RESEARCH ARTICLE

The Blockade of Glutamate N-methyl-D-aspartate Receptors into the Prelimbic of Prefrontal Cortex Decreases Morphine-induced Conditioned Place Preference in Rat

Samad Javadi[1,2], Hojjatallah Alaei[3], Ebrahim Hosseini[2,*], Mohammad Amin Edalatmanesh[2]

[1]Department of Biology, Fars Science and Research Branch, Islamic Azad University, Fars, Iran
[2]Department of Biology, Shiraz Branch, Islamic Azad University, Shiraz, Iran
[3]Department of Physiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

*Corresponding author. E-mail: ebrahim.hossini@yahoo.com

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Abstract

BACKGROUND: The prelimbic area (PL) of the prefrontal cortex is susceptible to abnormal developmental stimuli that raises the risk of addiction. Glutamate receptors play a key role in opiate reinforcement and reward functions in this area. Therefore, we examined the effect of the DL-2-amino-5-phosphonopentanoic acid (AP5), as N-methyl-D-aspartate (NMDA) receptor antagonist into the PL on the phases of conditioned place preference (CPP) induced by morphine.

METHODS: Male Wistar rats were divided into 12 groups (3 surgical groups for each dose of morphine in any phase of CPP) and anaesthetized with chloral hydrate. Cannula was implanted into the PL and the AP5 was injected into this area and morphine-induced CPP was investigated. Data were processed with the commercially available SPSS 22 software using one-way ANOVA and Tukey's test. $p<0.05$ were considered statistically significant.

RESULTS: Our findings indicated, morphine in doses of 2.5 to 10 mg/kg induced CPP. Microinjection of various doses of the AP5 into the PL before the administration of the effective dose of morphine significantly reduced place preference in the acquisition and the expression phases of the CPP test compared to the sham group ($p<0.001$). In another set of our experiments was seen that, different doses of the AP5 with the ineffective dose of morphine only reduced the expression phase of the CPP ($p<0.001$) while, produced neither preference nor aversion effect on the acquisition phase ($p=0.147$).

CONCLUSION: It seems that the glutamate NMDA receptors in the PL through memory formation and morphine-related reward signals play a critical role in addiction process during morphine-induced CPP.

KEYWORDS: N-methyl-aspartate, morphine, glutamate receptor, prefrontal cortex, reward

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Introduction

Prelimbic area (PL) is a part of the prefrontal cortex (1) that modulates synaptic plasticity differently in nucleus accumbens during drug seeking (2). On the other hand, scientific evidences have also shown that glutamate transmission play a central role in synaptic plasticity.(3) The PL is also susceptible to abnormal developmental targets that raises the risk for addiction and other psychiatric disorders.(4,5) The PL is a section of the reward system which role of the glutamate transmission in case of morphine addiction in this part of the brain is not entirely clear. Hence, a series of behavioral studies were conducted to examine the role of the PL glutamate transmission during morphine related reward, learning and memory formation.

The glutamate is one of the most important stimulant neurotransmitter in the brain.(6) The glutamate system also controls opiate addiction in the PL with the N-methyl-D-aspartate (NMDA) receptors.(7) NMDA receptor is a ligand gated ion channel (8) and one of the fundamental neurotransmitter receptors in the brain (9) that is required

for activity of dopamine neurons in the ventral tegmental area (VTA).(10) The NMDA is a molecular target for several abuse drugs.(11) Also, this glutamate receptor plays a special role in reward (7), addiction (12) and recalling process (13). So, the current study was designed to evaluate the effect of intra-PL microinjection of the DL-2-amino-5-phosphonopentanoic acid (AP5) on the effective and the ineffective doses of morphine-induced conditioned place preference (CPP).

Methods

Animals

Our experiments were performed on male Wistar rats (weighing 250-300 g at the beginning of the experiment) provided by the Institute of Pasteur, Tehran. Five rats were housed per cage, with the room temperature maintaned at 20-24ºC, under a relative humidity of 40% and 12-hours period of light-dark.(14) All experiments were conducted in accordance to the international guiding for biomedical researches and the committee on animal care which is used in Isfahan University of Medical Sciences. All experimental protocols were confirmed by the Ethics Committee of the Isfahan University of Medical Science, Isfahan, Iran, followed the "Principles of Laboratory Animal Care" and performed in accordant with the European Communities Council Directive of 24 November 1986 (86/609/EEC).

Drug

Morphine was purchased from Temad (Tehran, Iran) and AP5 was bought from Sigma (California, USA). Morphine and AP5 were dissolved in saline.(14,15)

Surgical Procedures

Chloral hydrate was used for anaesthetizing of rats (400 mg/kg, intraperitoneally) then their heads were shaved and were located in a stereotaxic device; a cannula (22 G) was transplanted into the PL (AP=3.2mm, L=0.7mm, DV=3mm), according to the point were defined by Paxinus and Watson. (16) Finally, the cannula was anchored in the skull by dental cement. In order to preempt infection, Gentamycin (40 mg/ml, intraperitoneally) was administered immediately following the surgery.

Microinjection Method

All animals were allowed to being recovered for 1 week before the beginning of the behavioral test (17,18) and they were infused for the CPP experiment, before every morphine conditioning session. Animals were tested in a morphine-free state.(19)

Initially, any rat was kept motionless and injection needle that was connected to the Hamilton syringe by polyethylene tube (PE20) was placed to the guide cannula into the PL. The microinjection was done unilaterally via lowering an injector needle with 1 mm length longer than the guide cannula; next, different doses of the AP5 (0.1µg/0.5µL and 1µg/0.5µL) were injected with rate of 2 µL/min into the PL, 5 minutes before the acquisition/ expression phases of the experiment.(18) The injection cannula was left in the guide cannula for an additional 60 second to facilitate diffusion of the drug and then removed.(15,18,19) Low or high dose of the AP5 was microinjected and any rat was examined only once for behavioral test of the CPP.

Behavioral Testing-place Preference Paradigm

Among the different behavioral methods were used to measure drug reward in laboratory animals, the CPP has been one of the most popular. The CPP apparatus consists of three chambers (A, B and C). Compartments A and B have the same size but different color. The walls inner surface and floor of compartment A are black and white while, the walls surface and floor of other compartment are all white. Compartment C is smaller that opens to parts A and B via a guillotine door. The Behavioral procedure of the CPP was done in five continuous days and has three distinct stages.(17,20)

Preconditioning

In the pre-test day, each rat was placed in chamber C while the middle door was opened and the rat was allowed move freely for 15 minutes in all chambers. The time spent in each chamber (A and B) was recorded by the apparatus.

Conditioning

This phase consists of 3 days (from day 2 to day 4 and six sessions, 3 saline and 3 morphine), each lasting 45 minutes. Guillotine door was closed and the daily injection was performed in two stages with a 6 hours interval. After the intraperitoneal injection of morphine, the animals were confined to morphine compartment of the CPP device for 45 minuts then, with an interval of 6 hours, following the injection of saline instead of morphine, the animals were housed to saline compartment of the CPP device for 45 minuts. On the 3rd day, morphine and saline injections were on the contrary to day 2, while on the day 4, morphine and saline injections were the same as day 2.(17,20)

Post Conditioning

In the post conditioning, after opening the guilltone door, animals moved freely in all the compartments of the device for 15 minutes. The elapsed time by morphine-recived animals in the morphine-paired compartment was recorded. The preference was calculated by discrepancy the time elapsed in the morphine-paired compartment on the post conditioning phase relate to preconditioning phase of the CPP paradigm.(17 20)

Morphine Dose-response on the CPP Paradigm

Different doses of morphine (0.5, 1, 2.5, 5, 7.5 and 10 mg/kg) were studied on the CPP. Animals were divided into 7 groups, each group including 7 rats; 6 groups received different doses of morphine while one group received saline. Morphine or saline was administrated intraperitoneally, according to the CPP paradigm and then calculated the changes of preference.

The Effect of the AP5 on Drug-naive and Morphine-received Animals

In another set of our experiments, we tested intra-PL AP5 versus intra-PL saline on three surgical groups of drug-naive animals. Also, difference score between intra-PL saline versus intra-PL AP5 groups was calculated by assessment the amount of time spent in saline-paired environment relative to the morphine-paired environment during the CPP.(21)

Microinjection of the AP5 Into the PL with Different Doses of Morphine

According to the experiment design, in this section of our experiment 12 groups of rats were used (7 in each group). The animals were divided into 3 surgical groups for each dose of morphine in any phase of the CPP; sham group and test groups (Table 1). Sham group received intra-PL saline and morphine via intraperitoneally without any microinjection of the AP5 but, test groups received intra-PL low or high doses of the AP5 before administration of morphine intraperitoneally on days 2, 3 and 4 during the acquisition phase of the CPP paradigm while animals only received the AP5 in the post conditioning of the expression phase of the CPP protocol.

Table 1. Experimental groups in the CPP test for microinjection of the AP5 into the PL with different doses of morphine.

Morphine dose	CPP Phase	
	Acquistion Phase	Expression Phase
Effective dose	Sham Group AP5 (0.1µg/0.5µL) group AP5 (1µg/0.5µL) group	Sham Group AP5 (0.1µg/0.5µL) group AP5 (1µg/0.5µL) group
Ineffective dose	Sham Group AP5 (0.1µg/0.5µL) group AP5 (1µg/0.5µL) group	Sham Group AP5 (0.1µg/0.5µL) group AP5 (1µg/0.5µL) group

Histology

After performing behavioral test, the animals were anesthetized and were perfused with 0.9% saline followed by 10% formalin, rats brains were pulled out carefully and were placed in 10% formalin for 72 hours before to being sliced.(20) In order to evaluate the place of the antagonist injection and cannula, the PL sections were checked (Figure 1).

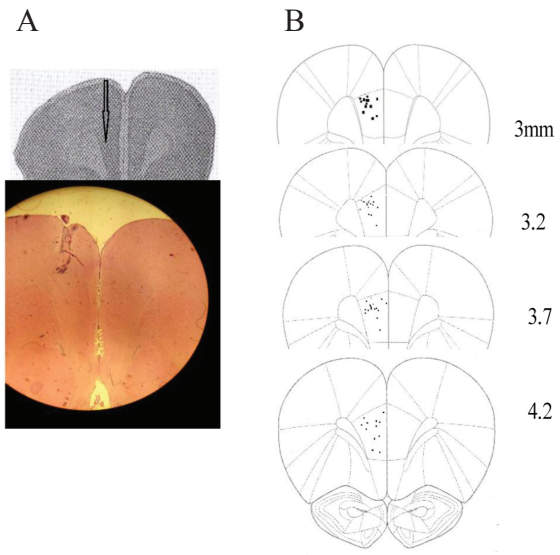

Figure 1. Photograph scan of rat brain's PL. A: Histological representation of cannula placement into the PL and site of antagonist microinjection in the brain of rat. B: Schematic representation of unilateral intra-PL cannula placement.

Statistical Analysis

Our data were analyzed by the commercially available SPSS 22 software (SPSS Inc, Chicago, IL) using one-way ANOVA and Tukey's test. Results are presented as means±s.e.m and the difference (with $p<0.05$) between the experimental groups was considered as statistically significant.

Result

Specify of the Effective Dose of Morphine-induced Place Preference

Saline and different doses of morphine (0.5, 1, 2.5, 5, 7.5 and 10 mg/kg) were tested for producing place preference in separate groups. Statistical analysis indicated that saline

did not induce place preference while, 2.5, 5, 7.5 and 10 mg/kg doses of morphine had a significant effect (p<0.05, p<0.001, p<0.01, p<0.001 respectively) but, 0.5 and 1 mg/kg doses of morphine did not induce significant effect on the CPP (p>0.05). Thus, based on this study 0.5 mg/kg, as the ineffective dose and 5 mg/kg, as the effective dose of morphine were selected for the subsequent experiment (Figure 2).

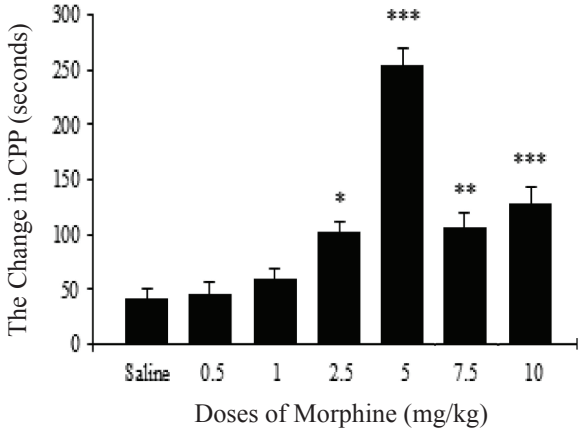

Figure 2. The effect of different doses of morphine on the CPP for determining the effective and the ineffective doses of morphine. Data was presented at mean±s.e.m and was analyzed using one-way ANOVA, Tukey's test. *p<0.05, **p<0.01 and ***p<0.001 are significant compared to saline group.

The Effect of the AP5 on Drug-naive and Morphine-received Animals

Our findings showed that, intra-PL microinjection different doses of the AP5 versus intra-PL saline produced no effects on drug-naive animals (p=0.181) (Figure 3A). Statistical analysis on difference score from baseline to test sessions can be performed to determine effects of drug. These results showed a significant effect of the AP5 on morphine-received animals while had no effect on drug-naive animals.

Data analysis indicated that difference score between intra-PL saline versus intra-PL AP5 groups showed a significant effect on time spent in morphine-paired compartment relative to saline-paired compartment (p<0.001) (Figure 3B).

Microinjection of Low-dose AP5 Into the PL with Different Doses of Morphine and Its Effect on the Acquisition and the Expression Phases of the CPP Paradigm

ANOVA analysis showed that the microinjection of low dose of the AP5 (0.1µg/0.5µL) into the PL before the administration of the effective dose (5mg/kg) of morphine significantly decreased the acquisition phase CPP compared to the sham group (p<0.001).

Based on statistically analysis, the microinjection of low-dose AP5 (0.1µg/0.5µL) produced neither preference nor aversion effect on the acquisition phase of the CPP with the ineffective dose (0.5mg/kg) of morphine (p=0.147) (Figure 4A).

Our results showed that the microinjection of low-dose AP5 into the PL before the administration of the effective dose of morphine significantly decreased the expression phase of the CPP compared to the sham group, also this

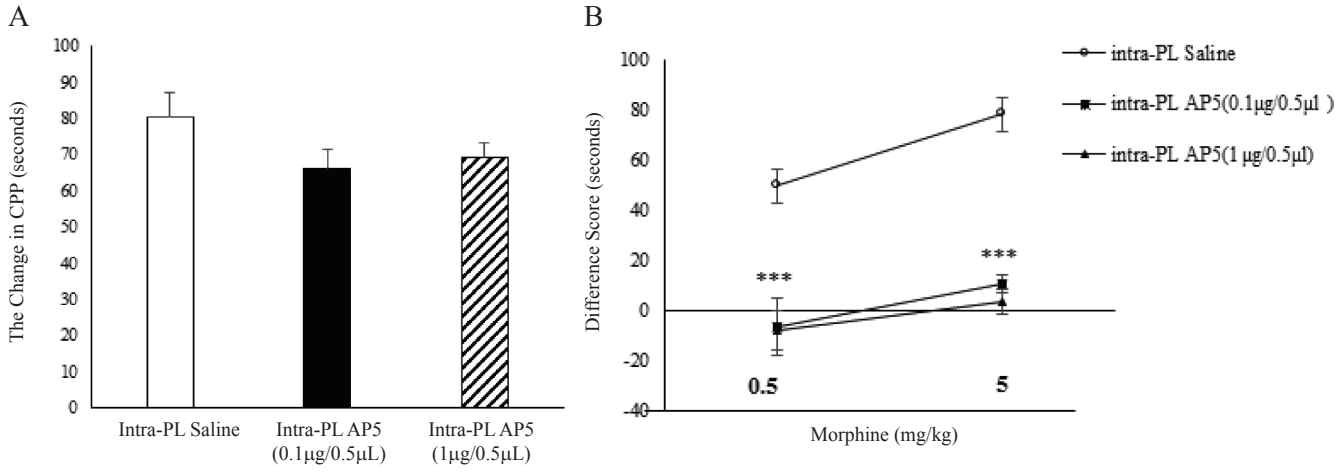

Figure 3. The effect of intra-PL saline or AP5 on drug-naïve animals and morphine-received animals. A: The effect of intra-PL microinjection different doses of the AP5 in drug-naive animals. B: Difference score between intra-PL saline and intra-PL AP5 in morphine-paired compartment relative to saline-paired environments groups. Data was presented at mean±s.e.m and was analyzed using one-way ANOVA, Tukey's test.***p<0.001 is significant compared to intra-PL saline group..

dose of the AP5 with the ineffective dose of morphine induced aversion effect on the expression phase of the CPP (p<0.001) (Figure 4B).

Microinjection of High-dose AP5 Into the PL with Different Doses of Morphine and Its Effect on the Acquisition and the Expression Phases of the CPP Paradigm

Our results showed that the microinjection of high-dose AP5 (1µg/0.5µL) into the PL before the administration of the effective dose of morphine (5mg/kg) significantly decreased the CPP in the acquisition phase compared to the sham group (p<0.001) but, the microinjection of this dose into the PL before the administration of the ineffective dose of morphine (0.5mg/kg) generated neither preference nor aversion effect on the acquisition phase of the CPP compared to the sham group, (p=0.314) (Figure 4A).

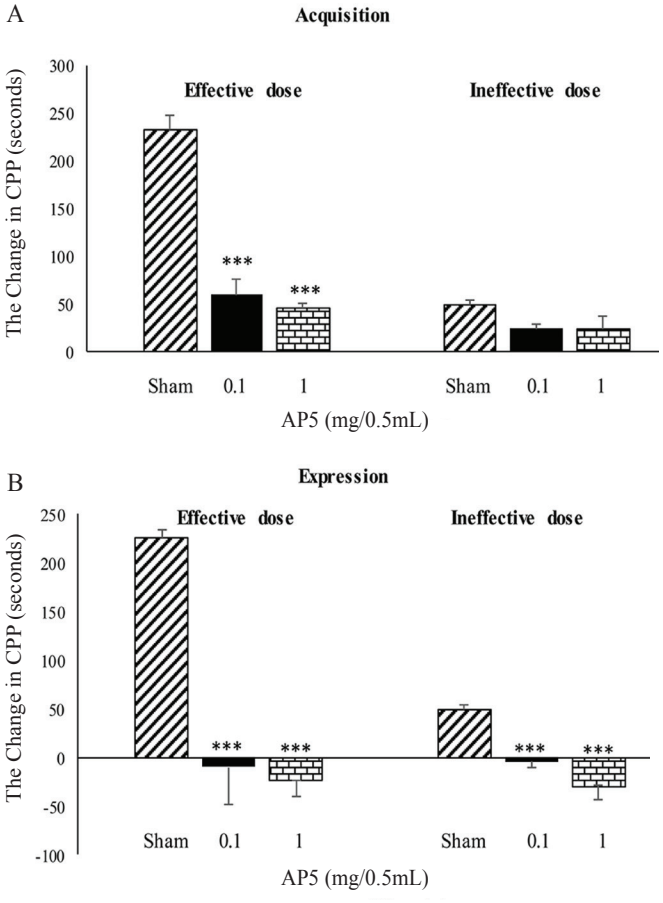

Figure 4. The effects of different doses of the AP5 with the effective and the ineffective doses of morphine on A: the acquisition and B: the expression phases of the CPP paradigm. Data was presented at mean±s.e.m and was analyzed using one-way ANOVA, Tukey's test. ***p<0.001 is significant compared to sham group.

Also, our findings indicated that the microinjection of high-dose AP5 (1µg/0.5µL) into the PL before the administration of 5 mg/kg or 0.5 mg/kg of morphine significantly reversed the effect of morphine on the expression phase of the CPP compared to the sham group, (p<0.001) (Figure 4B).

Discussion

Our findings showed that place preference increased significantly by administration high doses of morphine (2.5, 5, 7.5 and 10 mg/kg) while low doses of morphine (0.5 and 1 mg/kg) generated neither preference nor disgust effect on the CPP test. The maximum response of the CPP, was relevant to dose of 5 mg/kg of morphine. Despite increasing dosage of morphine, the dose-response of 7.5 and 10 mg/kg of morphine were less than 5 mg/kg, especially 7.5 mg/kg. This different response can be related to neuroplasticity and adaptation (22) and disorders such as respiratory problems (23), nausea and vomiting (24) and drowsiness (25) due to morphine receiving. Also, it can be related to the response of different sections of brain to morphine.(26) Especially so, it has been demonstrated that different molecular factors, various neuronal pathways and non-rewarding systems are involved in this process.(27, 28) Therefore, it seems that place preference due to morphine is not dose dependent, especially in high doses.

Previous studies have confirmed these results so that, morphine induces rewarding effects which is connected to environmental consequences.(17,29) In agreement with these results, Kargari *et al.,* and Ghavipanjeh *et al.,* reported that systemic administration of morphine induced CPP.(17,30) Also, unilateral injection of morphine into the nucleus accumbens (NAc) and VTA produced CPP in rats.(29) In another set of our experiments, as the calculation of difference score showed the effects of drug, the microinjection of different doses of the AP5 into the PL with the effective dose of morphine noticeably reduced the acquisition and the expression phases of the CPP paradigm. To support with these results, previous studies indicated that the AP5 attenuates the CPP induced by morphine (31) and reduces the response to repeated injection of morphine (18). It has been published that, the AP5 inhibits the acquisition and the expression phases of the CPP that reflect the involvement of the NMDA receptors in memory consolidation.(32) Agreement with our finding, several studies have highlighted the glutamate NMDA

receptor antagonists inhibit the acquisition of morphine-induced CPP (33) and morphine-rewarding properties.(29)

Glutamate receptor antagonists disrupt learning and memory processes, because the NMDA receptors play important roles in regulating the synaptic plasticity.(5) Therefore, glutamate antagonists block both the acquisition and the expression of morphine induced CPP.(7) Recent data have indicated that the activation of glutamatergic efferents from the prefrontal cortex to VTA is critical in the expression of addictive behaviors (34) and also, similar projects to NAc, activate dopamine cells which are essential for learning particularly in the acquisition stages.(35) It has been found that dopamine-glutamate coactivation is neccessary for a number of prefrontal function.(36) One probably mechanism is that, the blockade of glutamate receptors in the PL disrupts the pathway between the prefrontal cortex, VTA and NAc, that probably this disorder alters dopaminergic neuronal activities and function of the reward system.(37) It seems that euphoria was produced by dopamine release, leading to morphine reinforcement. Dopamine has an important role in the rewarding pathway and it has been clarified that glutamatergic neurons in the nucleus accumbens regulate dopamine release. Therefore, glutamatergic pathways of NAc have key role on the regulation of the mesolimbic dopaminergic system as well as such drugs susceptible to abuse as morphine.(33) Accordingly, microinjection of glutamate antagonist into the PL may alter morphine-related dopaminergic signals from the VTA to the NAc, just like that, many of the brain's reward systems converge on the NAc.(38) Evidences have been shown that descending projections from prefrontal cortex to NAc and other regions of the brain appear to exert regulatory control over reward-seeking behavior.(39) Therefore addiction is a disregulation between core reward system including the PFC, VTA and NAc.(40)

In another set of our experiments, results revealed that the microinjection of different doses of the AP5 into the PL before the administration of the ineffective dose of morphine established neither preference nor abhorrence effect on the acquisition phase of the CPP. Probably, the glutamate balance plays an important role in opiate-conditioned memories.(41) Recent findings suggest that memory systems are involved in the establishment of drug addiction.(42) On the other hand, the interaction between antagonist and balance in glutamate homeostasis (41) may alter the level of glutamate available for binding to glutamate receptor in the acquisition phase of the CPP with the ineffective dose of morphine.(7) In our results, it was also found that the microinjection of different doses of the AP5 into the PL reversed the effect of the morphine-ineffective dose in the expression phase of the CPP, which can due to the brain other regions that respond to reward systems.(4,21) Probably, the effect of glutamate antagonists on the expression phase of the CPP with the ineffective dose of morphine can due to synergism effects of these agents or the activation of the another neuronal pathway.(1) Therefore, the PL of the medial prefrontal cortex (mPFC) via glutamatergic system has a critical role in morphine-induced CPP. Since, the decrease in morphine-induced CPP due to the impairment of learning and memory formation in the conditioning process that could be reversed by physical activities prolonging the long term potentiation (LTP) in the neuronal synaptic.(43)

Conclussion

This study showed that low and high doses of the AP5 with the effective dose of morphine significantly reduced the CPP index in the acquisition and the expression phases. The possibility mechanism is that intra-PL AP5 microinjection may change morphine-related dopaminergic signals from the VTA to the NAc. Thus, the blockade of glutamate NMDA receptors with the AP5 into the PL disrupts the neuronal pathways between the PFC, VTA and NAc that will change function of reward system and memory process. In contrast different doses of the AP5 with the ineffective dose of morphine only decreased the expression phase of the CPP that this response may due to the modulation of reward system by another neuronal centres or synaptic plasticity in the brain. Therefore, it seems that NMDA receptor in the PL modulates opiate-related reward signalling and memory processing during addiction.

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