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Morphine pre-exposure facilitates reinstatement but attenuates retention of morphine-induced place preference***☆

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Abstract

BACKGROUND: Drug-associated conditioned stimuli are a key factor to induce morphine relapse. To date, limited evidence is available regarding the impact of drug history on propensity or vulnerability to relapse after long-term abstinence.

OBJECTIVE: To determine the effect of morphine pre-exposure on acquisition, maintenance and reinstatement of morphine-induced conditioned place preference (CPP) in rats.

DESIGN, TIME AND SETTING: A randomized, controlled, animal experiment was performed at the Laboratory of Behavior Pharmacology, Institute of Psychology, the Chinese Academy of Sciences, from March to September, 2006.

MATERIALS: Morphine hydrochloride was purchased from Qinghai Pharmaceutical, China; CPP software was designed and developed by Taiji Software Company, Beijing, China.

METHODS: A total of 64 Sprague Dawley rats were randomly assigned to eight groups (n = 8). Four morphine pretreatment regimens were used (subcutaneous injections, twice daily for 5 consecutive days and a total of 10 times): (1) “intensive” (morphine injections with doses escalating from 10 to 60 mg/kg; (2) “moderate” (one morphine injection at 5 mg/kg dose and one saline injection at 1 mL/kg daily for 5 days); and (3) “single” (nine saline injections at 1 mL/kg followed by one morphine injection at 5 mg/kg; (4) control (ten saline injections at 1 mL/kg). At 5 days after morphine pretreatment, animals were divided into two subgroups that underwent morphine conditioned or saline conditioned training. The test for acquisition of CPP was performed 24 hours after CPP training. The retention of morphine CPP was measured by repeated tests performed weekly for 1 month after the initial test of place preference. After extinction by pairing each chamber with saline, the reinstatement of place preference by low doses of morphine (0.05, 0.15, 0.45 mg/kg) was tested.

MAIN OUTCOME MEASURES: Acquisition, maintenance, and recovery response of CPP behavior.

RESULTS: The acquisition magnitude of morphine-induced CPP was not affected by prior morphine exposure ($F_{3, 56}$=0.17, P > 0.05). However, rats treated with moderate or intensive morphine pretreatment showed a less persistent CPP (t = –1.36, P > 0.05; t = –1.18, P > 0.05), but their place preference was reinstated by a low dose of morphine priming (t = –2.55, P < 0.05; t = –2.54, P < 0.05). The retention and reinstatement of morphine-induced CPP did not differ between rats with single morphine pre-exposure and control rats.

CONCLUSION: Morphine pretreatment enhanced reinstatement of morphine-induced CPP but with less persistence. Individuals with heavy drug exposure are more susceptible to drug relapse when re-exposed to addictive drugs.

Key Words: conditioned place preference; morphine; reinstatement; drug history; addiction; relapse; neuropharmacology; neural regeneration

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INTRODUCTION

Drug-associated conditioned stimuli are a key factor to induce relapse[1]. In the absence of the drug itself, these conditioned stimuli maintain and renew drug-seeking behavior[2]. The experience of previous drug exposure affects the role of conditioned stimuli on the drug-related behavior. For example, repeated morphine pre-exposure enhances the morphine-induced conditioned rewarding effect[3-4]. Compared with rats given brief drug access, those with prolonged access are slower to end conditioned cue-induced drug-seeking behavior and show increased motivation for drug reward as measured under a progressive ratio schedule of self-administration[5]. These earlier studies examined how previous drug experience affects the initiation and maintenance of conditioned stimuli-induced addiction-related behavior. However, limited evidence is available regarding the impact of drug exposure history on another core feature of addiction: the propensity or vulnerability to relapse after long-term

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abstinence[6-7]. Rats with high-dose drug experience show greater propensity to the reinstating effects of drug and stress compared with rats with low-dose drug experience[8-9]. Similar findings using a conditioned place preference (CPP) model have not been reported. CPP, based on the Pavlovian learning paradigm, is an animal model of cue-elicited conditioning. CPP and self-administration paradigms evaluate different aspects of reward and, thus, different characteristics of relapse and addictive behavior[7, 10]. However, no systematic studies about the effect of drug exposure history on persistence and reinstatement of morphine-induced place preference, primary features of drug addiction[11-12], are available. We compared four pretreatments in the subsequent test for acquisition, maintenance, and reinstatement of morphine-induced CPP. The pretreatments included control, “single”, “moderate”, and “intensive” morphine exposure patterns. Intensive morphine exposure was designed to induce tolerance and physical dependence, while the moderate treatment was intended to induce no physical dependence. The doses and temporal patterns of drug administration were based on previous data[3, 13]. The present study aimed to examine the effect of the four regimens of morphine administration on subsequent drug-seeking behavior by measuring the acquisition, maintenance, and reinstatement of morphine-induced CPP.

MATERIALS AND METHODS

Design

A randomized, controlled, animal experiment.

Time and setting

The experiments were performed at the Laboratory of Behavior Pharmacology, Institute of Psychology, the Chinese Academy of Sciences, from March to September, 2006.

Materials

A total of 64 healthy male, Sprague Dawley rats (Charles River Laboratories of Beijing, China), weighing 240–260 g, were housed individually in stainless-steel wire cages (25 cm × 22.5 cm × 30 cm) in a temperature-controlled colony room (20–24 °C). They were maintained on a 12-hour light/dark cycle (lights on at 8:00 am) with free access to food and water. The experimental protocol and procedures were performed in accordance with the *Guidance Suggestions for the Care and Use of Laboratory Animals*, issued by the Ministry of Science and Technology of the People’s Republic of China[14]. Reagents and equipment are as follows:

Reagent and equipment	Source
Morphine hydrochloride	Qinghai Pharmaceutical, China
CPP analysis software	Taiji Software Company, Beijing, China
CPP apparatus	Behavior Pharmacology Laboratory, Institute of Psychology, Chinese Academy of Sciences, China

Methods

Grouping

A total of 64 rats were randomly assigned to four morphine pre-exposure groups: intensive, moderate, single and control groups (n = 16). At 5 days after morphine pretreatment, the four groups were subdivided into two subgroups: morphine conditioning subgroup and saline conditioning subgroup for conditioned place preference training. That is, 64 animals were equally divided into eight subgroups (n = 8): “intensive-morphine”, “intensive-saline”, “moderate-morphine”, “moderate-saline”, “single-morphine”, “single-saline”, “control-morphine” and “control-saline”.

Morphine pre-exposure protocol

The four distinct morphine pretreatment regimens were performed as follows (twice-daily subcutaneous injections for 5 days for a total of 10 times). In the “intensive” morphine pre-exposure, rats were injected with morphine 10 times at ascending doses (10–60 mg/kg). The dose of morphine (mg/kg) was: first day (10, 20), second day (20, 30), third day (30, 40), fourth day (40, 50), fifth day (50, 60)[15]. In the “moderate” morphine pre-exposure, rats were injected once with morphine at 5 mg/kg and once with saline at 1 mg/kg daily for 5 days. In the “single” morphine pre-exposure, animals were injected nine times with saline at 1 mg/kg followed by one injection of morphine at 5 mg/kg. Control animals were injected with 1 mg/kg saline twice daily for 5 days.

Morphine-induced CPP protocol

The CPP procedure was performed according to method described previously[16-18]. Behavior consisted of three phases: acquisition, maintenance, and reinstatement of CPP.

Acquisition of CPP

The acquisition of CPP involved four phases in this sequence: habituation, pre-conditioning test (Pre-test), conditioning, and post-conditioning test (Post-test)[16-18]. In habituation (day 1), each rat was placed midway between two compartments and was allowed to explore the apparatus freely for 15 minutes. The time in each compartment was not recorded. Pre-tests were performed on the next two days (days 2 and 3). In the Pre-test, the same operation was performed but the time in each chamber was monitored to assess unconditioned preferences. The average Pre-test time was used as the unconditioned preference score. Because there was a significant difference between time spent in the striped, smooth floor compartment [(399 ± 9) seconds, n = 64] and the black, grid floor compartment [(501 ± 9) seconds, n = 64], a bias procedure was used in the conditioning phase. During that phase (days 5–12), morphine-conditioned rats were injected subcutaneously with saline and confined to the grid floor compartment for 45 minutes. On the alternative day, the rats were treated with morphine (3 mg/kg) and confined to the other compartment for 45 minutes. Saline conditioning rats were injected with saline at each compartment and confined for 45 minutes. The post-conditioning test was

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performed on day 13. Each rat was again placed in midway between two compartments and allowed to explore freely for 15 minutes, with time in each compartment recorded automatically.

Maintenance of morphine-induced CPP

After the establishment of morphine-induced CPP, repeated-test sessions were performed to assess the effect of morphine pre-exposure on the persistence of morphine-induced CPP. All animals were treated for 15 minutes, once per week for 4 weeks.

Extinction and drug-induced reinstatement of CPP

After four retests in 4 weeks, animals were trained to extinguish the acquired CPP[19]. During this CPP extinction phase, rats were subjected to saline injections and alternately confined to the previous drug- or saline-conditioned compartment for 45 minutes daily for 14 days. Rats underwent a CPP "extinction test" the day after the last extinction trial, which was expected to eliminate conditioned preference for the previous drug-conditioned side[15]. One day after the extinction test, all animals received a priming injection of morphine (0.05 mg/kg) immediately before a re-test for CPP. This procedure was repeated the next day with a greater priming dose (0.15 mg/kg) and with a still higher dose (0.45 mg/kg) on the following day.

Morphine-induced CPP behavior measured by CPP scores

The acquisition and maintenance CPP scores were calculated for each animal by subtracting the time in the drug-conditioned compartment in the Pre-test from the time staying in that compartment in the Post-test[20-21]. The CPP scores for drug-induced reinstatement were calculated somewhat differently from the acquisition scores, with the difference between the time in the drug-conditioned compartment during the reinstatement test, and the time previously staying in that compartment during the extinction test.

Main outcome measures

The CPP score in acquisition, maintenance, and reinstatement phase of morphine-induced CPP.

Statistical analysis

SPSS 13.0 software (SPSS, Chicago, IL, USA) was used. All data were expressed as Mean ± SEM and analyzed with one-way analysis of variance with a complete random design. Differences in acquisition and reinstatement of morphine-induced CPP were analyzed using intergroup two-way analysis of variance. Differences in maintenance of morphine-induced CPP were analyzed using repeated measures analysis of variance. Intergroup differences were compared with independent-sample student's *t*-test. $P < 0.05$ was considered statistically significant.

RESULTS

Quantitative analysis of animals

All 64 animals were included in final analysis, with no death or infection.

Effects of morphine pretreatment on acquisition of morphine CPP

The two-way analysis of variance revealed the interaction effect was not significant ($F_{3, 56} = 0.17$, $P > 0.05$) and only a significant main effect of conditioning type (morphine or saline) ($F_{1, 56} = 48.27$, $P < 0.001$). In all pretreatment conditions, morphine-conditioned animals showed a significant preference for the drug-conditioned compartment compared with saline-conditioned animals ($P < 0.01$) (Figure 1).

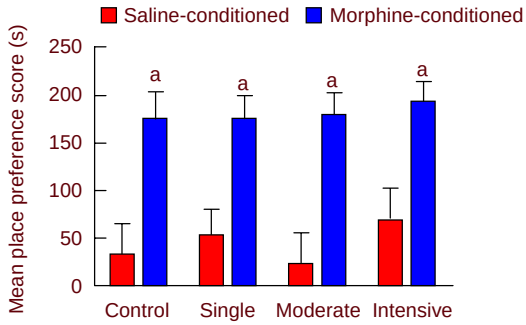

Figure 1 Effects of morphine pretreatment on acquisition of morphine-induced conditioned place preference. Each column represents the Mean ± SEM of place preference score. [a]$P < 0.01$ vs. corresponding saline-conditioned group.

Effects of morphine pretreatment on maintenance of morphine CPP

Figure 2 shows the maintenance of CPP results in each pretreatment condition tested at 1, 2, 3, 4 weeks after the initial CPP test (week 0). Animals with control pretreatment or single morphine pre-exposure maintained their preference for the drug-paired compartment over the 4-week testing period (Figures 2A, B). The repeated measures analysis of variance revealed a significant main effect for conditioning type (morphine or saline, $F_{1, 14} = 11.35$, $P < 0.01$; $F_{1, 14} = 16.30$, $P < 0.01$). Student's *t*-test showed significant morphine-induced CPP at all time points compared with saline-conditioned animals ($P < 0.05$). Figure 2C shows the CPP score for moderate morphine pretreatment animals tested weekly for four weeks. The repeated measures analysis of variance for conditioning type by week revealed a significant main effect of conditioning type ($F_{1, 14} = 6.81$, $P < 0.05$), and a significant conditioning type by week interaction ($F_{4, 56} = 43.99$, $P < 0.01$). Morphine-conditioned animals showed significant CPP at weeks 0, 1 and 2 ($t = –4.01$, $P < 0.01$; $t = –2.60$, $P < 0.05$; $t = –2.39$, $P < 0.05$). At weeks 3 and 4, morphine-conditioned animals did not differ from the saline-conditioned animals ($t = –1.36$, $P > 0.05$; $t = –1.53$, $P > 0.05$). CPP scores for animals with intensive morphine pre-exposure over the 4-week testing periods showed significant main effects of week ($F_{4, 56} = 2.83$, $P < 0.05$) and conditioning type ($F_{1, 14} = 6.27$, $P < 0.05$), and a significant interaction effect of conditioning type by week ($F_{4, 56} = 3.48$, $P < 0.05$) (Figure 2D). Animals with morphine conditioning showed a significant preference

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for the drug-paired compartment at weeks 0 and 1 (t = –3.13, P < 0.01; t = –2.79, P < 0.05), but not at weeks 2, 3, or 4 (t = –1.18, P > 0.05; t = –1.01, P > 0.05; t = –1.11, P > 0.05).

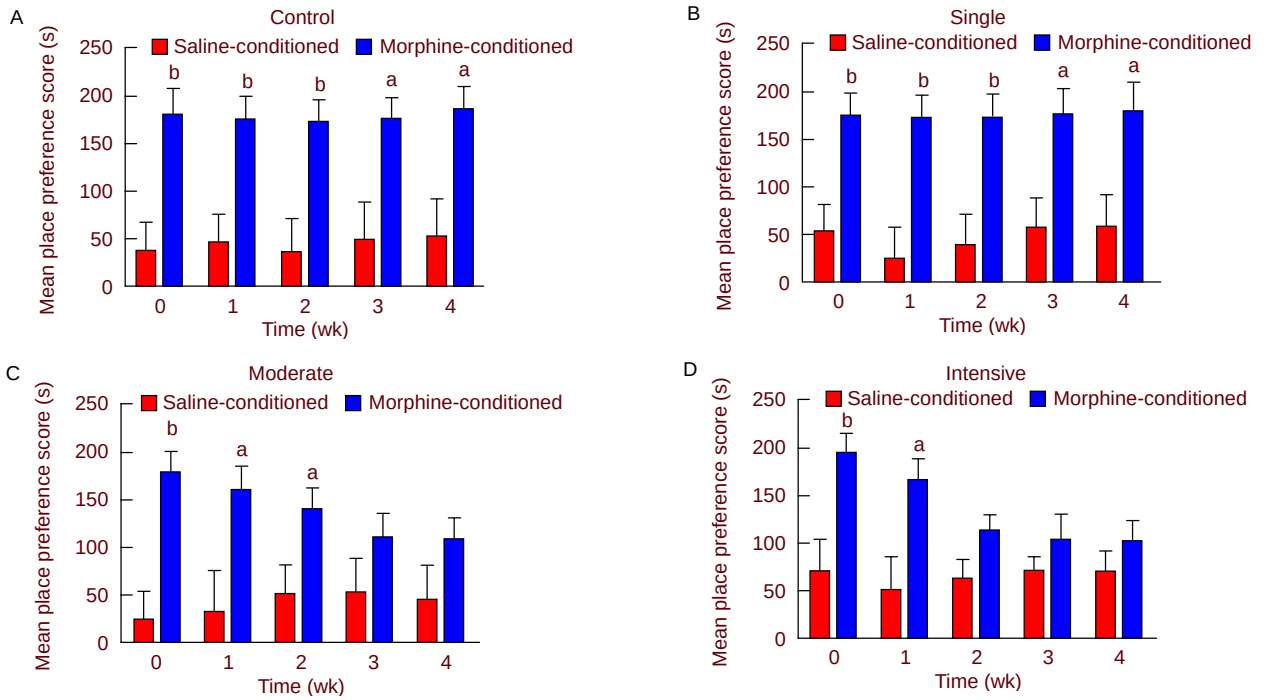

Figure 2 Effects of morphine pretreatment on maintenance of conditioned place preference. Repeated tests were performed once weekly for 4 wk after the initial test. Place preference was scored by the difference between the time spent in the drug-paired compartment before and after conditioning (Mean ± SEM). [a]P < 0.05, [b]P < 0.01, *vs*. corresponding saline-conditioned group.

Effect of morphine pretreatment on drug-induced reinstatement of CPP

Figure 3 shows the CPP scores for animals primed successively on 3 consecutive days by three doses of morphine (0.05, 0.15, 0.45 mg/kg). At the priming dose of 0.05 mg/kg morphine (Figure 3A), the 4 × 2 analysis of variance showed neither a significant main effect nor an interaction effect. Student's t-tests indicated no significant place preferences for any group after this small priming dose (t = –0.08, P > 0.05; t = 0.24, P > 0.05; t = –0.10, P > 0.05; t = –0.53, P > 0.05).

At the priming dose of 0.15 mg/kg (Figure 3B), the intergroup 4 × 2 analysis of variance showed that there was a significant main effect of conditioning type ($F_{1, 56}$ = 8.29, P < 0.01), but not a marked interaction of treatment condition by conditioning type ($F_{3, 56}$ = 2.08, P = 0.114). Student's t-tests showed that morphine-conditioned animals with moderate or intensive morphine pre-exposure reinstated a significant place preference after this middle priming dose of morphine (t = –2.55, P < 0.05; t = –2.54, P < 0.05). At the final day, with a priming injection of 0.45 mg/kg morphine (Figure 3C), all morphine-conditioned animals renewed their preference for the previous drug-paired chamber (t = –2.31, P < 0.05; t = –2.49, P < 0.05; t = –3.12, P < 0.05; t = –2.82, P < 0.05). Two-way analysis of variance showed only a significant main effect of conditioning type ($F_{1, 56}$ = 28.57, P < 0.001).

DISCUSSION

The acquisition of morphine-induced CPP was not affected by morphine pre-exposure. However, compared with controls, rats that received moderate or intensive morphine pretreatment showed less persistent morphine-induced CPP. This effect did not appear in rats undergoing a single morphine pretreatment; they retained morphine-induced CPP at control levels.

Another feature unique to animals with moderate or intensive morphine pre-exposure was reinstatement of place preference by low dose of morphine priming. In addition, there was no difference between the effects of moderate and intensive morphine pre-exposure, either in the degree of acquisition or in the reinstatement of morphine-induced CPP.

However, we failed to detect the effect of morphine pretreatment on the acquisition of morphine-induced CPP, consistent with the findings of Martin *et al*[22]. In contrast, other studies have reported that morphine pre-exposure increases the rate of acquisition of morphine-induced place preference[3] and decreases the dose at which preferences can be conditioned[4]. The cause of this discrepancy may reflect procedural differences. Two or three conditioning trials were performed in the previous studies, whereas we used four drug-pairing sessions which is sufficient for naive rats to

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produce a significant CPP[23-25]. In fact, animals with drug pre-exposure demonstrated enhanced place preferences only in earlier trials[4]. Another factor that has contributed to the enhancement of CPP by drug pre-exposure is the dosage used for conditioning. Although morphine is effective in inducing place preference over a broad dose-range, the steep part of the dose-response curve for subcutaneously administrated morphine is between 0.04 and 1.0 mg/kg[26]. Enhanced CPP occurred after two conditioning trials for rats pre-exposed at 1 mg/kg morphine, but not at 5 mg/kg morphine, between pre-exposed and non-exposed animals tested after two conditioning trials[4]. Therefore, in the present study, the sensitization effect of drug pre-exposure on place preference may have been masked after four drug-pairing sessions at the conditioning dose of 3 mg/kg morphine.

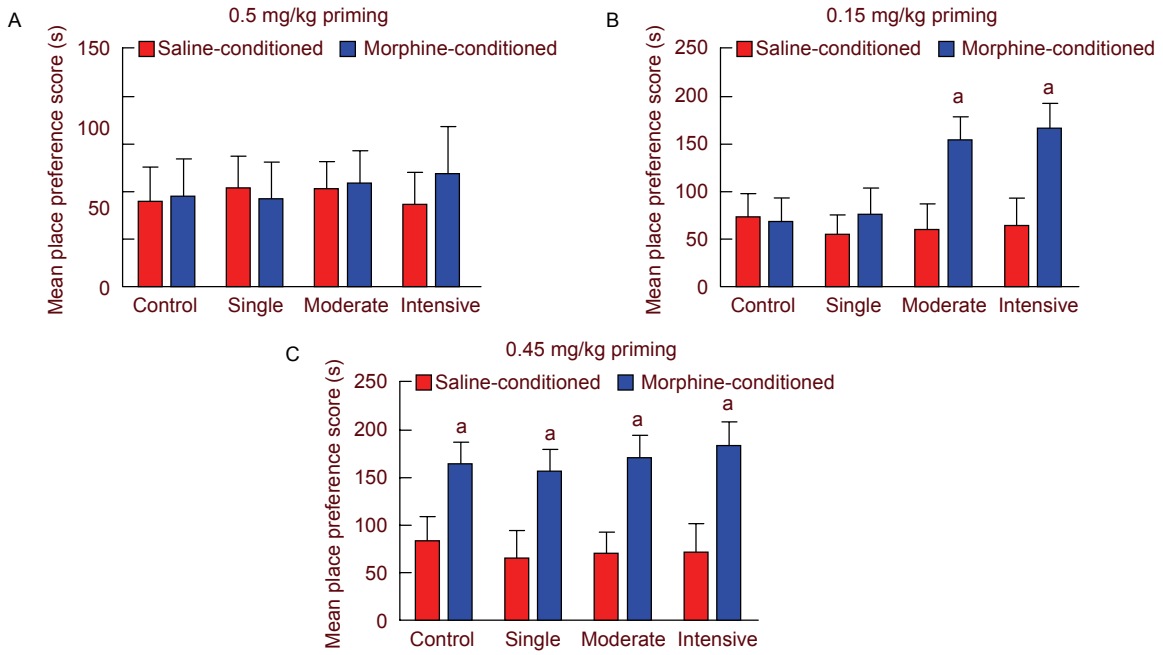

Figure 3 Effects of morphine pretreatment on drug-induced reinstatement of conditioned place preference. Three priming doses of morphine (0.05, 0.15, 0.45 mg/kg) were administered for 3 successive days. Place preference was scored by the difference between the time spent in the drug-paired compartment after priming and after extinction. Each column represents the Mean ± SEM of place preference scores. $^aP < 0.05$, *vs.* corresponding saline conditioned group.

It is surprising that animals with moderate or intensive morphine pretreatment showed less persistence of morphine-induced CPP than single morphine pretreatment animals or saline pretreatment control group. This result seemingly contradicts the phenomena observed in humans that addicts persist in a long-term craving after repeated opioid exposures. It might argue that the short maintenance of CPP is due to the general memory impairment seen after repeated morphine exposure. Chronic use of opiates leads to impairment of the performances in the Morris water maze test[27-28], but spatial learning and conditioning learning are different in many aspects. Moreover, repeated morphine administration could reverse the acute morphine-induced amnesia[29]. Another possible explanation for the rapid decrease in CPP in rats with repeated morphine pretreatment could be a reduction in the incentive value or salience of morphine-related cues during the early stages of morphine withdrawal. A related effect has been observed in studies of cocaine withdrawal: rats with 12-hour access to cocaine during training responded less in the tests of extinction than those rats given 2-hour access[30]. In any case, the observed acceleration of extinction in moderate and intensive morphine pre-exposure groups is not explained by the removal of conditioned association, because CPP in these rats was reinstated by a low dose of morphine. In summary, the present study clearly showed that morphine pre-exposure weakens the retention of morphine CPP, but the mechanism remains unclear.

In addition, the present study showed that morphine-conditioned animals with moderate or intensive morphine pre-exposure renewed their place preference after a lower priming dose of drug than required by animals with saline pre-exposure or a single pre-exposure to morphine. This indicates that repeated morphine pre-exposure made rats more susceptible to drug-seeking long after the extinction of drug-related context. If the ability of drug to induce reinstatement depends on the incentive salience of drug-related stimuli renewed by re-exposure[7, 31], the drug's rewarding properties are crucial to the reinstatement process. Thus we interpreted the low-dose reinstatement in rats with repeated morphine pretreatment as a result of sensitization to the rewarding effect of morphine. Similarly, enhanced rewarding effects have been observed[32]. Priming drug may produce internal cues by acting on its receptors[33], and opioid receptors may

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determine the susceptibility to priming drugs. A previous study shows that repeated but not single morphine administration evokes a long-lasting down-regulation of the density of delta 1 and delta 2 opioid receptors[34]. Susceptibility to drug-induced reinstatement depends, at least partially, on the amount or intensity of drug pre-exposure.

In conclusion, reinstatement of CPP is more important than acquisition of CPP as a predictor of vulnerability to drug-seeking. Moreover, individuals with a history of more intense drug exposure will be more susceptible to drug-primed relapse.

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REFERENCES

[1] Brown RM, Lawrence AJ. Neurochemistry underlying relapse to opiate seeking behaviour. Neurochem Res. 2009;34(10):1976-1887.
[2] Van den Oever MC, Goriounova NA, Li KW, et al. Prefrontal cortex AMPA receptor plasticity is crucial for cue-induced relapse to heroin-seeking. Nat Neurosci. 2008;11(9):1053-1058.
[3] Shippenberg TS, Heidbreder C, Lefevour A. Sensitization to the conditioned rewarding effects of morphine: Pharmacology and temporal characteristics. Eur J Pharmacol. 1996;299(1-3):33-39.
[4] Simpson GR, Riley AL. Morphine preexposure facilitates morphine place preference and attenuates morphine taste aversion. Pharmacol Biochem Behav. 2005;80(3):471-479.
[5] Paterson NE, Markou A. Increased motivation for self-administered cocaine after escalated cocaine intake. Neuroreport. 2003;14(17):2229-2232.
[6] Le Moal M. Drug abuse: vulnerability and transition to addiction. Pharmacopsychiatry. 2009;42(Suppl 1):S42-55.
[7] Aguilar MA, Rodríguez-Arias M, Miñarro J. Neurobiological mechanisms of the reinstatement of drug-conditioned place preference. Brain Res Rev. 2009;59(2):253-277.
[8] Ahmed SH, Walker JR, Koob GF. Persistent increase in the motivation to take heroin in rats with a history of drug escalation. Neuropsychopharmacology. 2000;22(4):413-421.
[9] Mantsch JR, Yuferov V, Mathieu-Kia AM, et al. Effects of extended access to high versus low cocaine doses on self-administration, cocaine-induced reinstatement and brain mRNA levels in rats. Psychopharmacology (Berl). 2004;175(1):26-36.
[10] Tzschentke TM. Measuring reward with the conditioned place preference (CPP) paradigm: update of the last decade. Addict Biol. 2007;12(3-4):227-462.
[11] Shaham Y, Shalev U, Lu L, et al. The reinstatement model of drug relapse: history, methodology and major findings. Psychopharmacology. 2003;168(1-2):3-20.
[12] Stewart J. Psychological and neural mechanisms of relapse. Philos Trans R Soc Lond B Biol Sci. 2008;363(1507):3147-3158.
[13] Vanderschuren LJ, Tjon GH, Nestby P, et al. Morphine-induced long-term sensitization to the locomotor effects of morphine and amphetamine depends on the temporal pattern of the pretreatment regimen. Psychopharmacology (Berl). 1997;131(2):115-122.
[14] The Ministry of Science and Technology of the People's Republic of China. Guidance Suggestions for the Care and Use of Laboratory Animals. 2006-09-30.
[15] Lu L, Chen H, Su W, et al. Role of withdrawal in reinstatement of morphine-conditioned place preference. Psychopharmacology (Berl). 2005;181(1):90-100.
[16] Yonghui L, Xigeng Z, Yunjing B, et al. Opposite effects of MK-801 on the expression of food and morphine-induced conditioned place preference in rats. J Psychopharmacol. 2006;20(1):40-46.
[17] Ribeiro Do Couto B, Aguilar MA, Lluch J, et al. Social experiences affect reinstatement of cocaine-induced place preference in mice. Psychopharmacology (Berl). 2009;207(3):485-498.
[18] Ma YY, Meng L, Guo CY, et al. Dose- and time-dependent, context-induced elevation of dopamine and its metabolites in the nucleus accumbens of morphine-induced CPP rats. Behav Brain Res. 2009;204(1):192-199.
[19] Lu L, Xu NJ, Ge X, et al. Reactivation of morphine conditioned place preference by drug priming: role of environmental cues and sensitization. Psychopharmacology (Berl). 2002;159(2):125-132.
[20] Tan SE. Roles of hippocampal NMDA receptors and nucleus accumbens D1 receptors in the amphetamine-produced conditioned place preference in rats. Brain Res Bull. 2008;77(6):412-419.
[21] Moaddab M, Haghparast A, Hassanpour-Ezatti M. Effects of reversible inactivation of the ventral tegmental area on the acquisition and expression of morphine-induced conditioned place preference in the rat. Behav Brain Res. 2009;198(2):466-471.
[22] Martin GM, Bechara A, van der Kooy D. Morphine preexposure attenuates the aversive properties of opiates without preexposure to the aversive properties. Pharmacol Biochem Behav. 1988;30(3):687-692.
[23] Mueller D, Perdikaris D, Stewart J. Persistence and drug-induced reinstatement of a morphine-induced conditioned place preference. Behav Brain Res. 2002;136(2):389-397.
[24] Yim AJ, Andersen ML, Soeiro AC, et al. Acute systemic blockade of D2 receptors does not accelerate the extinction of cocaine-associated place preference. Brain Res. 2009;1304:122-128.
[25] Paolone G, Botreau F, Stewart J. The facilitative effects of d-cycloserine on extinction of a cocaine-induced conditioned place preference can be long lasting and resistant to reinstatement. Psychopharmacology. 2009;202(1-3):403-409.
[26] Mucha RF, Iversen SD. Reinforcing properties of morphine and naloxone revealed by conditioned place preferences: a procedural examination. Psychopharmacology (Berl). 1984;82(3):241-247.
[27] Tramullas M, Martínez-Cué C, Hurlé MA. Chronic administration of heroin to mice produces up-regulation of brain apoptosis-related proteins and impairs spatial learning and memory. Neuropharmacology. 2008;54(4):640-652.
[28] Miladi Gorji H, Rashidy-Pour A, Fathollahi Y. Effects of morphine dependence on the performance of rats in reference and working versions of the water maze. Physiol Behav. 2008;93(3):622-627.
[29] Zarrindast MR, Farajzadeh Z, Rostami P, et al. Involvement of the ventral tegmental area (VTA) in morphine-induced memory retention in morphine-sensitized rats. Behav Brain Res. 2005;163(1):100-106.
[30] Sorge RE, Stewart J. The contribution of drug history and time since termination of drug taking to footshock stress-induced cocaine seeking in rats. Psychopharmacology. 2005;183(2):210-217.
[31] Nair SG, Adams-Deutsch T, Epstein DH, et al. The neuropharmacology of relapse to food seeking: Methodology, main findings, and comparison with relapse to drug seeking. Prog Neurobiol. 2009;89(1):18-45.
[32] He S, Grasing K. Chronic opiate treatment enhances both cocaine-reinforced and cocaine-seeking behaviors following opiate withdrawal. Drug Alcohol Depend. 2004;75(2):215-221.
[33] Ambrose-Lanci LM, Peiris NB, Unterwald EM, et al. Cocaine withdrawal-induced trafficking of delta-opioid receptors in rat nucleus accumbens. Brain Res. 2008;1210:92-102.
[34] Turchan J, Przewlocka B, Toth G, et al.The effect of repeated administration of morphine, cocaine and ethanol on mu and delta opioid receptor density in the nucleus accumbens and striatum of the rat. Neuroscience. 1999;91(3):971-977.

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