, naloxone precipitates jumping behavior in previously dependent animals that have been morphine free during 3 days preceding the second test (Table 1, upper panel), but withdrawal signs were essentially abolished in animals maintained on memantine during this morphine free period. To exclude the possibility that this was a memantine-specific effect, we examined the effect of a structurally unrelated, competitive NMDA antagonist on maintenance of opioid dependence. Like memantine, the ability of NPC 17742 (13) to produce a reduction in naloxone-precipitated jumping behavior is consistent with the hypothesis that NMDA antagonists may be useful in the treatment of opioid dependence.

In contrast, the maintenance of morphine dependence was apparently unaffected by memantine in animals continuously injected with morphine (Table 1, lower panel). This observation indicates that NMDA antagonists may not be effective in treating an established, ongoing dependence. The results of the experiment in which memantine was co-administered with morphine to mice with a previously established dependence (Table 1, lower panel) also provide an additional insight into understanding the effects of NMDA antagonists on opioid dependence. Thus, it may be hypothesized that despite the ability of memantine to reduce the expression of morphine dependence (Fig. 1), morphine dependence *per se* was not affected in these animals. However, it must be noted that the naloxone–precipitated withdrawal syndrome is a complex phenomenon, and that the current studies quantitated only one endpoint while other behavioral and physiological phenomena associated with this syndrome were not measured. Whether memantine and other NMDA antagonists uniformly attenuate all signs and symptoms of this syndrome requires additional investigation.

These findings may also provide some insights into the appropriate use of NMDA antagonists in opioid dependence, indicating the most efficacious use of these compounds would be in detoxified addicted individuals rather than in individuals currently abusing opioids. Furthermore, this suggestion is supported by the observation that co-administration of morphine and NMDA antagonists results in a increased mortality and catalepsy (54). The molecular mechanisms responsible for the regimen-dependent efficacy of NMDA antagonists in blocking the maintenance of opiate dependence are unknown and require further investigation.

The attenuation of morphine dependence and tolerance (3,11,24,29,48,55) by NMDA antagonists has been attributed to the "amnestic" properties of these agents (e.g., [55]). Drug dependence and tolerance phenomena are generally considered plastic changes, resembling learning processes (22,42,43), and NMDA antagonists interfere with learning processes (9,17,44,50). However, the ability of memantine to disrupt the maintenance of opioid dependence appears unrelated to an amnestic action, since NMDA antagonists block acquisition or consolidation of learning processes but not memories that are well established (e.g., [40]). Finally, although tolerance and dependence to opioids are distinct phenomena, they develop together. Ben-Eliyahu et al. (3), have demonstrated that an uncompetitive NMDA antagonist attenuated nonassociative morphine tolerance as well as tolerance involving learning factors. Several other potential mechanisms have been invoked to explain the ability of NMDA antagonists to reduce the expression and development of morphine dependence. These mechanisms include changes in glutamatergic firing from nucleus paragigantocellularis to the locus coeruleus (1) and alterations in the dynamics of opioid κ receptors and/or elaboration of dysphoric κ opioid peptides (53). However, these theories do not directly address the ability of NMDA antagonists to disrupt the maintenance of opioid dependence.

While current theories cannot adequately explain the ability of NMDA antagonists to affect the maintenance of opioid dependence, the present findings raise the possibility that this class of compounds may be beneficial in the treatment of acute opioid withdrawal as well as the maintenance of opioid dependence. This possibility is consistent with preliminary clinical results indicating that the use-dependent (uncompetitive) NMDA antagonists dextromethorphan (27) and ibogaine (28,38,41) are effective in the treatment of opiate dependence in humans.

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