Pharmacology, Biochemistry and Behavior 90 (2008) 404–408

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Blockade of cue- and drug-induced reinstatement of morphine-induced conditioned place preference with intermittent sucrose intake

Haifeng Zhai, Ping Wu, Chunmei Xu, Yu Liu, Lin Lu *

Department of Neuropharmacology, National Institute on Drug Dependence, Peking University, Beijing 100083, China

ARTICLE INFO

Article history:
Received 4 November 2007
Received in revised form 17 March 2008
Accepted 28 March 2008
Available online 4 April 2008

Keywords:
Morphine
Sucrose
Conditioned place preference
Natural reward
Extinction
Relapse

ABSTRACT

Sucrose intake has been suggested to alter the expression of morphine-induced conditioned place preference (CPP). To date, the potential effects of sucrose intake on the extinction and drug-induced reinstatement of CPP have not been determined. In the present study, sucrose solution (15%) was given prior to, during, and following the acquisition of morphine-induced CPP. Place preference was subsequently assessed during expression, extinction, and morphine-induced reinstatement. The results showed that the sucrose solution given prior to place conditioning training transiently suppressed the expression of morphine CPP. Sucrose solution given during place conditioning training had no effects on the expression, extinction, and reinstatement of CPP. When the sucrose solution was given following the acquisition of morphine CPP, the extinction of morphine CPP was accelerated, and morphine-induced reinstatement was profoundly inhibited. The above results demonstrated that sucrose intake could differentially affect the expression, extinction, and reinstatement of morphine-induced CPP, depending on the interference schedules. Our findings suggest that offering non-drug rewards could be a valuable approach to maintain abstinence and preventing relapse in drug addicts.

1. Introduction

Accumulating preclinical and clinical studies have provided evidence that the availability of a sweetened diet or solution, as a non-drug reward, has great influence on the behavioral properties of addictive drugs (Carroll, 1998; Lynch and Carroll, 2001). Individual differences in intake of a sweetened solution in animals have been shown to be associated with ethanol consumption (Gosnell and Krahn, 1992; Overstreet et al., 1993) and cocaine self-administration (DeSousa et al., 1996; Gosnell, 2000). The correlation between sucrose preference and the behavioral effects of addictive drugs has been examined extensively by directly comparing the responses of rats selectively bred for high and low saccharin intake (Carroll et al., 2007a, b; Perry et al., 2007a,b). Moreover, previous exposure to a sweetened solution can facilitate the formation of drug-induced conditioned place preference (CPP) (Lett, 1989; Vitale et al., 2003) and locomotor sensitization (Gosnell, 2005). A concurrently available sweetened solution can reduce drug preference and acquisition and maintenance of drug self-administration (Carroll et al., 1989; Lenoir et al., 2007; Rodefer and Carroll, 1997). The correlation between sucrose and the behavioral effects of addictive drugs also has been investigated in clinical settings (Higgins et al., 1994). Both alcohol-dependent (Kampov-Polevoy et al., 1997) and cocaine-dependent (Janowsky et al., 2003) patients have shown altered preference for high-concentration sucrose. Evidence for the involvement of the dopamine system in sucrose reward (Hernandez and Hoebel, 1988) also supports the hypothesis that a common neurochemical pathway underlies the behavioral interaction between sucrose and other addictive drugs.

The influence of sucrose consumption on the rewarding effects of opioids has been investigated in numerous studies using the CPP model. Lett (1989) reported that rats with acute (30 min) and chronic (5-day) exposure to sweetened water spent significantly more time in the drug-paired environment during the CPP test. Chronic access to a sucrose solution also is sufficient to enhance the development of CPP and the tail-flick response induced by the μ-opioid receptor agonist fentanyl (Vitale et al., 2003). Enhancement of the CPP response to these drugs following chronic sucrose exposure could be explained by cross-sensitization demonstrated by the interaction of sucrose and the opioid receptor antagonist naloxone (Colantuoni et al., 2002; Rudski et al., 1997). Although cross-sensitization between sucrose and opioids has been established, the attenuation of morphine-induced analgesia by chronic access to sucrose has revealed an opposite phenomenon, cross-tolerance (Holder, 1988; Lieblich et al., 1983). Chronic sucrose exposure likely plays a dual role in the induction of either sensitization or tolerance to opioids.

Both Lett (1989) and Vitale et al. (2003) focused on the effects of sucrose intake on the acquisition of drug-induced CPP. Extinction and reinstatement have been explored in a growing number of CPP studies because various factors contributing to extinction and reinstatement of drug CPP have been considered to be predictive of relapse (Lu et al.,

* Corresponding author. National Institute on Drug Dependence, Peking University, 38, Xue Yuan Road, Hai Dian District, Beijing 100083, China. Tel.: +86 10 82802459; fax: +86 10 62032624.
E-mail address: linlu@bjmu.edu.cn (L. Lu).

0091-3057/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2008.03.023

2000, 2001, 2002, 2003; Mueller et al., 2002; Ribeiro Do Couto et al., 2005, 2006). The effects of sucrose intake on the extinction and reinstatement of drug-induced CPP have not been fully characterized. The purpose of the present study was to determine the effects of sucrose on the expression, extinction, and reinstatement of morphine-induced CPP in rats by offering the sucrose solution to rats prior to, during, and following induction of morphine-induced CPP.

2. Materials and methods

2.1. Subjects

Animals were male Sprague–Dawley rats purchased from the Department of Laboratory Animal Science, Peking University Health Science Center. The rats weighed 200–220 g upon arrival in the laboratory and were habituated for approximately 7 days prior to the experiments. All animals were housed in groups of 4–5 rats per cage and were allowed free access to food and water except as indicated. Constant temperature (21±2 °C) and humidity (about 60%) and a 12-h light/dark cycle (lights on at 8:00 am) were maintained throughout the experiments. All experimental procedures were conducted in accordance with the *National Institutes of Health Guide for the Care and Use of Laboratory Animals* and were approved by the Local Committee of Animal Use and Protection of the Peking University Health Science Center.

2.2. Drugs

Morphine hydrochloride was obtained from Qinghai Pharmaceutical, Ltd. (Xining, China). Morphine was dissolved in saline and administered subcutaneously (s.c.) in a volume of 1 ml/kg. Sucrose was commercial analytically pure powder (purity>99.9%) and was dissolved in distilled water.

2.3. Sucrose administration

In all of the experiments, rats were assigned randomly to either the Control group or Sucrose group. Rats in the Sucrose group were given daily access to 15% (w/v) sucrose solution for 2 h in the morning (8:00–10:00 am) and 2 h in the afternoon (4:00–6:00 pm) in their home cages. Both water and the sucrose solution were presented in plastic bottles with rubber stoppers and drip-proof stainless-steel spouts. The weight of the sucrose bottle was recorded before and after the sucrose bottle was placed into the housing cage. The method of sucrose administration was determined by one pilot experiment containing two groups of rats. Six rats in one group were housed individually, and six rats in another group were housed six per cage. This setting allowed us to determine whether the housing condition was a factor that could influence sucrose intake and body weight gain. Rats in the two groups were offered the sucrose solution for seven consecutive days with an access schedule of 2 h in the morning (8:00–10:00 am) and 2 h in the afternoon (4:00–6:00 pm) daily. No rat failed to drink the sucrose solution in the individually housed group. No significant difference in sucrose intake was observed each day between the two housing conditions (mean±SEM: 31.3±2.0 g/day/rat for individual housing; 29.5±1.9 g/day/rat for group housing). An equal increase in body weight was observed across days between the two housing conditions (mean±SEM: 233.3±3.0 g on Day 1 to 293.2±3.0 g on Day 7 for individual housing; 240.7±4.6 g on Day 1 to 298.0±8.7 g on Day 7 for group housing). Body weight gains over seven days were normal in comparison with other rats in our laboratory. Based on these pilot observations, rats were group-housed for sucrose administration.

2.4. Conditioning apparatus

CPP training was conducted in five identical Plexiglas boxes, each divided into three chambers by two removable guillotine doors and consisting of one large chamber (27.9×21.0×20.9 cm) on each side with a smaller chamber (12.1×21.0×20.9 cm) in the middle. All three chambers were black with different visual and textural cues. One large chamber had a floor with stainless-steel bars (diameter 4.8 mm placed every 1.6 cm on center), while the other large chamber had a floor with stainless-steel mesh (1.3×1.3 cm). The smaller middle chamber had a smooth polyvinyl chloride floor. Time spent in each chamber during the test sessions was recorded with a computer system. Conditioned place preference was indicated by a preference score that was defined as the difference in time spent in the morphine-paired chamber minus time spent in the morphine non-paired chamber (Wang et al., 2006; Zhai et al., 2007).

2.5. Place conditioning regimen

All experiments consisted of five phases: Pre-conditioning, Place conditioning, Post-conditioning, Extinction, and Reinstatement.

2.5.1. Pre-conditioning (Day 1)

Rats were initially placed in the chamber with the guillotine doors removed for a period of 15 min. Rats that spent 150 s more in one large chamber than in the other were considered to have chamber bias and were excluded from subsequent testing. Approximately 15% of the rats were excluded based on these criteria.

2.5.2. Place conditioning (Days 2–7)

Place conditioning was conducted with a counterbalanced protocol similar to our previous studies (Lu et al., 2000, 2002, 2003; Wang et al., 2006). Briefly, each rat was treated with alternating injections of morphine (5 mg/kg, s.c.) and saline (1 ml/kg, s.c.) for six consecutive days. On conditioning days, the guillotine doors were closed to restrict the animal to its designated conditioning chamber. The chamber in which morphine or saline was administered was assigned randomly.

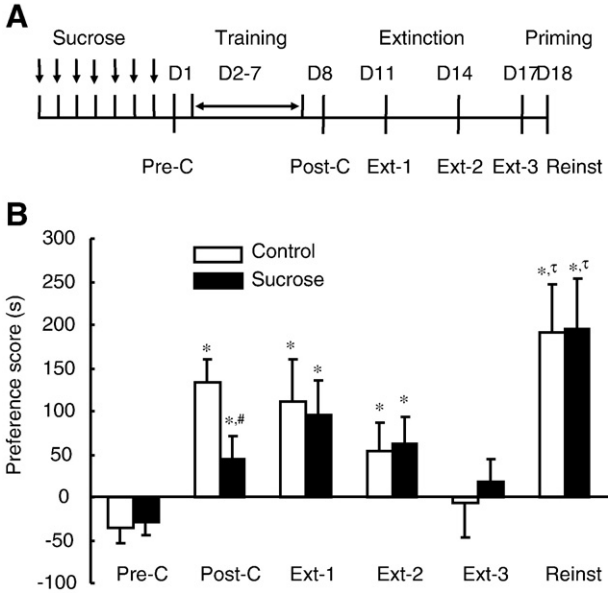

Fig. 1. Effect of sucrose intake prior to conditioning days on the expression, extinction, and reinstatement of morphine-induced CPP. (A): Timeline of the experimental procedure. Rats in the Sucrose group were offered 15% sucrose solution for seven days prior to CPP conditioning. CPP tests in Pre-conditioning (*Pre-c*), Post-conditioning (*Post-c*), Extinction-1 (*EXT-1*), Extinction-2 (*EXT-2*), Extinction-3 (*EXT-3*), and Reinstatement (*Reinst*) were performed on Days 1, 8, 11, 14, 17, and 18, respectively. (B): Preference scores during Pre-conditioning, Post-conditioning, Extinction-1, Extinction-2, Extinction-3, and Reinstatement. Data are expressed as mean±SEM. $^{*}p<0.05$ compared with Pre-conditioning in the same group; $^{\tau}p<0.05$ compared with Extinction-3 in the same group; $^{\#}p<0.05$ compared with the Control group in the same phase.

Rats given either saline or morphine injections were immediately placed into the assigned chambers for 30 min before being returned to their home cages.

2.5.3. Post-conditioning (Day 8)

The effect of place conditioning was examined in rats with no morphine or saline injections. Rats were placed into the middle chamber and allowed to move freely across the three chambers for 15 min.

2.5.4. Extinction tests 1, 2, and 3 (Days 11, 14, and 17, respectively)

The extinction procedure was identical to Post-conditioning. Three extinction tests (Extinction-1, Extinction-2, and Extinction-3) were conducted on Days 11, 14, and 17, respectively.

2.5.5. Reinstatement test (Day 18)

The Reinstatement procedure was identical to Post-conditioning, with the exception that rats were given a priming dose of morphine (1 mg/kg, s.c.) 20 min before CPP testing.

2.6. Experimental design

In experiment 1, the sucrose solution was given for seven consecutive days prior to CPP conditioning (Fig. 1A). Twelve and 14 rats were used in the Control group and Sucrose group, respectively. In experiment 2, the sucrose solution was given on Days 2, 4, and 6 during the Place conditioning phase (Fig. 2A). Place conditioning was conducted at least 1.5 h after sucrose administration in the morning and at least 1.5 h before sucrose administration in the afternoon. The Control group and Sucrose group consisted of 11 rats each. In experiment 3, the sucrose solution was given following the acquisition of morphine CPP on Day 9 (Post-conditioning) and Day 10 (Extinction-1) (Fig. 3). The Control group and Sucrose group consisted of 12 rats each.

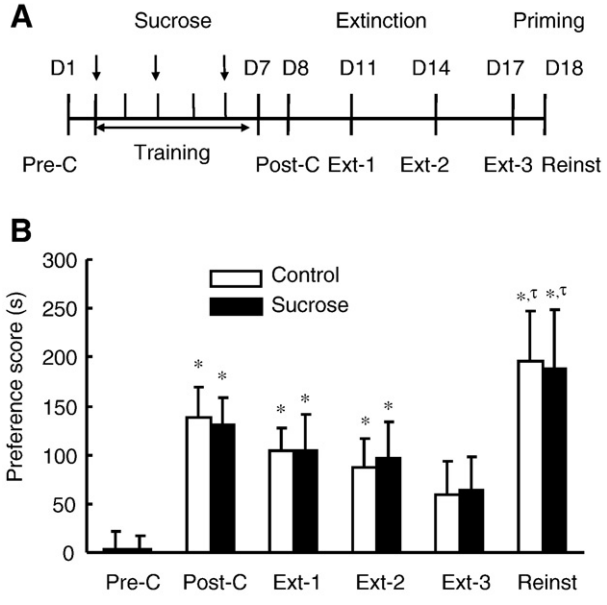

Fig. 2. Effect of sucrose intake during conditioning days on the expression, extinction, and reinstatement of morphine-induced CPP. (A) Timeline of the experimental procedure. The sucrose solution was administered on Days 2, 4, and 6 during the CPP conditioning phase. CPP tests in Pre-conditioning (*Pre-c*), Post-conditioning (*Post-c*), Extinction-1 (*EXT-1*), Extinction-2 (*EXT-2*), Extinction-3 (*EXT-3*), and Reinstatement (*Reinst*) were performed on Days 1, 8, 11, 14, 17, and 18, respectively. (B) Preference scores during Pre-conditioning, Post-conditioning, Extinction-1, Extinction-2, Extinction-3, and Reinstatement. Data are expressed as mean ± SEM. $^{*}p<0.05$ compared with Pre-conditioning in the same group; $^{\tau}p<0.05$ compared with Extinction-3 in the same group.

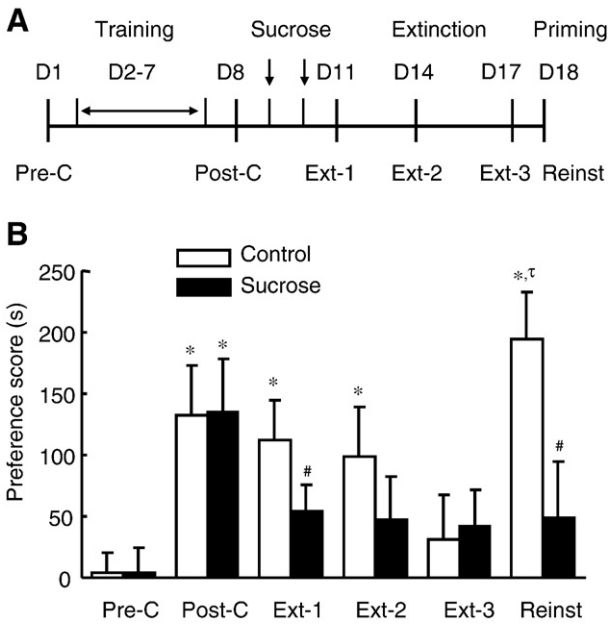

Fig. 3. Effect of sucrose intake following acquisition of morphine-induced CPP on the extinction and reinstatement of morphine CPP. (A) Timeline of the experimental procedure. The sucrose solution was administered daily on Days 9 and 10 following CPP conditioning. CPP tests in Pre-conditioning (*Pre-c*), Post-conditioning (*Post-c*), Extinction-1 (*EXT-1*), Extinction-2 (*EXT-2*), Extinction-3 (*EXT-3*), and Reinstatement (*Reinst*) were performed on Days 1, 8, 11, 14, 17, and 18, respectively. (B) Preference scores during Pre-conditioning, Post-conditioning, Extinction-1, Extinction-2, Extinction-3, and Reinstatement. Data are expressed as mean ± SEM. $^{*}p<0.05$ compared with Pre-conditioning in the same group; $^{\tau}p<0.05$ compared with Extinction-3 in the same group; $^{\#}p<0.05$ compared with the Control group in the same phase.

2.7. Statistical analysis

Preference score was the dependent variable. Two-way analysis of variance (ANOVA) followed by Fisher Least Significant Difference *post hoc* test (SPSS, v. 15, Chicago, IL, USA) were used to evaluate the differences in CPP scores between the Control group and Sucrose group and across CPP tests in each phase. Sucrose treatment (Sucrose *vs.* Control) was the between-subjects factor. For acquisition of CPP, Pre-conditioning *vs.* Post-conditioning was the within-subjects factor. For extinction of CPP, Extinction test (Extinction-1 *vs.* Extinction-2 *vs.* Extinction-3) was the within-subjects factor. For reinstatement of CPP, Extinction-3 *vs.* Reinstatement was the within-subjects factor. A value of $p<0.05$ was considered statistically significant.

3. Results

3.1. Effects of sucrose solution administered prior to conditioning days on the expression, extinction, and reinstatement of morphine-induced CPP

Experiment 1 was conducted to determine the effects of a sucrose solution, administered prior to morphine conditioning training, on the expression, extinction, and morphine-induced reinstatement of CPP (Fig. 1). For acquisition of CPP, a significant difference in CPP score was observed between Pre-conditioning and Post-conditioning ($F(1,24)=23.5$, $p<0.001$) and between the Control group and Sucrose group ($F(1,24)=4.5$, $p=0.04$). After the 6-day conditioning training, rats acquired CPP in both the Control group and Sucrose group, while rats in the Control group had a higher preference score than the Sucrose group ($p<0.05$). Following three extinction tests (Extinction-1, -2, and -3), rats showed a gradual decrease in preference scores, indicating

significant CPP extinction ($F(2,48)=3.8$, $p=0.02$), but rats in the Control group and Sucrose group had a similar CPP extinction rate ($p>0.05$). In the Reinstatement phase, preference scores were significantly higher after priming than in Extinction-3 ($F(1,24)=18.7$, $p<0.001$), indicating that a low dose of morphine was sufficient to reinstate conditioned place preference previously established by morphine. Preference scores between the Control group and Sucrose group showed no significant difference ($p>0.05$). These results suggest that sucrose solution, given prior to conditioning training for acquisition of morphine CPP, could significantly suppress the expression of CPP, while leaving extinction and morphine-induced reinstatement intact.

3.2. Effects of sucrose solution administered during conditioning days on the expression, extinction, and reinstatement of morphine-induced CPP

Experiment 2 was conducted to determine the effects of a sucrose solution, administered during conditioning training, on the expression, extinction, and reinstatement of morphine-induced CPP (Fig. 2). For CPP acquisition, significant differences in preference scores were observed between Pre-conditioning and Post-conditioning ($F(1,22)=29.1$, $p<0.001$) but not between the Control group and Sucrose group ($p>0.05$). After the 6-day conditioning training, rats acquired CPP in both the Control group and Sucrose group, indicated by significant increases in place preference scores in both the Control group ($p<0.05$) and Sucrose group ($p<0.05$). After three sessions of extinction, rats showed a gradual decrease in the time spent in the morphine-paired chamber, indicating the occurrence of extinguished behaviors in both the Control group and Sucrose group. However, preference scores in the Control group and Sucrose group showed no significant difference in all three extinction tests ($p>0.05$). In the Reinstatement phase, a low-dose morphine priming injection significantly reinstated extinguished morphine CPP. Preference scores were significantly higher after priming than in Extinction-3 ($F(1,22)=10.2$, $p=0.004$), but the preference scores between the Control group and Sucrose group showed no significant difference ($p>0.05$), suggesting that the sucrose solution, given during conditioning days, did not alter the expression, extinction, and reinstatement of CPP.

3.3. Effects of sucrose solution administered after acquisition of morphine-induced CPP on extinction and reinstatement of morphine-induced CPP

Experiment 3 was conducted to determine the effects of a sucrose solution, administered following the acquisition of morphine CPP, on the extinction and reinstatement of CPP (Fig. 3). Consistent with experiments 1 and 2, significant differences in preference scores were observed between Pre-conditioning and Post-conditioning ($F(1,20)=19.6$, $p<0.001$) but not between the Control group and Sucrose group ($p>0.05$). After the 6-day conditioning training, rats acquired CPP in both the Control group and Sucrose group. After three extinction tests (Extinction-1, -2, and -3), a gradual decrease in time spent in the morphine-paired chamber was observed, indicating the occurrence of extinguished behaviors after extinction training. However, preference scores in the Control group and Sucrose group showed a significant difference ($F(1,20)=6.2$, $p=0.02$). *Post hoc* analysis revealed significantly lower preference scores in the Sucrose group than in the Control group ($p<0.05$) in Extinction-1. In the Reinstatement phase, preference scores were significantly higher after priming than in Extinction-3 ($F(1,20)=7.7$, $p=0.01$). Preference scores in the Control group were significantly different from those in the Sucrose group ($F(1,20)=5.4$, $p=0.03$). After priming with 1 mg/kg morphine, rats in the Control group showed higher preference scores than the Sucrose group ($p<0.05$). Taken together, administration of a sucrose solution after acquisition of morphine-induced CPP effectively accelerated the extinction of CPP and prevented the reinstatement of morphine-induced CPP by a low-dose morphine priming injection.

4. Discussion

The present study demonstrates that sucrose intake can affect the expression, extinction, and reinstatement of morphine CPP. The sucrose solution given prior to place conditioning transiently suppressed the expression of morphine CPP. The sucrose solution given during the place conditioning days had no effect on the expression, extinction, and reinstatement of morphine-induced CPP. The sucrose solution given following place conditioning profoundly promoted the initial extinction and inhibited morphine-induced reinstatement of CPP. The present study extends previous findings examining the effects of sucrose solutions on the expression of morphine-induced CPP (Lett, 1989) and characterizes the effects of the sucrose solution on the extinction and reinstatement of morphine CPP.

Multiple neurochemical mechanisms could be responsible for the role of the sucrose solution in modulating the expression, extinction, and reinstatement of morphine-induced CPP. Morphine is a highly potent opiate analgesic drug and a principal active component in opium. Sucrose has been shown to have effects on the endogenous opioid system (Colantuoni et al., 2002; Spangler et al., 2004). Behavioral studies also have shown a strong correlation between sucrose consumption and opioid-mediated behavioral effects. Intake of a palatable sucrose solution may modify the action of morphine (Coy and Kanarek, 2006; d'Anci et al., 1996; Kanarek and Homoleski, 2000) and other opioid drugs (Kanarek et al., 2000, 2001) on pain perception. Ingestion of high concentrations of sucrose solutions for shorter durations may activate the endogenous opioid system and appears to play an important role in modifying morphine withdrawal (Jain et al., 2004). Sucrose consumption has been shown to elevate extracellular dopamine levels in the striatal forebrain of rats (Hernandez and Hoebel, 1988).

The findings of the present study somewhat contradict with a previous report in which ingestion of sweetened water enhanced the development of morphine CPP in rats (Lett, 1989). The conflicting results are likely the result of procedural differences. The sucrose solution was continuously available for 5 days in the Lett study; in contrast, the sucrose solution was only available for 4 h (8:00–10:00 am and 4:00–6:00 pm) for 7 days in the present study. Whether the amount or duration of sucrose availability could differentially affect morphine-induced CPP remains unresolved. However, d'Anci et al. (1996) reported that rats exhibited suppressed or enhanced morphine-induced analgesia following acute (5-h) or chronic (3-week) access to a sucrose solution, indicating either cross-sensitization or cross-tolerance between sucrose and the analgesic effect of morphine, depending on the length of sucrose exposure. The amount or duration of sucrose consumption also may have distinct influences on morphine-induced CPP. Lett (1989) suggested that sucrose exposure was less likely to produce cross-tolerance to the rewarding effect of morphine because cross-tolerance was predominantly observed in morphine-induced analgesia. However, we would argue that cross-tolerance between sucrose and morphine can parallel the process of cross-sensitization, and the induction of either cross-tolerance or -sensitization can be determined by the duration or amount of sugar availability. When the sucrose solution was administered during the extinction of morphine CPP, morphine-induced reinstatement was significantly suppressed. As noted above, sucrose could potentially influence the endogenous opioid and dopamine systems, which ultimately could modulate the rewarding properties of morphine and could be the underlying cause of the attenuated responses during morphine-induced reinstatement.

The present study has several limitations. First, the duration of sucrose exposure before, during, and after the conditioning trial of morphine-induced CPP varied in experiments 1, 2, and 3, possibly

resulting in differing sucrose intake between experiments. Second, the amount of sucrose intake was not recorded when it was administered during the conditioning phase of morphine CPP. Sucrose was given on morphine conditioning days 2, 4, and 6; therefore, the rats may have developed conditioned taste aversion to sucrose, thereby reducing their sucrose intake. Furthermore, the group-housed rats may have ingested sucrose competitively, thereby eliciting social stress and subsequently affecting the effects of morphine. Indeed, the amount of sucrose intake itself, rather than the time when the sucrose solution was administered, may have differentially affected the expression, extinction, and reinstatement of morphine-induced CPP.

In conclusion, administration of a sucrose solution at different time-points may affect the expression, extinction, and reinstatement of morphine-induced CPP. More importantly, the sucrose solution administered during the extinction of morphine-induced CPP robustly suppressed morphine-induced reinstatement. The present results provide insight into non-drug reward as a possible means to maintain abstinence and prevent relapse in drug addicts.

Acknowledgments

This work was supported in part by the Program for New Century Excellent Talents in University, the National Basic Research Program of China (973 Program, 2007CB512302 and 2003CB515400), the National High Technology Research and Development Program of China (863 Program, 2006AA02Z4D1), and the Natural Science Foundation of China (Nos.: 30570576 and 30670713).

References

Carroll ME. Acquisition and reacquisition (relapse) of drug abuse: modulation by alternative reinforcers. NIDA Res Monogr 1998;169:6–25.
Carroll ME, Anderson MM, Morgan AD. Higher locomotor response to cocaine in female (*vs.* male) rats selectively bred for high (HiS) and low (LoS) saccharin intake. Pharmacol Biochem Behav 2007a;88:94–104.
Carroll ME, Anderson MM, Morgan AD. Regulation of intravenous cocaine self-administration in rats selectively bred for high (HiS) and low (LoS) saccharin intake. Psychopharmacology 2007b;190:331–41.
Carroll ME, Lac ST, Nygaard SL. A concurrently available nondrug reinforcer prevents the acquisition or decreases the maintenance of cocaine-reinforced behavior. Psychopharmacology 1989;97:23–9.
Colantuoni C, Rada P, McCarthy J, Patten C, Avena NM, Chadeayne A, et al. Evidence that intermittent, excessive sugar intake causes endogenous opioid dependence. Obes Res 2002;10:478–88.
Coy RT, Kanarek RB. Chronic sucrose intake reduces the antagonist effect of b-funaltrexamine on morphine-induced antinociception in female but not in male rats. Nutr Neurosci 2006;9:131–9.
d'Anci KE, Kanarek RB, Marks-Kaufman R. Duration of sucrose availability differentially alters morphine-induced analgesia in rats. Pharmacol Biochem Behav 1996;54:693–7.
DeSousa NJ, Bush DEA, Vaccarino FJ. Individual differences in sucrose intake are predictive of intravenous amphetamine self-administration levels. Soc Neurosci Abstr 1996;22:705.
Gosnell BA. Sucrose intake enhances behavioral sensitization produced by cocaine. Brain Res 2005;1031:194–201.
Gosnell BA. Sucrose intake predicts rate of acquisition of cocaine self-administration. Psychopharmacology 2000;149:286–92.
Gosnell BA, Krahn DD. The relationship between saccharin and alcohol intake in rats. Alcohol 1992;9:203–6.
Hernandez L, Hoebel BG. Food reward and cocaine increase extracellular dopamine in the nucleus accumbens as measured by microdialysis. Life Sci 1988;42:1705–12.
Higgins ST, Budney AJ, Bickel WK, Foerg FE, Donham R, Badger GJ. Incentives improve outcome in outpatient behavioral treatment of cocaine dependence. Arch Gen Psychiatry 1994;51:568–76.
Holder MD. Responsivity to pain in rats changed by the ingestion of flavored water. Behav Neural Biol 1988;49:45–53.
Jain R, Mukherjee K, Singh R. Influence of sweet tasting solutions on opioid withdrawal. Brain Res Bull 2004;64:319–22.
Janowsky DS, Pucilowski O, Buyinza M. Preference for higher sucrose concentrations in cocaine abusing-dependent patients. J Psychiatr Res 2003;37:35–41.
Kampov-Polevoy A, Garbutt JC, Janowsky D. Evidence of preference for a high-concentration sucrose solution in alcoholic men. Am J Psychiatry 1997;154:269–70.
Kanarek RB, Homoleski BA. Modulation of morphine-induced antinociception by palatable solutions in male and female rats. Pharmacol Biochem Behav 2000;66:653–9.
Kanarek RB, Mandillo S, Wiatr C. Chronic sucrose intake augments antinociception induced by injections of mu but not kappa opioid receptor agonists into the periaqueductal gray matter in male and female rats. Brain Res 2001;920:97–105.
Lenoir M, Serre F, Cantin L, Ahmed SH. Intense sweetness surpasses cocaine reward. PLoS ONE 2007;2:e698.
Lett BT. Ingestion of sweet water enhances the rewarding effect of morphine in rats. Psychobiology 1989;17:191–4.
Lieblich I, Cohen E, Ganchrow JR, Blass EM, Bergmann F. Morphine tolerance in genetically selected rats induced by chronically elevated saccharin intake. Science 1983;221:871–3.
Lu L, Liu D, Ceng X, Ma L. Differential roles of corticotropin-releasing factor receptor subtypes 1 and 2 in opiate withdrawal and in relapse to opiate dependence. Eur J Neurosci 2000;12:4398–404.
Lu L, Liu D, Ceng X. Corticotropin-releasing factor receptor type 1 mediates stress-induced relapse to cocaine-conditioned place preference in rats. Eur J Pharmacol 2001;415:203–8.
Lu L, Shepard JD, Hall FS, Shaham Y. Effect of environmental stressors on opiate and psychostimulant reinforcement, reinstatement and discrimination in rats: a review. Neurosci Biobehav Rev 2003;27:457–91.
Lu L, Xu NJ, Ge X, Yue W, Su WJ, Pei G, et al. Reactivation of morphine conditioned place preference by drug priming: role of environmental cues and sensitization. Psychopharmacology 2002;159:125–32.
Lynch WJ, Carroll ME. Regulation of drug intake. Exp Clin Psychopharmacol 2001;9:131–43.
Mueller D, Perdikaris D, Stewart J. Persistence and drug-induced reinstatement of a morphine-induced conditioned place preference. Behav Brain Res 2002;136:389–97.
Overstreet DH, Kampov-Polevoy AB, Rezvani AH, Murrelle L, Halikas JA, Janowsky DS. Saccharin intake predicts ethanol intake in genetically heterogeneous rats as well as different rat strains. Alcohol Clin Exp Res 1993;17:366–9.
Perry JL, Anderson MM, Nelson SE, Carroll ME. Acquisition of i.v. cocaine self-administration in adolescent and adult male rats selectively bred for high and low saccharin intake. Physiol Behav 2007a;91:126–33.
Perry JL, Nelson SE, Anderson MM, Morgan AD, Carroll ME. Impulsivity (delay discounting) for food and cocaine in male and female rats selectively bred for high and low saccharin intake. Pharmacol Biochem Behav 2007b;86:822–37.
Ribeiro Do Couto B, Aguilar MA, Manzanedo C, Rodriguez-Arias M, Minarro J. Social stress is as effective as physical stress in reinstating morphine-induced place preference in mice. Psychopharmacology 2006;185:459–70.
Ribeiro Do Couto B, Aguilar MA, Rodriguez-Arias M, Minarro J. Long-lasting rewarding effects of morphine induced by drug primings. Brain Res 2005;1050:53–63.
Rodefer JS, Carroll ME. A comparison of progressive ratio schedules *versus* behavioral economic measures: effect of an alternative reinforcer on the reinforcing efficacy of phencyclidine. Psychopharmacology 1997;132:95–103.
Rudski JM, Billington CJ, Levine AS. A sucrose-based maintenance diet increases sensitivity to appetite suppressant effects of naloxone. Pharmacol Biochem Behav 1997;58:679–82.
Spangler R, Wittkowski KM, Goddard NL, Avena NM, Hoebel BG, Leibowitz SF. Opiate-like effects of sugar on gene expression in reward areas of the rat brain. Brain Res Mol Brain Res 2004;124:134–42.
Vitale MA, Chen D, Kanarek RB. Chronic access to a sucrose solution enhances the development of conditioned place preferences for fentanyl and amphetamine in male Long-Evans rats. Pharmacol Biochem Behav 2003;74:529–39.
Wang J, Fang Q, Liu Z, Lu L. Region-specific effects of brain corticotropin-releasing factor receptor type 1 blockade on footshock-stress- or drug-priming-induced reinstatement of morphine conditioned place preference in rats. Psychopharmacology 2006;185:19–28.
Zhai HF, Zhang ZY, Zhao M, Qiu Y, Ghitza UE, Lu L. Conditioned drug reward enhances subsequent spatial learning and memory in rats. Psychopharmacology 2007;195:193–201.