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Pretreatment with morphine potentiates naloxone-conditioned place aversion in mice: effects of NMDA receptor antagonists

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Abstract

Acute pretreatment with opioid receptor agonists potentiates behavioral effects of opioid antagonists. This phenomenon was suggested to serve as an acute model of opioid dependence. Since antagonists acting at *N*-methyl-D-aspartate (NMDA) receptors were repeatedly shown to attenuate development, maintenance, and expression of opioid dependence, the present study evaluated the effects of competitive NMDA receptor antagonist, D-CPPene (SDZ EAA 494; 3-(2-carboxypiperazin-4-yl)-1-propenyl-1-phosphonic acid), and low-affinity channel blocker, 1-amino-3,5-dimethyl adamantane hydrochloride (memantine), on establishment of naloxone-conditioned place aversion in mice that were pre-exposed to morphine. Morphine (20 mg/kg) pretreatment significantly potentiated the ability of naloxone (0.01–0.3 mg/kg) to produce place aversion. The place aversion produced by naloxone (0.1 mg/kg) was attenuated by D-CPPene (1 and 3 mg/kg but not 0.1 or 0.3 mg/kg) when it was administered 3.5 h after morphine (0.5 h prior to conditioning trial with naloxone) but not 0.5 h prior to morphine. Memantine (1–10 mg/kg) had no effect under any treatment condition (0.5 h prior to morphine, simultaneously with morphine, 2 or 3.5 h after morphine). Thus, the ability of NMDA receptor antagonist to affect development and/or expression of morphine dependence may not be a good predictor of their effects on establishment of morphine-potentiated naloxone-conditioned place aversion.

Keywords: Naloxone; Morphine; Sensitization; Place conditioning; NMDA receptor antagonist; Mice

1. Introduction

A substantial body of evidence suggests that acute pretreatment with opioid receptor agonists may sensitize animals to subsequent challenge with opioid antagonists (Adams and Holtzman, 1990; Meyer and Sparber, 1977; Young, 1986). The phenomenon of sensitization to behavioral effects of antagonists was repeatedly replicated with different antagonists (naloxone, naltrexone) and agonists (morphine, heroin, fentanil). For example, doses of naloxone that do not alter response rates in opioid-free subjects can dramatically decrease rates in subjects receiving a single acute morphine dose (Meyer and Sparber, 1977).

Experimental variables that determine the expression of the acute sensitization were vigorously analyzed in several studies (e.g., Adams and Holtzman, 1990; Young, 1986). Opioid antagonists were administered at different intervals after the agonist drug and the maximum sensitization was observed when this interval was about 4 h. For instance, in rats trained to lever-press for food, an acute pretreatment with 10 mg/kg of morphine, given 4 h prior to the session, decreased the cumulative dose of naloxone required to suppress the response rate 10- to 30-fold (Young, 1986).

Acute sensitization studies had typically employed operant conditioning methodology. Effects of opioid antagonists were studied in animals trained to respond for food (Adams and Holtzman, 1990; Young, 1986) or electrical stimulation of brain reward sites (Easterling et al., 1998). The first aim of this study was to reproduce the phenomenon of increased sensitivity to naloxone induced by morphine pretreatment using place conditioning technique. Place conditioning paradigm offers a reliable measure for assessing the behavioral effects of opioid antagonists and opioid antagonist-induced place aversion may reflect negative motivational value of interoceptive effects produced by opioid receptor blockade (Higgins et al., 1992; Popik and Danysz, 1997).

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One of the major unwanted properties of opioids is their ability to produce physical dependence upon a chronic administration. It was proposed that the acute sensitization phenomenon is a reflection of acute dependence produced by opioid receptor agonists and may be relevant for studying the mechanisms of opioid dependence.

The opioid dependence produced by repeated opioid receptor agonist exposures is known to be influenced by the activity of glutamatergic system. Antagonists acting at *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors block both development and expression of opioid dependence in laboratory rodents (Herman et al., 1995; Trujillo and Akil, 1991). NMDA receptor antagonists were shown to attenuate not only somatic signs of opioid withdrawal but also its discriminative stimulus effects (Medvedev et al., 1998) as well as aggressogenic properties (Sukhotina and Bespalov, 2000).

If the agonist-induced acute sensitization to opioid antagonists shares common mechanisms with opioid dependence, one may expect that NMDA receptor antagonists would affect expression of increased sensitivity to opioid antagonists. Thus, the second aim of this study was to evaluate whether pretreatment with NMDA receptor antagonists would block naloxone-conditioned place aversion in a paradigm similar to that used in acute sensitization studies (i.e., morphine injection 4 h prior to conditioning sessions). Two NMDA receptor antagonists were selected for this study — competitive antagonist, D-CPPene (SDZ EAA 494; 3-(2-carboxypiperazin-4-yl)-1-propenyl-1-phosphonic acid; Herrling et al., 1997), and channel blocker, 1-amino-3,5-dimethyl adamantane hydrochloride (memantine; Danysz et al., 1997). Both D-CPPene and memantine were earlier shown to affect expression of morphine dependence (Medvedev et al., 1998; Popik and Skolnick, 1996).

2. Methods

2.1. Animals

Adult male albino Swiss mice (20–35 g) bred at State Breeding Farm "Rappolovo" (St. Petersburg, Russia) were housed in groups of eight in plastic cages ($22 \times 40 \times 9$ cm) with food and water ad libitum. All experiments were conducted during the light period of a 12-h/12-h light–dark cycle (09:00–21:00 h). The experiments were approved by the Institutional Ethics Committee of Pavlov Medical University and were performed in accordance with the recommendations and policies of the US National Institutes of Health Guidelines for the Use of Animals.

2.2. Drugs

Morphine hydrochloride ("Endocrinnyj Zavod", Moscow, Russia) and naloxone hydrochloride (Sigma, St. Louis, MO, USA) were dissolved in physiological saline. D-CPPene (3-(2-carboxypiperazine-4-yl)-1-propenil-1-phosphonic acid; SDZ EAA 494; Novartis Pharma, Basel, Switzerland) was dissolved in equimolar NaOH to form stock solutions; further dilutions were made with physiological saline. Memantine (Merz + Co., Frankfurt-am-Main, Germany) was dissolved in physiological saline. Morphine, naloxone, and their vehicles were injected subcutaneously while D-CPPene, memantine and their vehicles were administered intraperitoneally. All injections were delivered in a volume of 10 ml/kg. Dosages are based upon the forms of the drugs listed below.

2.3. Apparatus

Experiments were performed in eight identical shuttle boxes ($30 \times 30 \times 30$ cm). Each shuttle box was divided into two compartments of equal size by a sliding partition. These compartments were distinguished by color (white vs. black) and floor texture (wire mesh in the black compartment vs. rubber pad in the white compartment). Illumination of the white and the black compartments were 240 and 220 lx, respectively. The general light intensity in the animal facility and experimental room (1 m off the floor) was approximately 350–370 lx. A partition was placed between the compartments, which could either restrict movement to one compartment only or allow movement between the compartments through a 10×8 cm^2 opening. Pyroelectric infrared detectors (Foton-6, Rielta, St. Petersburg) based on a Lhi 954 sensing element (EG&G Heimann, Germany) were mounted above each of the compartments. The infrared detectors were interfaced to a custom-designed, PC-based data acquisition system that recorded transitions mice made between compartments and thereby, their position within the apparatus.

2.4. Place conditioning procedure

Immediately after arrival from the breeding center, mice were housed in groups. Housing conditions were stable for 1 week prior to and throughout the conditioning and testing.

The place conditioning procedure consisted of conditioning and post-conditioning periods. The conditioning period consisted of 30-min experimental sessions run twice a day for 4 consecutive days (days 1–4). Each day, the animals received a saline injection before being confined to one compartment for 30 min, then were returned to home cages and injected with 20 mg/kg of morphine (or saline) 1 h later. Second daily conditioning trial took place 4 h after morphine injection. Mice were injected with naloxone (or saline) before placement into the compartment opposite to the one paired with saline injection during the first daily trial. Injections were performed 2 min before sessions.

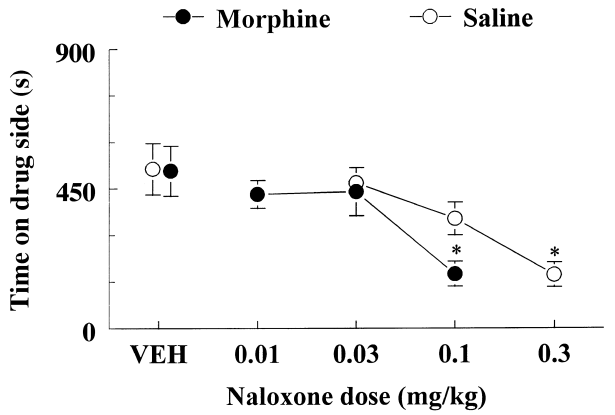

Fig. 1. Place conditioning with naloxone in mice. On 4 consecutive days, there were two daily 30-min place conditioning trials separated by an interval of 5 h. Saline and naloxone injections were paired with two distinctive compartments of the two-compartment shuttle box. Four hours prior to conditioning trial with naloxone (vehicle, 0.01–0.3 mg/kg), mice were administered either saline (open circles) or morphine (20 mg/kg, closed circles) and were returned to home cages. Post-conditioning tests were held 72 h after the last conditioning session. Data are represented as mean (±S.E.M.) time spent in drug-paired compartment during the test (s). $N = 7–8$ mice per group. $^{*}P < 0.05$ (Dunnett's test), compared to the group conditioned with vehicle instead of naloxone ('VEH').

To study the effects of NMDA receptor antagonists on naloxone-conditioned place aversion, separate groups of mice received various doses of D-CPPene, memantine or their vehicles that were administered 30 min prior to morphine, simultaneously with morphine, 2 or 3.5 h after morphine. Drug-paired compartment (i.e., white or black) was counterbalanced across each treatment group.

Post-conditioning tests were conducted 72 h after the last conditioning session. Mice were injected with saline and were allowed to freely explore both compartments for 900 s (15 min). Each post-conditioning session began with the initial placement of the mouse into the white compartment. Shuttle boxes were deodorized with H_2O_2 solution after each animal placement.

Our pilot experiments demonstrated that preconditioning tests, which are often employed in place conditioning studies, dramatically affected the magnitude (greater variability) of place conditioning with several classical agents such as morphine. Thus, the present study was based on an experimental design consisting of only two phases — conditioning and post-conditioning. To control for possible initial place preferences caused by apparatus or light conditions, nine groups of 10 mice each were formed from a separate pool of experimentally and drug-naive mice. For each of these groups, a 15-min test was conducted, in which the animals were allowed to explore both compartments freely. These tests have confirmed that there were no significant initial place preferences for drug- and experimentally naive mice allowed to explore the shuttle boxes freely. The mean (±S.E.M.) time spent in the white compartment was 439 ± 8 s (median = 435 s, inter-quantile range = 81 s; $N = 90$).

2.5. Dose–effect relationships for naloxone-induced place aversion

The first set of experiments compared the ability of several doses of naloxone (0.01, 0.03, 0.1 and 0.3 mg/kg) to produce place aversion in mice pretreated with either saline or morphine (20 mg/kg). No NMDA receptor antagonists were given in these experiments.

2.6. Effects of NMDA-receptor antagonists on naloxone-induced place aversion

Based on the results from naloxone dose–effect study, the dose of naloxone of 0.1 mg/kg was selected for further experiments. This dose failed to produce significant place aversion in saline-pretreated mice but was clearly effective in mice pretreated with morphine 4 h prior to conditioning trials. D-CPPene (vehicle, 0.1, 0.3, 1 or 3 mg/kg) was administered either 0.5 h prior to or 3.5 h after morphine injection. Memantine (vehicle, 1, 3 or 10

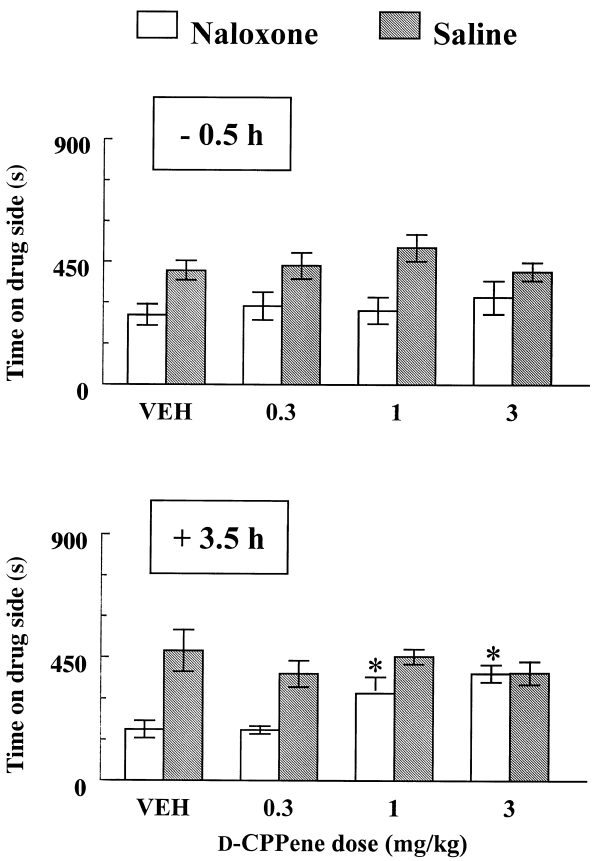

Fig. 2. Effects of D-CPPene on morphine-potentiated naloxone place aversion. Four hours prior to conditioning trials with naloxone (0.1 mg/kg, open bars) or saline (hatched bars), mice were administered morphine (20 mg/kg). D-CPPene was injected either 0.5 h prior to morphine (−0.5 h) or 3.5 h after morphine (+3.5 h). Data are represented as mean (±S.E.M.) time spent in drug-paired compartment during the test (s). $N = 7–8$ mice per group. $^{*}P < 0.05$ (Dunnett's test), compared to respective groups conditioned with naloxone instead of saline (open bars).

mg/kg) was administered 0.5 h prior to, simultaneously with, 2 or 3.5 h after morphine.

2.7. Data analysis

During each post-conditioning session, time spent in the drug-paired compartment was recorded. Statistical analysis was conducted using SAS-STAT software (release 6.11, SAS Institute, Cary, NC). Analysis of the descriptive statistics demonstrated that some of the data were not distributed normally (Wilks–Shapiro's test). Following rank transformation, the data were subjected to analysis of variance (ANOVA) for designs with unequal cell sizes ($N = 7$ or 8 mice per each treatment group). Independent variables were: (a) naloxone dose, (b) morphine pretreatment, and (c) dose of NMDA receptor antagonist. Dunnett's *t*-test was used for pairwise between group comparisons.

3. Results

3.1. Dose–effect relationships for naloxone-induced place aversion

Following four drug-place pairings with naloxone in morphine-naive mice, significant place aversion was observed only for a group of mice that received 0.3 mg/kg of naloxone during the conditioning period (Fig. 1, open circles). Meanwhile, lower dose of naloxone (0.1 mg/kg) was sufficient for establishing place aversion in mice that were exposed to morphine 4 h prior to each conditioning trial with naloxone (Fig. 1, closed circles). Thus, unless specified otherwise, this dose of naloxone (0.1 mg/kg) was used in subsequent experiments. Global ANOVA confirmed that effects of naloxone significantly depended on whether or not mice were pretreated with morphine ($F(4,65) = 3.1$, $P < 0.05$).

3.2. Effects of NMDA-receptor antagonists on naloxone-induced place aversion

In this set of experiments with morphine pre-exposures, aversive place conditioning with 0.1 mg/kg of naloxone was reproduced several times when vehicle was administered instead of D-CPPene or memantine (Figs. 2 and 3; data points above 'VEH'). D-CPPene dose-dependently attenuated naloxone-induced place aversion in mice that received D-CPPene 3.5 h after morphine (main effect of D-CPPene dose: $F(3,53) = 4.0$, $P < 0.05$; D-CPPene by naloxone interaction: $F(3,53) = 4.2$, $P < 0.01$; Fig. 2, lower panel). When D-CPPene was administered 30 min prior to morphine, naloxone produced significant place aversion ($F(1,56) = 24.2$, $P < 0.01$) but effects of D-CPPene were not statistically significant (main effect of D-CPPene dose: $F(3,56) = 0.3$; D-CPPene by naloxone interaction: $F(3,56) = 0.6$; Fig. 2, upper panel).

Treatment with memantine had no effect on place conditioning with naloxone irrespective of injection time (Fig. 3; memantine by naloxone interaction: 30 min prior to morphine, $F(3,53) = 0.4$; simultaneously with morphine: $F(3,55) = 1.6$; 2 h after morphine: $F(3,54) = 2.2$; 3.5 h after morphine: $F(3,55) = 0.1$).

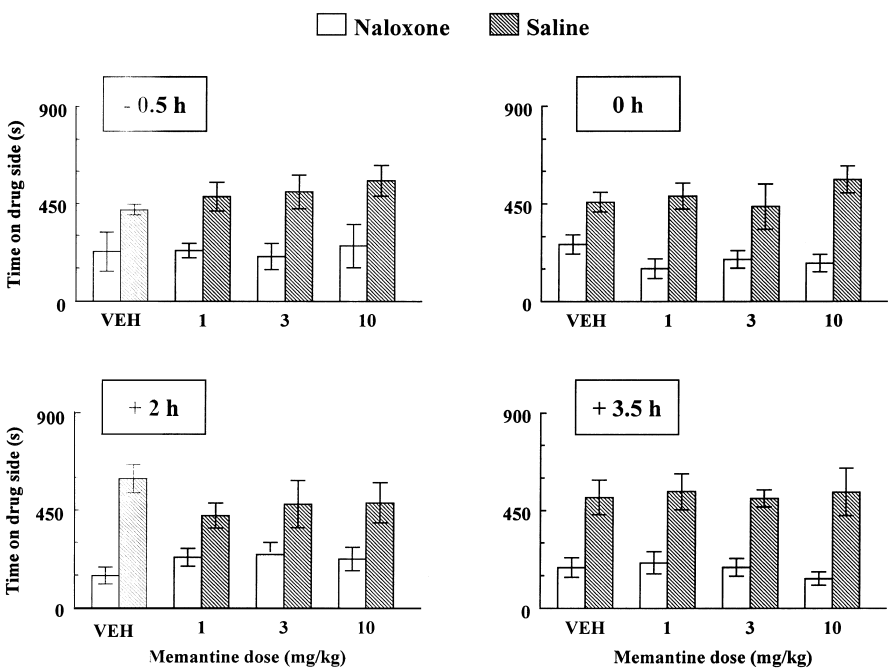

Fig. 3. Effects of memantine on morphine-potentiated naloxone place aversion. Four hours prior to conditioning trials with naloxone (0.1 mg/kg, open bars) or saline (hatched bars), mice were administered morphine (20 mg/kg). Memantine was injected either 0.5 h prior to (−0.5 h), simultaneously (0 h), 2 h (+2 h) or 3.5 h after morphine (+3.5 h). Data are represented as mean (±S.E.M.) time spent in drug-paired compartment during the test (s). $N = 7–8$ mice per group.

4. Discussion

There were two major findings in this study. First, place conditioning with opioid antagonist naloxone was found to be significantly potentiated by morphine administration prior to each conditioning trial with naloxone. Similarly to earlier studies with operant conditioning procedures (Adams and Holtzman, 1990; Young, 1986), place conditioning successfully revealed potentiation of behavioral effects of the opioid antagonist by pre-exposure to an opioid receptor agonist. These results are also in compliance with the recent report by Parker and Cyr (1999) where single trial conditioning with naloxone produced significant place aversion in rats pretreated with morphine (20 mg/kg) 6, 24 or 48 h prior to conditioning. In these experiments, the effect of the time interval between morphine and naloxone was less important than in operant conditioning studies (Young, 1986) that may at least in part be due to relatively high dose of naloxone (1 mg/kg) that is aversive by itself.

In the present study, the dose of naloxone (0.1 mg/kg) that failed to produce conditioned place aversion on its own, was effective in mice that received injection of morphine 4 h prior to naloxone. In other words, morphine-induced potentiation of behavioral effects of naloxone was evidenced as a rightward shift in naloxone dose–effect curve (Fig. 1). The magnitude of this shift was relatively small but would most likely be more pronounced if it had been possible for the study design to involve more morphine and naloxone administrations and to use a wider range of naloxone doses. Operant conditioning studies have clearly demonstrated that repeated tests facilitated the expression of the morphine-induced sensitization where crucial role is played by classical conditioning factors and cumulative naloxone dosing (Adams and Holtzman, 1990; Schindler et al., 1990).

The place conditioning procedure has certain advantages over the traditional operant methodology and may be especially useful in pharmacological studies that explore the mechanisms of agonist-induced facilitation of behavioral effects of an antagonist drug. For instance, various drugs may be used to probe the neurotransmitter mechanisms of this phenomenon. Such studies would require the administration of the test drugs with morphine and/or naloxone. The results obtained with the operant conditioning techniques may be dramatically affected by the ability of the test drugs per se to produce operant decrement. Indeed, our own data suggested that NMDA receptor antagonists (e.g., competitive antagonist D-CPPene) decreased response rate that significantly complicated the analysis of their effects on morphine-induced sensitization to naloxone's effects (Medvedev et al., in preparation).

The second finding of the present study illustrates this distinction between place conditioning and operant conditioning approaches. The second set of experiments reported here evaluated the ability of two NMDA receptor antagonists to prevent the establishment of naloxone place aversion. Competitive NMDA receptor antagonist, D-CPPene, exerted inhibitory influences on place conditioning with naloxone but did not induce any effect by itself (i.e., place preference or place aversion). It is noteworthy that D-CPPene prevented the establishment of naloxone-conditioned place aversion in mice that received this drug 0.5 h prior to the conditioning trial with naloxone. When D-CPPene was administered 0.5 h prior to morphine (i.e., 4.5 h prior to naloxone), no such effect was observed that may be due to relatively short half-life of D-CPPene, which was estimated to be approximately 0.6 h (Herrling et al., 1997).

Assuming that the morphine-induced potentiation of behavioral effects of naloxone shares common mechanisms with opioid dependence induced by repeated morphine exposures, this finding is in line with the well-described effects of NMDA receptor antagonists on both the development and expression of opioid dependence (Herman et al., 1995).

However, it may be argued that the effects of D-CPPene observed in the present study may be due to general non-selective impairment of place conditioning produced by NMDA receptor antagonists. Previous studies have repeatedly shown that establishment of drug conditioned place preference is retarded by concurrent administration of NMDA receptor antagonists. For instance, NMDA receptor antagonists were demonstrated to attenuate place preferences conditioned with morphine and cocaine (Cervo and Samanin, 1995; Tzschentke and Schmidt, 1995). Nevertheless, there are reasons to believe that effects of NMDA receptor antagonists are due to specific pharmacological interactions with the drugs used for place conditioning. There is some evidence suggesting that NMDA receptor antagonists may be ineffective against place conditioning with food in food-deprived animals (Popik and Danysz, 1997).

Furthermore, the specificity of the effects of D-CPPene is also suggested by the negative results obtained with memantine. Memantine was administered in separate groups of mice at different intervals prior to or after morphine but the results were almost invariably the same. Importantly, memantine, like D-CPPene, is known to affect opioid dependence (Medvedev et al., 1998; Popik and Danysz, 1997; Popik and Skolnick, 1996) and was also shown to retard establishment of drug conditioned place preference (Popik and Danysz, 1997). It is of special relevance to this study that memantine prevented the establishment of naloxone-conditioned place aversion in rats with pre-established morphine dependence. In this study (Popik and Danysz, 1997), rats were exposed to morphine (10 mg/kg, b.i.d., 8 days) prior to one-trial conditioning with naloxone (0.1 mg/kg) that occurred 1.5 h after the last morphine injection.

Another potential explanation of the results with D-CPPene is the state-dependency phenomenon. During the conditioning trials, mice were exposed to naloxone and

naloxone-paired environment while being drugged (i.e., after D-CPPene administration) while tests were held in D-CPPene-free state. However, such interpretation of the results is again confounded by the results with memantine that is known to produce partial substitution for phencyclidine within the dose range used in this study (Nickolson et al., 1998). In other words, it is unlikely that negative results with memantine were due to less intense interoceptive effects produced by this drug.

Instead, the present results may further support the evidence on the existing differences between competitive and noncompetitive NMDA receptor antagonists (Wiley and Balster, 1994; Willetts and Balster, 1989). Both agents used in this study are capable of retarding NMDA receptor-mediated neurotransmission but apparently do that in an essentially different way that determines their pharmacological profile. For instance, it was suggested that noncompetitive antagonists are more effective under conditions of tonic activation of neural pathways while competitive antagonists are more advantageous when phasic processes dominate (Carlsson, 1993).

Thus, two conclusions may follow. First, the ability of an NMDA receptor antagonist to interfere with the maintenance or expression of opioid dependence does not predict its effects on morphine-potentiated naloxone-conditioned place preference. Second, the NMDA receptor blockade produced by competitive antagonists (e.g., D-CPPene) and channel blockers (e.g., memantine) is functionally distinct and these drugs may differentially affect certain phenomena such as naloxone-induced place aversion in morphine-pretreated mice.

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