Reduction of the Morphine Maintenance by Blockade of the NMDA Receptors during Extinction Period in Conditioned Place Preference Paradigm of Rats

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ABSTRACT

Introduction: Activation of N-methyl-d-aspartate (NMDA) glutamate receptors in the nucleus accumbens is a component of drug-induced reward mechanism. In addition, NMDA receptors play a major role in brain reward system and activation of these receptors can change firing pattern of dopamine neurons. Blockade of glutamatergic neurotransmission reduces the expression of conditioned place preference (CPP) induced by morphine. Therefore, in this study, by using an NMDA receptor antagonist, DL-2-Amino-5-phosphonopentanoic acid sodium salt (AP5), the role of NMDA receptors on the maintenance and reinstatement of morphine-CPP was investigated.

Methods: Forty-three adult male albino Wistar rats were used in this study. After subcutaneous administration of effective dose of morphine (5 mg/kg) during CPP paradigm, the animals received intracerebroventricular doses of AP5(1, 5, and 25 mM/5µL saline) during extinction period (free morphine stage). Conditioning score was recorded during extinction period and reinstatement phase. Besides, another group of the animals received a single dose administration of AP5(5 mM) just before the administration of ineffective dose of morphine (1 mg/kg) in reinstatement phase.

Results: The results revealed that two doses of this antagonist (5 and 25 mM) significantly shortened the extinction period of morphine-CPP but did not reduce reinstatement induced by priming dose of morphine. Moreover, the single dose administration of AP5(5 mM) just before prime-morphine injection decreased reinstatement of morphine-CPP.

Conclusion: These findings indicate that blockade of NMDA receptors during extinction period reduces maintenance but not reinstatement of morphine. In addition, blocking these receptors in reinstatement phase decreases reinstatement to extinguished morphine.

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1. Introduction

Glutamate is the most important excitatory neurotransmitter in the brain and modulates as much as 70% of synaptic neurotransmission in the central nervous system (Gass & Olive, 2008). Several studies have found that glutamate receptors are involved in memory consolidation, and also the role of N-methyl-d-aspartate (NMDA) receptors in learning and memory has been well-recognized (Ben Mamou, Gamache, & Nader, 2006; Suzuki et al., 2004).

Several lines of evidence have demonstrated that glutamatergic systems are involved in different stages of brain reward system, including development (acquisition), expression, and maintenance (Koyuncuoglu, Dizdar, Aricioglu, & Sayin, 1992; Tokuyama, Wakabayashi, & Ho, 1996; Tzschentke & Schmidt, 1995). Glutamate synaptic transmission at NMDA receptor site facilitates the acquisition, expression, and maintenance of morphine (Noda & Nabeshima, 2004). Activation of these receptors in the nucleus accumbens (NAc) and ventral tegmental area (VTA) is essential for the realization of previous environments related to drug seeking (e.g. morphine craving) (Popik & Kolasiewicz, 1999). Furthermore, dopaminergic and glutamatergic systems have critical roles in reward-related phenomena and dopaminergic projections from VTA to NAc and many other areas such as prefrontal cortex, amygdala, as well as hippocampus releasing dopamine in response to reward-induced stimuli (Ikemoto, 2010; Ikemoto & Bonci, 2013).

Many studies have indicated the interaction of NMDA receptors and morphine usage. For example, Murray et al. (2007) reported that morphine usage could change expression of NMDA receptor subunit in the NAc; indicating that NMDA receptors in this region are implicated in the development of opiate dependence. Studies have shown that ionotropic glutamate receptors, especially NMDA receptors contribute in the processing of drug-related reward system (Bisaga & Popik, 2000; Harris, Wimmer, Byrne, & Aston-Jones, 2004). Moreover, there are numerous NMDA receptors in the NAc (Kombian & Malenka, 1994) which play a modulatory role in consolidation of reward-induced memory, including odor- and drug-induced reward system (Lee, Milton, & Everitt, 2006; Torras-Garcia, Lelong, Tronel, & Sara, 2005).

Evidence suggests that repeated drug treatment can lead to neuroplasticity in the hippocampus that may play a role in memory of drug craving-related cues (Fakira, Portugal, Carusillo, Melyan, & Moron, 2014). Infusion of NMDA receptor antagonists can block the development and expression of morphine-induced reward (Ma et al., 2006). Also, glutamate NMDA receptors are involved in reconsolidating of morphine-related memories (Wu, Li, Gao, & Sui, 2012). Although glutamate participation in modulation of the morphine-induced reward is well-documented, more investigations are needed to confirm its role in different stages such as extinction (maintenance period) and reinstatement of morphine.

Reinstatement to morphine usage after long-term extinction or abstinence is a common feature of drug users and has remained a main problem in treating drug abuse (Ribeiro Do Couto, Aguilar, Manzanedo, Rodriguez-Arias, & Minarro, 2003). Therefore, in this study, we tried to investigate the effects of intracerebroventricular (ICV) injection of NMDA receptor antagonist, AP5, on maintenance and reinstatement of morphine-induced conditioned place preference (CPP) in rats.

2. Methods

2.1. Animals

Forty-three male Wistar rats (230-280 g weight) were obtained from Pasture Institute, Tehran, Iran. Throughout the experiments, the animals were housed under controlled environmental conditions (temperature 22±2°C; Humidity 60%-65%) on a 12:12 h light/dark cycle and permitted to acclimate for several days before the experiment. Food and water were available ad libitum, except during the experiments. All protocols for this research were approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran. All experiments were in accordance with the internationally accepted principles for the Care and Use of Laboratory Animals as found in the US guidelines (NIH publication No. 80-23, revised in 1996).

2.2. Drugs

Morphine sulfate (Temad, Iran) was dissolved in physiological saline (0.9% NaCl) and injected subcutaneously (SC). NMDA receptor antagonist, AP5(DL-2-Amino-5-phosphonopentanoic acid sodium salt) (bought from Tocris Bioscience, Bristol, UK) was diluted in 0.9% saline as a vehicle.

2.3. Surgical preparation

Rats were anesthetized with intraperitoneal (IP) injection of a mixture containing ketamine 10%(100 mg/kg) and xylazine 2%(10 mg/kg). A cannula (Stoelting, stereotaxic apparatus, USA) was stereotaxically placed in the

lateral ventricle. The location was defined by the rat brain atlas (Paxinos & Watson, 2007) as AP=-0.5 mm caudal to bregma, Lat=1.6 mm lateral to midline, DV=4.2 mm ventral from the skull surface (guide cannula was 1 mm above the suitable injection place). After the cement was completely dried and compacted, stainless steel wire was used to close the guide cannula during recovery period. Animals were allowed to recover from surgery for 5-7 days before testing.

2.4. Drug administration

Microinjection was done by lowering stainless steel infusion cannula (30-gauge needle) with a length of 1 mm longer than the guide cannula into the lateral ventricle. The infusion cannula was connected to a 5-µL Hamilton syringe by polyethylene tubing (PE-20).

2.5. Behavioral test

2.5.1. Conditioning apparatus and paradigm

In this study, morphine rewarding properties in all stages were assessed by using a homemade 3-chamber CPP box (Borj Sanat, Iran). It was made of Plexiglas and its 2 large chambers were equal in size (30×30×40 cm), but distinct in shading and texture. To distinguish these two chambers from each other, chamber A was white with black horizontal stripes 2 cm wide on walls and also had a textured floor. Chamber B was black with vertical white stripes 2 cm wide and also had a smooth floor. The third compartment (C) was a red tunnel (30×15×40 cm) that was not paired with saline or morphine treatment. It protruded from the back of the 2 large chambers and connected to their entrances. In this apparatus, rats showed no consistent preference for either compartment, which supports our unbiased CPP paradigm. CPP comprised 3 phases with a 5-day schedule, and was carried out following an unbiased procedure: Preconditioning, conditioning, and postconditioning.

2.5.1.1. Preconditioning phase

During this phase (day 1), each animal was located individually into the apparatus and allow access to all chambers for 10 minutes. Each animal's motion was recorded by EthoVision software (Version 3.1), a video tracking system for automation of behavioral experiments (Noldus information Technology, the Netherlands) and using a 3CCD camera (Panasonic Inc., Japan) placed 2 m above the CPP box. In the experimental setup, the animals did not show any preference for either of chambers. Then, animals were randomly determined to one of the two chambers for place conditioning.

2.5.1.2. Conditioning phase

This phase started 1 day after the preconditioning phase. It comprised six, 30-minute sessions (3 with saline and 3 drug pairing) in a 3-day schedule. These sessions were conducted twice each day (from day 2 to day 4) with 6 hours intervals. On each day, separate groups of animals received conditioning sessions with morphine and another with saline. Conditioning sessions comprised one in the morning and the other in the afternoon.

Based on our recent studies (Haghparast, Azizi, Hassanpour-Ezatti, Khorrami, & Naderi, 2009; Haghparast et al., 2013; Taslimi, Haghparast, Hassanpour-Ezatti, & Safari, 2011), 5 mg/kg morphine (SC) was chosen as the effective dose for the present experiments. During the 30-minute interval sessions for morphine or saline treatment, the animals were immediately confined in the cue-specific chamber by closing the removable wall. The treatment compartment and the order of presentation of morphine/saline were counterbalanced for either group.

Postconditioning phase. After 3 consecutive sessions, on the fifth day (test day), the gate was removed, and the rats were allowed free access to all chambers for 10 minutes. The mean time spent for each rat in all chambers was recorded by EthoVision software. Conditioning score (CPP score) represents the time spent in the drug-paired compartment minus the time spent in saline-paired compartment during a 10-minute period (Azizi, Haghparast, & Hassanpour-Ezatti, 2009).

2.5.2. Extinction and reinstatement of morphine-induced CPP

After finishing CPP paradigm, the animals were placed in CPP apparatus (on days 6-13) without any morphine injection (extinction period) and conditioning score was recorded every day. This procedure was repeated for each animal until the calculated CPP scores in 2 consecutive days in extinction period became equal to those on the preconditioning day. Thus, the scale for extinction or maintenance of morphine rewarding properties in all groups was a lack of significant differences in preference scores between 2 consecutive days in the extinction period and the preference score on the preconditioning day.

Morphine reinstatement was measured by giving rats a priming injection of morphine (ineffective dose; 1mg/kg, SC) immediately prior to placing animals in the CPP apparatus with free access to all compartments. The amount of time spent in each chamber was also recorded for calculation of place preference in this phase (Khaleghzadeh-Ahangar & Haghparast, 2015).

2.6. Experimental design

In the present study, morphine-CPP was initially done. Then, the animals were entered to extinction and reinstatement phases (n=6-8 in each group).

2.6.1. Effects of ICV daily administration of different doses of NMDA receptor antagonist, AP5, during the extinction period on maintenance and reinstatement of morphine

In this set of experiments, to evaluate the effect of NMDA receptor antagonist on morphine rewarding properties, the animals received AP5 at different doses (1, 5, and 25 mM/5 µL saline, ICV) every day, 30 minutes prior to CPP test, during extinction period. Conditioning score was calculated in each day. Additionally, after determining the duration of extinction period, morphine reinstatement was measured by giving rats a priming injection of morphine (ineffective dose; 1 mg/kg, SC) immediately prior to placing animals in the CPP apparatus with free access to both sides. In the vehicle group, saline (instead of AP5) was unilaterally microinjected into the lateral ventricle.

2.6.2. Effects of ICV single administration of NMDA receptor antagonist on the maintenance of morphine

To evaluate the effects of single injection of NMDA receptor antagonist on extinction period, ICV single administration of maximal effective dose of AP5(25 mM) was performed after postconditioning test (before extinction period). Then, 30 minutes after microinjection, the animals were exposed to CPP apparatus daily without morphine or drug injections, and conditioning score was calculated.

2.6.3. Effects of ICV single administration of NMDA receptor antagonist on reinstatement of morphine

In this experiment, to investigate the effect of ICV single injection of NMDA receptor antagonist on the reinstatement of morphine, an effective dose of NMDA receptor antagonist was microinjected into the lateral ventricle, prior to the administration of ineffective dose of morphine (1 mg/kg; SC). In fact, ICV single microinjection was performed after the extinction period. Animals were exposed to the CPP apparatus 30 minutes after microinjection and conditioning score was calculated.

2.7. Histology

After completion of behavioral testing, including extinction and reinstatement experiments, the animals were deeply anesthetized with ketamine and xylazine. Then, they were transcardially perfused with 0.9% saline and 10% formalin solution. The brains were removed, fixed, and cut coronally in 50 µm sections through the cannula placement. The neuroanatomical location of cannula tip placement was confirmed using Paxinos and Watson rat brain atlas (Paxinos & Watson, 2007). Only the animals with correct cannulae placements were included in the data analysis (Figure 1).

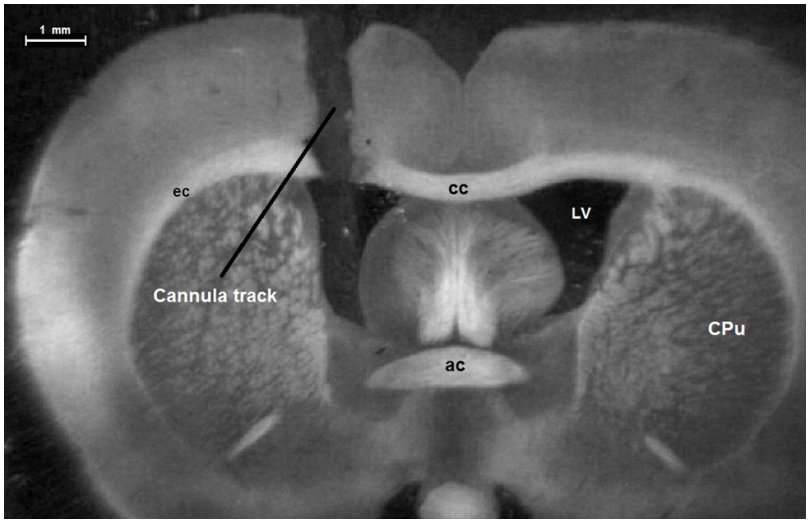

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Figure 1. Coronal photomicrograph of representative cannula placement and unilateral microinjection site (AP5 or vehicle [saline]) in the lateral ventricle of the rat brain.

Abbreviations: ac: anterior commissure, cc: corpus callosum, CPu: Caudate Putamen (striatum), ec: external capsule, LV: Lateral ventricle.

Scale bar=1 mm.

2.8. Statistics

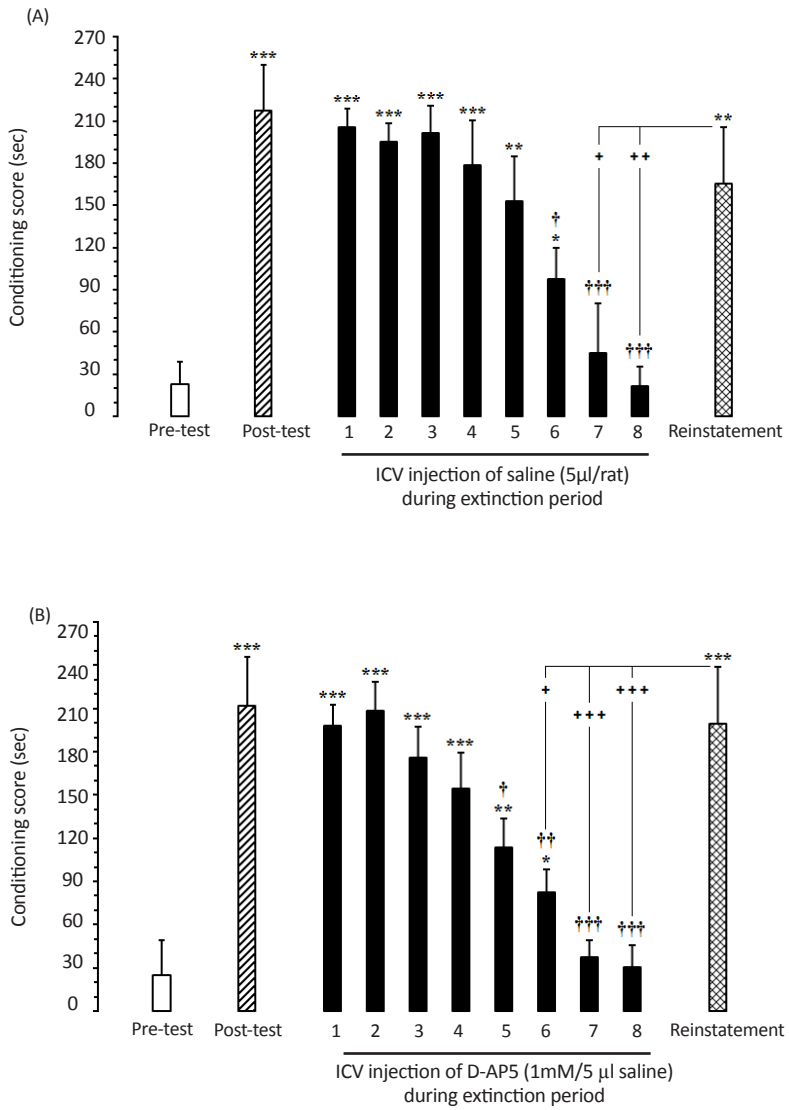
Conditioning score was expressed as mean±SEM (standard error of mean). Data were analyzed by Graph Pad Prism® (Version 5.0) software. In order to compare the conditioning scores in the control and experimental groups, repeated measures 1-way analysis of variance (ANOVA) followed by post hoc analysis (Newman-Keuls) was used. P values less than 0.05 were considered to be statistically significant.

3. Results

3.1. Effects of ICV daily administration of different doses of NMDA receptor antagonist, AP5, during the extinction period on the maintenance and reinstatement of morphine

Obtained data in this set of experiment showed that daily ICV injection of saline (5 µL/rat) during the extinction period did not affect the duration of this period in morphine-induced CPP paradigm (Figure 2A). Repeated measures 1-way ANOVA followed by Newman-Keuls multiple comparison test ($F(10, 76)=8.137$; $P<0.0001$) showed that in saline-received group, the animals had lost their preference for the morphine-paired compartment in the seventh and eighth extinction days (i.e. no significant difference between time spent in saline- and morphine-paired compartments).

However, the priming dose of morphine (1 mg/kg; SC) reinstated the extinguished morphine-induced CPP and there was a significant change in magnitude of CPP scores in pre-test and reinstatement days ($P<0.01$; Figure 2A). One-way repeated measures ANOVA ($F(10, 65)=11.53$; $P<0.0001$) followed by Newman-Keuls multiple comparison test indicated that ICV injection of 1mM dose of AP5 during extinction period did not affect the maintenance and reinstatement of morphine (Figure 2B) compared to saline-control group.



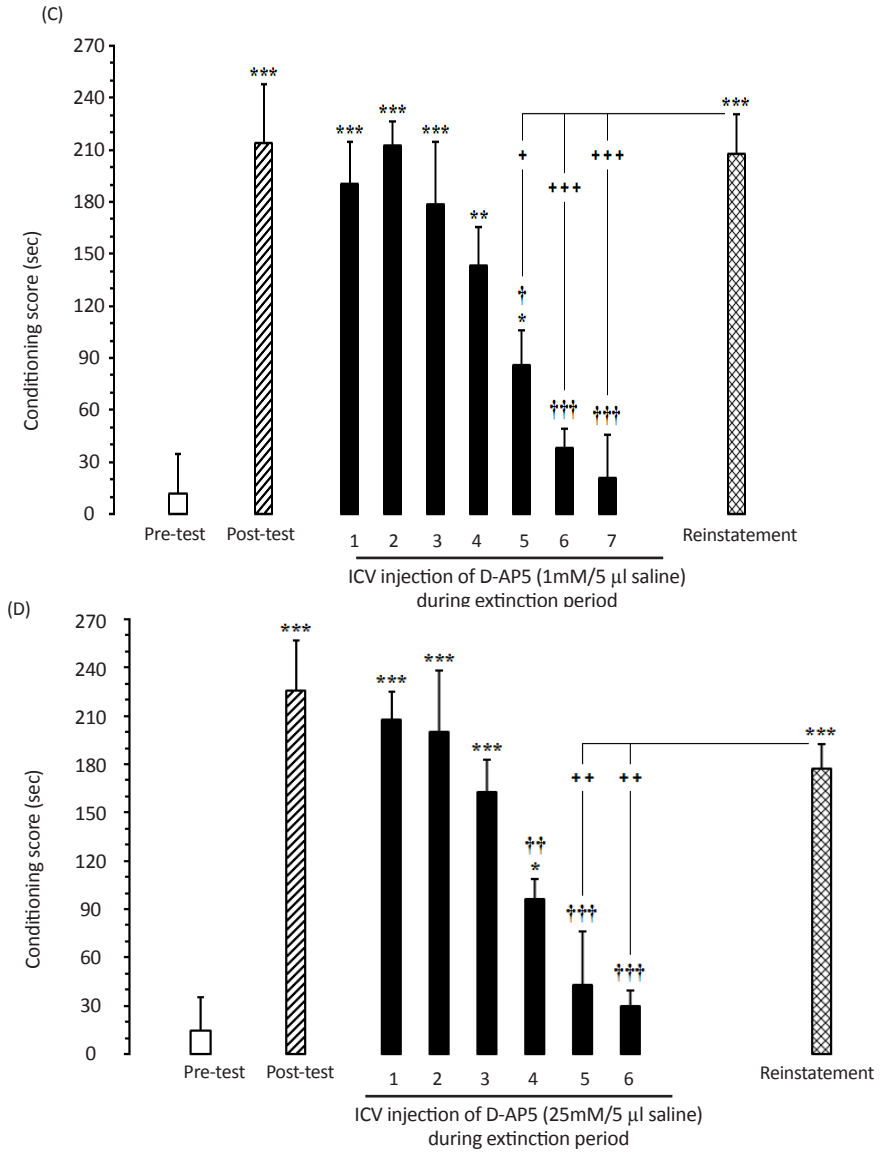


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Figure 2. Effects of ICV injection of (A) saline or different doses of AP5 (NMDA receptor antagonist) (B) 1 mM (C) 5 mM, and (D) 25 mM/5 µL saline into the lateral ventricle on the maintenance and reinstatement of morphine in conditioned place preference paradigm. Animals received saline or AP5 during the extinction period (free morphine period). In the reinstatement day, animals received only priming dose of morphine (1 mg/kg; SC). Data are presented as mean±SEM for 6-7 rats.

*P<0.05, **P<0.01, and ***P<0.001 different from the pretest day.

†P<0.05, ††P<0.01, and †††P<0.001 different from the posttest day.

+P<0.05, ++P<0.01, and +++P<0.001 different from the reinstatement day.

In another part of these experiments, animals received a higher dose of AP5 (5 mM/5 µL saline; ICV) during extinction period. One-way repeated measures ANOVA ($F(9, 59)=10.82$; $P<0.0001$) followed by Newman-Keuls multiple comparison test revealed that rats lost their preference for morphine on the sixth and seventh extinction days ($P<0.001$ vs posttest day; Figure 2C). However, in this group, animals were reinstated by administration of a priming dose of morphine ($P<0.001$ compared with preconditioning preference score). Besides, as shown in Figure 2D, 1-way repeated measures ANOVA ($F(8, 53)=11.61$; $P<0.0001$) followed by Newman-Keuls multiple comparison test confirmed that ICV injection of the highest dose of AP5 (25 mM/5 µL saline) can facilitate the extinction (reduce the maintenance of morphine rewarding properties) from 8 days to 6 days. Nevertheless, although this dose of

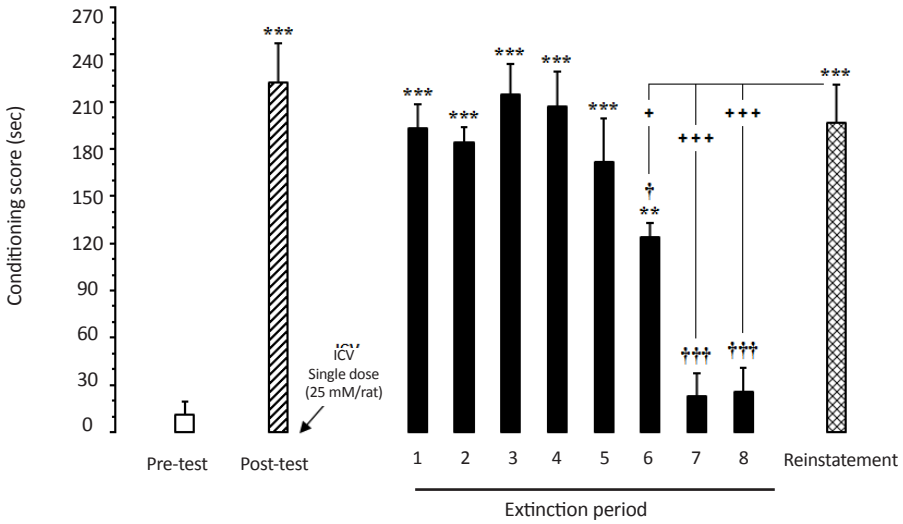

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Figure 3. Effects of single dose injection of NMDA receptor antagonist (before extinction period) on the maintenance and reinstatement of morphine rewarding properties in conditioned place preference paradigm. Animals received a single injection of AP5(25 mM/5 µL saline; ICV) just after postconditioning CPP test. In this set of experiment, animals did not receive any drug (AP5) or saline/morphine during the extinction or reinstatement days. Data are presented as mean±SEM for 8 rats.

**P<0.01 and ***P<0.001 different from the pretest day.

†P<0.05 and †††P<0.001 different from the posttest day.

+P<0.05 and +++P<0.001 different from the reinstatement day.

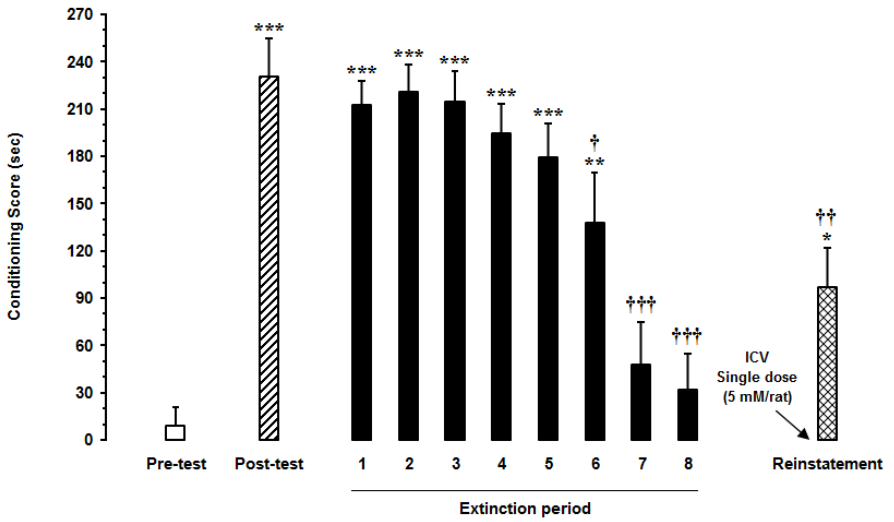

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Figure 4. Effects of single dose injection of NMDA receptor antagonist on the reinstatement of morphine in conditioned place preference paradigm. Animals received a single injection of AP5(5 mM/5 µl saline; ICV) just prior to administration of priming dose of morphine (1 mg/kg; SC) in reinstatement day. Data are presented as mean±SEM for 8 rats.

*P<0.05, **P<0.01, and ***P<0.001 different from the pretest day.

†P<0.05, ††P<0.01, and †††P<0.001 different from the posttest day.

AP5 could reduce the magnitude of the conditioning score in the reinstatement of morphine, this effect was not significant compared to the magnitude of this score in posttest day.

3.2. Effects of ICV single administration of NMDA receptor antagonist on the maintenance and reinstatement of morphine

We administered AP5 (25 mM/5 µL saline) after postconditioning phase to examine the effect of a single dose of NMDA receptor antagonist on maintenance and reinstatement of morphine-induced CPP. Regarding the place preference, 1-way repeated measures ANOVA ($F(10, 87)=20.53$; $P<0.0001$) followed by Newman-Keuls multiple comparison test confirmed that animals have lost morphine CPP on the seventh and eighth extinction days (similar to saline and AP5 1-mM treated groups; Figure 3). Also, priming dose of morphine could reinstate the extinguished rats. These data showed that, single ICV injection of the highest effective dose of AP5 after induction of CPP does not have any significant effect on the maintenance and reinstatement of morphine (Figure 3).

3.3. Effects of ICV single administration of NMDA receptor antagonist on the reinstatement of morphine

To evaluate the effect of single administration of NMDA receptor antagonist on morphine-induced reinstatement, the animals received ICV single injection of AP5 (5 mM/5 µL saline) just before the injection of ineffective dose of morphine (1 mg/kg). One-way repeated measures ANOVA ($F(10, 87)=14.5$; $P<0.0001$; Figure 4) followed by Newman-Keuls multiple comparison test indicated that AP5 (5 mM) could attenuate morphine reinstatement so that, conditioning score significantly decreased compared to postconditioning day ($P<0.01$).

4. Discussion

The aim of the present work was to evaluate the blockade of NMDA receptors during maintenance and reinstatement phases of morphine-induced CPP. The major findings were as follows: 1) Daily ICV microinjection of NMDA receptor antagonist (AP5) during extinction period can dose-dependently decrease morphine maintenance while it does not affect the morphine-induced reinstatement, 2) ICV single microinjection of AP5 before extinction period does not have any effect on the maintenance and reinstatement of morphine, and 3) ICV administration of this antagonist just before morphine-priming injection, attenuates reinstatement to morphine.

In our study, daily ICV microinjection of NMDA receptor antagonist, AP5, with high doses (5 and 25 mM) shortened extinction period and reduced the maintenance of morphine reward. These findings have approved previous studies that NMDA receptors have an important role in morphine-induced reward (Ma et al., 2006) and also drug-induced reward properties are associated with NMDA receptors (Panos, Rademacher, Renner, & Steinpreis, 1999). Systemic administration of NMDA receptor antagonists blocks maintenance or relapse when injected immediately after fear extinction phase (Myers, Carlezon, & Davis, 2011).

Also, systemic administration of NMDA receptor antagonist (NPC 17742) blocks the acquisition and extinction of conditioning paradigm (Popik & Kolasiewicz, 1999), but intra-medial prefrontal cortex infusions of AP5 prior to extinction disrupts extinction of amphetamine-induced CPP (Hsu & Packard, 2008). Besides, ICV infusion of this antagonist before extinction prevents extinction of conditioned opiate (Coleman, Carlezon, & Myers, 2013). Finally, systemic injection of NMDA receptor antagonist in a dose-dependent manner facilitates extinction of cocaine-induced CPP (Gass & Olive, 2009). Pretreatment with NMDA receptor antagonist (AP5) when injected into the VTA inhibits the acquisition of morphine-induced CPP (Harris et al., 2004).

In contrast, some studies have shown that d-cycloserine (DCS; NMDA partial agonist) facilitates the extinction of conditioned fear properties (Vervliet, 2008) and drug-craving behavior (Botreau, Paolone, & Stewart, 2006). Systemic administration of low dose of NMDA receptor antagonist (MK-801) does not affect the acquisition, extinction, and reinstatement of morphine-induced CPP (Fan et al., 2012). Additionally, systemic injection of the potent NMDA receptor antagonist (CPP) with low dose does not impair extinction memory in a self-administration paradigm (Kelamangalath, Swant, Stramiello, & Wagner, 2007). However, it seems that these discrepancies in results are probably due to different duration of drug receiving, route of administration, and dosage of the drug. Microinjection of NMDA receptor antagonists, D-AP5, before fear extinction paradigm damages memories related to both extinction period and reinstatement phase (Laurent & Westbrook, 2009) indicating that NMDA receptors are involved in consolidation despite of encoding extinction memory.

In our study, ICV single microinjection of AP5 prior to reinstatement phase attenuated prime-induced reinstatement of morphine. Reinstatement can occur by exposure to a priming dose of abused drug. Likewise, craving and drug seeking after treatment or after a period of abstinence is common among human drug users (Conklin & Tiffany,

2002). Modulation in synaptic plasticity and glutamatergic neurotransmission play a major role in the reinstatement of morphine-induced CPP (Portugal et al., 2014). Drugs that modulate the glutamate system could be important for treating reinstatement to multiple types of drugs (Knackstedt & Kalivas, 2009). AP5 injection directly into reward-related areas of the brain is capable of reducing cue-induced reinstatement (McFarland, Lapish, & Kalivas, 2003).

Administration of AP5 into NAc core dose-dependently attenuates reinstatement of cocaine (Backstrom & Hyytia, 2007). Many studies link glutamate NMDA receptors to the consolidation cue-paired memory. For example, NMDA receptor antagonists disrupt the NMDA-related calcium signaling and the cellular cascades that produce long-term memory as well as impair learning and memory (Abel & Lattal, 2001). Blockade of the glutamatergic system with NMDA receptor antagonists can prevent the reinstatement of morphine-induced CPP. Therefore, drug-induced reinstatement of morphine CPP may be dependent on NMDA neurotransmission (Ribeiro Do Couto et al., 2003; Ribeiro Do Couto, Aguilar, Manzanedo, Rodriguez-Arias, & Minarro, 2005). In conclusion, considering the results of the present study, ICV administration of NMDA receptor antagonist during extinction period shortens morphine extinction but does not affect morphine reinstatement. Moreover, administration of this antagonist in reinstatement phase attenuates morphine reinstatement.

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Conflict of Interest

All authors declared no conflict of interest.

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