Psychopharmacology (2009) 204:203–211
DOI 10.1007/s00213-008-1450-y

ORIGINAL INVESTIGATION

Effects of cannabinoid CB1 receptor antagonist rimonabant in consolidation and reconsolidation of methamphetamine reward memory in mice

Lu-lu Yu · Xue-yi Wang · Mei Zhao · Yu Liu · Yan-qin Li · Fang-qiong Li · Xiaoyi Wang · Yan-xue Xue · Lin Lu

Received: 11 May 2008 / Accepted: 20 December 2008 / Published online: 16 January 2009

Abstract
Rationale Previous studies have shown that cannabinoid CB1 receptors play an important role in specific aspects of learning and memory, yet there has been no systematic study focusing on the involvement of cannabinoid CB1 receptors in methamphetamine-related reward memory.
Objectives The purpose of this study was to examine whether rimonabant, a cannabinoid CB1 receptor antagonist, would disrupt the consolidation and reconsolidation of methamphetamine-related reward memory, using conditioned place preference paradigm (CPP).
Materials and methods Separate groups of male Kunming mice were trained to acquire methamphetamine CPP. Vehicle or rimonabant (1 mg/kg or 3 mg/kg, i.p.) was given at different time points: immediately after each CPP training session (consolidation), 30 min before the reactivation of CPP (retrieval), or immediately after the reactivation of CPP (reconsolidation). Methamphetamine CPP was retested 24 h and 1 and 2 weeks after rimonabant administration.
Results Rimonabant at doses of 1 and 3 mg/kg significantly inhibited the consolidation of methamphetamine CPP. Only high-dose rimonabant (3 mg/kg) disrupted the retrieval and reconsolidation of methamphetamine CPP. Rimonabant had no effect on methamphetamine CPP in the absence of methamphetamine CPP reactivation.
Conclusions Our findings suggest that cannabinoid CB1 receptors play a major role in methamphetamine reward memory, and cannabinoid CB1 receptor antagonists may be a potential pharmacotherapy to manage relapse associated with drug-reward-related memory.

Keywords Cannabinoid CB1 receptor antagonist · Conditioned place preference · Methamphetamine · Consolidation · Reconsolidation

Introduction

Methamphetamine (METH), also known as “ice”, is a commonly used addictive drug and it is also a powerful stimulant that affects the central nervous system. It belongs to the type of amphetamine, a class of stimulant drugs, which is associated with a number of extremely serious negative health effects (Darke et al. 2008). The prevalence of METH abuse has increased dramatically in many countries in recent years, which has resulted in serious health and social problems (Degenhardt et al. 2008; Fang et al. 2006; Griffiths et al. 2008; Maxwell and Rutkowski 2008; Michels et al. 2007; Pluddemann et al. 2008). The powerful rewarding effects of METH are thought to be attributed to multiple pharmacological actions, including the blockade of plasma membrane transporters of all monoamines, the suppression of dopamine transporter

L.-l. Yu · X.-y. Wang (✉)
Insititute of Mental Health and Hebei Brain Ageing and Cognitive Neuroscience Laboratory, Hebei Medical University,
Shijiazhuang 050031, China
e-mail: nzhwxy@heinfo.net

M. Zhao · Y. Liu · Y.-q. Li · F.-q. Li · X. Wang · Y.-x. Xue · L. Lu (✉)
National Institute on Drug Dependence, Peking University,
38 Xueyuan Road,
Beijing, China
e-mail: linlu@bjmu.edu.cn

expression, and the inhibition of monoamine oxidase activity while increasing tyrosine hydroxylase activity (Kalivas 2007; Pulvirenti and Koob 1994; Treweek et al. 2007; Vezina 2004). Worth noting is that the majorities of studies have directed their focus on the effect of monoamine system on the neurochemical mechanism of METH.

A growing number of studies have identified the important role of cannabinoid receptors in the effect of METH. Cannabinoid CB1 receptors are primarily expressed in the brain's motivational circuitry, including the prefrontal cortex, amygdala, nucleus accumbens, striatum, and hippocampus (De Vries and Schoffelmeer 2005). Cannabinoid CB1 receptors are also widely distributed in memory-related brain regions (i.e., nucleus accumbens, cortex, amygdale, and hippocampus), and they have been suggested to participate in memory modulation (Katona et al. 2001; Li et al. 2008a, b; Tsou et al. 1998; Wilson and Nicoll 2002). Central distribution of cannabinoid CB1 receptors has led a great deal of investigations on the mediating role of cannabinoid CB1 receptors in neuronal processes underlying drug addiction, including METH (Chiang and Chen 2007) and cocaine (De Vries et al. 2001; Xi et al. 2006). For example, SR141716A, a cannabinoid CB1 receptor antagonist, blocked the reinstatement of METH self-administration; in contrast, administration of a small dose of THC enhanced the effects of a subthreshold dose of METH (Anggadiredja et al. 2004). AM251, another cannabinoid CB1 receptor antagonist, has also been demonstrated to inhibit voluntary intake of METH in rats (Vinklerova et al. 2002). Furthermore, METH-induced anxiety-related behaviors can be substantially altered by cannabinoids (Hayase et al. 2005). Taken together, cannabinoid CB1 receptors may be involved in various behavioral effects of METH (Gardner 2005; Yamamoto and Takada 2000).

It has recently been proposed that abused drugs can pathologically usurp the neural mechanisms of learning and memory that shape behaviors under normal circumstances (Hyman 2005; Hyman et al. 2006; Lu et al. 2006; Nestler 2001; Robinson and Kolb 2004; White 1996). Consolidation and reconsolidation are two distinctive stages of memory process. Consolidation refers to a poorly defined set of processes which take an initial, unstable memory representation and convert it into a form that is more stable and effective. Reconsolidation is that reactivation of consolidated memory returns this memory to a labile, sensitive state, during which it can be disturbed (Nader 2003). Cumulating evidence has indicated that the blockade of consolidation of drug-related reward memories could inhibit memory formation while interrupting its reconsolidation process may modify, change, or even erase original drug-related reward memories (de Oliveira Alvares et al. 2005; Nader 2003; Robinson and Franklin 2007). The role of CB1 receptors in different aspects of learning and memory in various behavioral tasks is complicated. Cannabinoid CB1 receptor agonists are more frequently described to cause disruptive effects on learning and memory (Ameri 1999; Hernandez-Tristan et al. 2000; Kobilo et al. 2007; Lin et al. 2006), but disrupted extinction learning in both the conditioned freezing and passive avoidance tasks has been found in rats treated with CB1 receptor antagonist (Niyuhire et al. 2007). Bucherelli and his colleagues have also found that reconsolidation of aversive memory can be disrupted by post-retrieval CB1 antagonist (Bucherelli et al. 2006). Although evidence has shown that a cannabinoid system may play a role in learning and memory process, little has been known about the effect of cannabinoid CB1 receptors on drug-related reward memories. The present study was designed to investigate the effect of cannabinoid CB1 receptor antagonist, rimonabant, in METH-related reward memory, using conditioned place preference paradigm which has been adopted to study drug-related reward memories in recent years (Kuo et al. 2007; Miller and Marshall 2005; Valjent et al. 2006). We hypothesized that the inhibition of cannabinoid receptors could profoundly affect the consolidation and reconsolidation of METH reward memory.

Materials and methods

Subjects

Male Kunming mice (Laboratory Animal Center of Peking University Health Science Center, Beijing, China) initially weighing 28–30 g with age of approximately 8 weeks at the start of the experiment were used as subjects in the current study. The animals were housed five per cage with free access to food and water and maintained on a 12-h light/dark cycle with a constant temperature (23±2°C) and humidity (50±5%). Mice with significant preference for any one chamber (spending more than 500 s in one of the chambers) were excluded. All the experiments were performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. The procedures were approved by the local Committee for Animal Use and Protection.

Drugs

The drugs used in the present study were methamphetamine hydrochloride (National Institute on Drug Dependence, China) and rimonabant (Xinxiang Crude Medicinal Drugs Co., Jiangsu, China). Methamphetamine was dissolved in saline and rimonabant was dissolved in a 1:1:18 solution of

ethanol/Tween 80/saline. All drugs were freshly prepared prior to the experiments. All injections were given intraperitoneally in a volume of 0.1 ml/10 g.

Conditioned place preference

The apparatus for the conditioned place preference (CPP) training and testing consisted of five identical three-chamber PVC boxes. Two large side chambers (15 cm long×15 cm wide×15 cm high) were separated by a smaller one (15 cm long×5 cm wide×15 cm high), with different wall colors (black or white) and floor textures (bar or grid, respectively). Three distinct chambers were separated by manual guillotine doors. Both large chambers had different visual cues on the walls (white chamber with horizontal shape and the black chamber with cross shape). Time spent in the previously saline- or METH-paired chambers during the 15-min conditioning session was determined by a computer which measured time spent in each compartment through interruption of infrared beams by animals.

Conditioning sessions were performed in an unbiased and balanced order (Song et al. 2007; Wang et al. 2006; Li et al. 2008a, b). The chamber in which METH was administered was assigned randomly for each animal. To determine baseline preference (pre-conditioning test), mice were initially placed in the middle chamber with the doors removed for a period of 15 min, and the time spent in each chamber was recorded by computer. During the conditioning session, each mouse was trained for eight consecutive sessions with alternate injections of METH (2 mg/kg, i.p.) and saline (0.1 ml/10 g, i.p.). Mice were confined to the conditioning chamber for 20 min immediately after METH injection. In alternate session, mice were given saline in the same volume as METH and placed into the other chamber. Following the eight session CPP training, the animals were tested for the expression of METH (post-conditioning test) CPP under conditions identical to those described in the pre-conditioning test. The place preference score (CPP score) was defined as the time spent in the methamphetamine-paired chamber minus that spent in the saline-paired chamber (Harris et al. 2005; Wang et al. 2008; Zhai et al. 2007).

Drug memory reactivation

A 15-min re-exposure to the METH-paired chamber was designed to serve as a retrieval trial to reactivate the memory of methamphetamine cue association acquired during the conditioning phase (Bernardi et al. 2006; Miller and Marshall 2005; Zhao et al. 2007). Different groups of mice were given distinct treatments either before or after the memory reactivation.

Retesting of methamphetamine CPP

One day (PT-24h test), 1 week (PT-1w test), or 2 weeks (PT-2w test) after memory reactivation, mice were retested for methamphetamine CPP. If mice did not present the CPP 2 weeks after the reactivation, they were administered a priming dose (0.5 mg/kg, i.p.) of METH and immediately tested for CPP again (priming test).

Procedure

Experiment 1: Effect of rimonabant on the consolidation of METH memory

Experiment 1 was performed to examine the effect of rimonabant on the consolidation of METH memory. Mice were alternately conditioned to METH in one compartment and to saline in the other compartment. To determinate the effects of rimonabant on the consolidation of METH memory, three groups of mice (n=10 per group) were given injections of different doses of rimonabant (0, 1.0, and 3.0 mg/kg, i.p.) immediately after each conditioning session. After the 8-day conditioning sessions, mice were tested for METH CPP as described above. The experimental design for experiment 1 is illustrated in Fig. 1a.

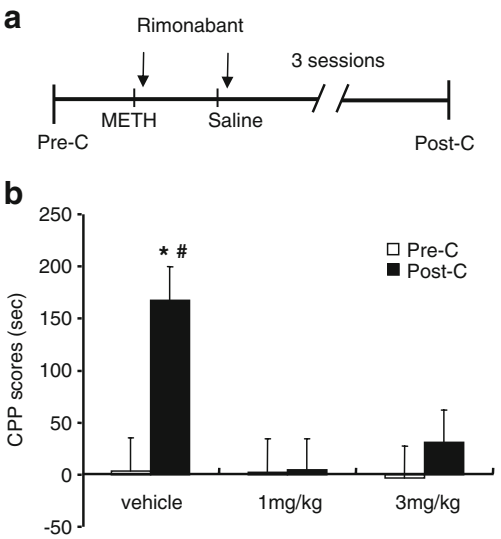

Fig. 1 Effect of rimonabant on the consolidation of METH reward memory. **a** Diagram outlines behavioural procedures. **b** Rimonabant disrupted the consolidation of METH reward memory. A significant difference was found for post-conditioning CPP scores between the 1-mg/kg group, 3-mg/kg group, and vehicle group (n= 10 per group). *p<0.01 compared with pre-conditioning of the same group. #p<0.01 compared with post-conditioning of the 1-mg/kg and 3-mg/kg groups. *Pre-C* pre-conditioning, *Post-C* post-conditioning

Experiment 2: Effect of rimonabant on the retrieval of METH memory

Experiment 2 was conducted to determine the effect of rimonabant on the retrieval of METH reward memory following the acquisition of METH CPP. A 15-min re-exposure to the METH-paired chamber was designed to serve as a retrieval trial. Mice were randomly assigned to three groups (n=8 per group) and received one of the following treatments 30 min before METH memory retrieval: vehicle, rimonabant (1.0 mg/kg, i.p.), and rimonabant (3.0 mg/kg, i.p.). Twenty-four hours later, METH CPP was retested (PT-24h). If mice did not present the CPP 2 weeks later, they were administered a priming dose (0.5 mg/kg, i.p.) of METH and immediately tested for CPP again (priming test). The experimental design for experiment 2 is illustrated in Fig. 2a.

Experiment 3: Effect of rimonabant on the reconsolidation of METH reward memory

Experiment 3 was performed to determine the effect of rimonabant on the reconsolidation of METH CPP. Mice were randomly assigned to three groups (n=9 per group) and received one of the following treatments immediately after the retrieval trial: vehicle, rimonabant (1.0 mg/kg, i.p.), and rimonabant (3.0 mg/kg, i.p.). Twenty-four hours later, METH CPP was retested in these animals (PT-24h). If mice did not present the CPP 2 weeks later, they were administered a priming dose (0.5 mg/kg, i.p.) of METH and immediately tested for CPP again (priming test). The experimental design for experiment 3 is illustrated in Fig. 3a.

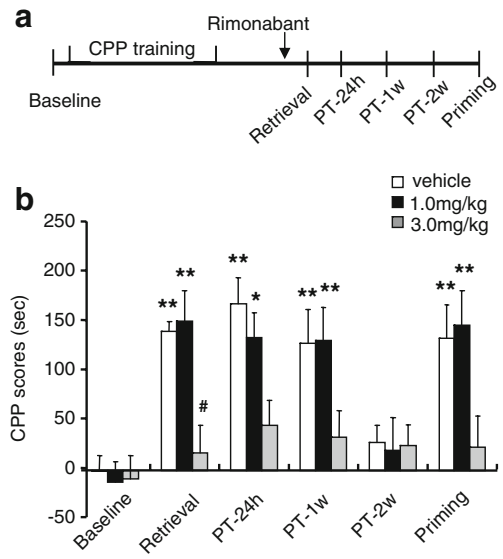

Fig. 2 Effect of rimonabant on the retrieval of METH reward memory. **a** Diagram outlines behavioral procedures. **b** Rimonabant disrupted the retrieval of METH reward memory. A significant difference was found for PT-30min CPP scores between the vehicle group, 1-mg/kg group, and 3-mg/kg group (n=8 per group). *p<0.05 compared with pre-conditioning of the same group. #p<0.01 compared with post-conditioning of the vehicle group. *PT-24h* post-treatment 24 h, *PT-1w* post-treatment 1 week, *PT-2w* post-treatment 2 weeks

Experiment 4: Effect of rimonabant on METH reward memory in the absence of retrieval

Experiment 4 was designed to determine whether the re-exposure to drug-associated context was necessary for the ability of rimonabant to disrupt the reconsolidation of METH CPP. Three groups of mice (n=7 per group) were given the same intra-peritoneal injections of rimonabant or vehicle as experiment 3 except for re-exposure to the METH-associated context. Twenty-four hours later, METH CPP was retested in these animals (PT-24h). The experimental design for experiment 4 is illustrated in Fig. 4a.

Data analysis

Data were expressed as mean ± SEM. Two-way repeated measure ANOVAs were used with between-subjects factor of treatment (different doses of rimonabant) and a within-subjects factor of test condition (baseline vs. post-conditioning test). To test the long-term effects of rimonabant, a two-way repeated measures ANOVA was used to analyze the differences in CPP score among test conditions. All post hoc comparisons were made using the Tukey's test. Results with p<0.05 were accepted as being statistically significant.

Results

Experiment 1: Rimonabant impaired the consolidation of METH CPP

A two-way ANOVA showed a significant interaction between dose (0, 1.0, and 3.0 mg/kg) and test condition (pre-conditioning, post-conditioning; $F_{(2,\ 59)}$=3.73, p=0.037). Post hoc analysis showed that after METH CPP training, the CPP score was significantly increased in the vehicle group (p=0.001) compared with baseline. In contrast, there was no significant difference between baseline and post-conditioning test in groups injected with 1.0 and 3.0 mg/kg rimonabant (p>0.05). The results indicate that the blockade of cannabinoid CB1 receptors by rimonabant substantially inhibited the consolidation of METH CPP.

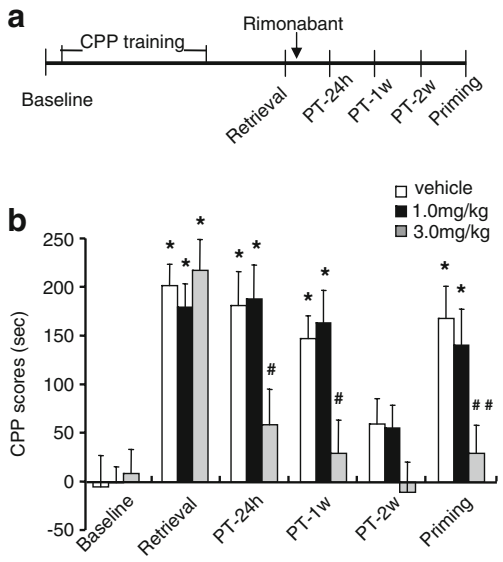

Fig. 3 Effect of rimonabant on the reconsolidation of METH reward memory. **a** Diagram outlines behavioral procedures. **b** Rimonabant disrupted the reconsolidation of METH reward memory. A significant difference was found for PT-24h and PT-1w CPP scores between the vehicle group, 1-mg/kg group, and 3-mg/kg group (n=9 per group). *p<0.01 compared with pre-conditioning of the same group. #p< 0.05, ##p<0.01 compared with post-conditioning of the vehicle group. *PT-24h* post-treatment 24 h, *PT-1w* post-treatment 1 week, *PT-2w* post-treatment 2 weeks

Experiment 2: Rimonabant impaired the retrieval of METH CPP

A two-way repeated measure ANOVA conducted on CPP score using doses of rimonabant (0, 1.0, and 3.0 mg/kg) as the between-subjects factors and test condition (baseline, retrieval, post-treatment 24 h, post-treatment 1 week, post-treatment 2 weeks, priming) as the within-subjects factor revealed a significant effect of dose ($F_{(2,\ 143)}$=16.527, p<0.001), and there were no significant differences in interaction between dose and test conditions. Post hoc analysis revealed that mice injected with vehicle or 1 mg/kg, but not 3 mg/kg, rimonabant showed a significant increase in the CPP score from baseline at pre-conditioning test (p<0.05). In addition, a significant difference was found for the CPP score between the 3-mg/kg and vehicle groups at PT-30min (p=0.004). A similar pattern was also found in the animals at 24 h after rimonabant treatment (PT-24h) in which significant differences for CPP score were only observed in the vehicle and 1-mg/kg groups, but not in the 3-mg/kg group, compared with baseline (p<0.05). These findings demonstrate that rimonabant blocked the expression of preference for the environment previously paired with METH.

To examine the long-term effect of rimonabant on retrieval of METH reward memory, mice were tested for the expression of METH CPP 1 (PT-1w) and 2 (PT-2w) weeks after rimonabant treatment, respectively. During PT-1w testing, there were still significant differences for the CPP score in the vehicle (p=0.015) and 1-mg/kg groups (p=0.004) compared with baseline. CPP was not altered in the 3-mg/kg group during these tests. Our results indicated that the effect of 3 mg/kg rimonabant was due to the disruption of the retrieval of methamphetamine reward memory rather than spontaneous extinction. At PT-2w test, all groups failed to show METH CPP.

Experiment 3: Rimonabant impaired reconsolidation of METH CPP

A two-way ANOVA showed a significant interaction between dose (0, 1.0, and 3.0 mg/kg) and test condition (baseline, retrieval, post-treatment 24 h, post-treatment 1 week, post-treatment 2 weeks, priming; $F_{(10,\ 143)}$=2.12, p=0.028) and a significant effect of doses ($F_{(2,\ 143)}$=7.53, p=0.003). Post hoc analysis revealed that after METH training, all groups acquired CPP (p<0.001), and there were no differences in CPP score between any two groups during post-conditioning (retrieval test). Compared with the vehicle and 1-mg/kg groups, the CPP score was significantly decreased in the 3-mg/kg group (p=0.002) at PT-24h testing. To examine the long-term effect of rimonabant on reconsolidation of METH memory, mice were tested for the expression of METH CPP after rimonabant administration (PT-1w and PT-2w tests). At

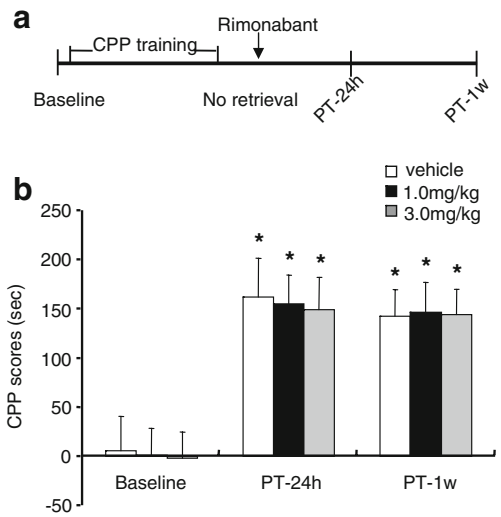

Fig. 4 Effect of rimonabant on METH CPP in the absence of memory retrieval. a Diagram outlines behavioral procedures. **b** Rimonabant had no effect on METH CPP without retrieval. There was no significant difference for the CPP scores between the vehicle group, 1-mg/kg group, and 3-mg/kg group during any test session (n=7 per group). *p<0.01 compared with pre-conditioning of the same group. *PT-24h* post-treatment 24 h, *PT-1w* post-treatment 1 week

the PT-1w test, there were still significant differences for the CPP score in the vehicle (p=0.015) and 1-mg/kg groups (p= 0.004), but not in the 3-mg/kg group, compared with baseline. Our results indicated that the effect of 3 mg/kg rimonabant was due to the disruption of the METH reconsolidation rather than spontaneous extinction. At the PT-2w test, all groups failed to show METH CPP. In the priming test, there was no significant difference for the CPP score in the 3-mg/kg group between the priming test and baseline, indicating that a priming injection of methamphetamine did not reinstate METH CPP. Taken together, these results demonstrated that the inhibitory effect of rimonabant on reconsolidation of METH reward memory lasted at least 2 weeks.

Experiment 4: Rimonabant had no effect on methamphetamine CPP in the absence of memory retrieval

The CPP score in all groups significant increased compared with baseline during PT-24h and PT-1w testing ($F_{(2,\ 62)}$= 25.52, p<0.01), indicating that rimonabant did not disrupt METH CPP in the absence of METH CPP reactivation.

Discussion

The current study was designed to examine the role of cannabinoid CB1 receptor antagonist, rimonabant, in METH-related reward memory, using the CPP paradigm. The main findings of present study were: (1) low- and high-dose cannabinoid CB1 receptor antagonist, rimonabant, impaired the consolidation of METH CPP; (2) the retrieval and reconsolidation of METH CPP were disrupted by high-dose rimonabant; and (3) rimonabant had no effect on the reconsolidation of METH CPP unless the reactivation process was associated with METH-paired context. Taken together, these findings demonstrated that cannabinoid CB1 receptors play an important role in METH-related reward memory.

Extensive evidence shows that cannabinoid CB1 receptors play a critical but complicated role in different aspects of learning and memory in various behavioral tasks. For example, memory consolidation in an inhibitory avoidance paradigm has been shown to be impaired by AM251, a cannabinoid CB1 receptor antagonist (de Oliveira Alvares et al. 2005, 2006, 2008). Disrupted extinction learning in both the conditioned freezing and passive avoidance tasks has also been found in rats treated with rimonabant (Niyuhire et al. 2007). Bucherelli et al. have found that reconsolidation of aversive memory can be disrupted by post-retrieval CB1 antagonist treatment (Bucherelli et al. 2006). In line with these findings, we reported that the blockade of cannabinoid CB1 receptors by rimonabant substantially inhibited the consolidation, retrieval, and reconsolidation of METH CPP which, in turn, indicates the impairment of METH-related reward memories. To examine whether the original drug-related reward memories were persistently disrupted by pre-retrieval rimonabant treatment, mice were administered a priming dose of METH (0.5 mg/kg, i.p), and CPP was retested again. There was no significant difference for CPP score in the 3-mg/kg group between priming test and baseline, indicating that the inhibitory effect of rimonabant on METH CPP lasted at least 2 weeks. Our results appear to contrast with some previous findings in the literature, where cannabinoid CB1 receptor agonists are more frequently described to cause disruptive effects on learning and memory (Ameri 1999; Hernandez-Tristan et al. 2000; Kobilo et al. 2007; Lin et al. 2006), while systematic administration or intra-hippocampus infusion of CB1 antagonist, rimonabant or AM251, can enhance retrieval or consolidation of spatial memory, taste memory, and object recognition memory (Clarke et al. 2008; Kobilo et al. 2007; Takahashi et al. 2005; Wolff and Leander 2003). The difference between their results and ours could be due to different regimes and different brain regions involved in various types of memory. Drug reward memory are mainly involved in motivational circuitry, especially the ventral tegmental area, nucleus accumbens, and amygdala (Hyman et al. 2006; White 1996), whereas spatial memory and object recognition memory critically requires the hippocampus (Bird and Burgess 2008; Eichenbaum et al. 2007; Spiers et al. 2001). Since CB1 receptors are widely expressed in the brain, the modulatory functions of CB1 receptors may be specific to its brain location. For example, the hippocampus and amygdala are involved in context fear memory (Anagnostaras et al. 2001; Laurent et al. 2008), while the amygdala is critical to cue-induced fear memory (Campeau and Davis 1995). It has been shown that intra-amygdala infusion of CB1 receptor agonists impaired the reconsolidation of fear-potentiated memory (Lin et al. 2006), whereas microinjection of AM251, a cannabinoid antagonist disrupted consolidation and reactivation of context fear memory (Bucherelli et al. 2006). These results implicated an interaction between the endocannabinoid system in the amygdala and hippocampus. This is in line with the results of de Oliveira Alvares et al. They showed the disruptive effects of intra-hippocampal CB1 receptor antagonist on inhibitory avoidance memory but not open field habituation memory, and it was indicated that the role of CB1 receptors in the hippocampus may require activation of the amygdalar endocannabinoid system (de Oliveira Alvares et al. 2005). Thus, our findings implied that the CB1 receptor antagonist rimonabant may impair METH rewarding memory through inactivation of CB1 receptors in

motivational circuitry that may interact with endocannabinoid systems of the hippocampus and amygdala.

Robinson and Franklin (2007) reported that intracerebroventricular infusions of anisomycin not only time-dependently inhibited the consolidation of morphine CPP, but also selectively disrupted morphine-paired reconsolidation. Briefly, diminished morphine CPP was only evident in the animals treated with anisomycin immediately after a morphine-paired, not a saline-paired, conditioning session. It appears that the engagement of cannabinoid receptors in the reconsolidation of drug CPP can be drug-context-dependent. Whether drug context exposure could influence the effect of rimonabant in the reconsolidation of METH CPP was also examined in the present study (experiment 4). Mice in experiments 3 and 4 were given intra-peritoneal injections of rimonabant or vehicle following the establishment of METH CPP, in the presence and absence of re-exposure to the METH-associated context, respectively. Consistent with the findings reported by Robinson and Franklin (2007), rimonabant was effective to impair the reconsolidation of morphine CPP when retrieval testing (exposure to drug context) was performed (experiment 3). In contrast, the animals treated with either vehicle or rimonabant exhibited similar CPP performance during the reactivation phase when the retrieval testing was not included (experiment 4). Taken together, the effect of cannabinoid CB1 receptor on the reconsolidation of METH drug memories appears to be drug-context-dependent.

Since the identification of cannabinoid CB1 and CB2 receptors (Howlett et al. 1990; Matsuda et al. 1990; Munro et al. 1993), more attention has been paid to the involvement of endogenous cannabinoid transmission in the resumption of drug-seeking behavior. Numerous studies have demonstrated that the important role of cannabinoid CB1 receptor in regulating consumption of cocaine (Arnold 2005), nicotine (Castane et al. 2002; Cohen et al. 2005), alcohol (Colombo et al. 2004; Gessa et al. 2005; Hungund and Basavarajappa 2004; Wang et al. 2003), and opioids (Fattore et al. 2007; Vigano et al. 2004). There are also several reports showing an involvement of the endocannabinoid system in drug-relapsing episodes. For example, Yamamoto found that priming with CB1 receptor agonists was able to resume extinguished operant behavior in rats (Anggadiredja et al. 2004). Blockade of the cannabinoid CB1 receptor by the specific antagonist, rimonabant, impairs the reinstatement of responding, confirming a cannabinoid mechanism in relapse to drug-seeking behavior (Le Foll and Goldberg 2005; De Vries and Schoffelmeer 2005). Indeed, the relapse-preventing properties of SR141716A (rimonabant) have already been confirmed in a first clinical trial in smokers, in which the rate of stopping smoking was doubled in smokers who were motivated to quit and who received SR141716A compared with those who received placebo (Le Foll and Goldberg 2005). Interrupting the reconsolidation process may add a new direction to prevent and treat relapse commonly found in drug-dependent individuals (de Oliveira Alvares et al. 2005; Nader 2003; Robinson and Franklin 2007).

In summary, under the framework of the effect of endocannabinoids on memory-related plasticity, the present study demonstrated that cannabinoid CB1 receptor antagonist, rimonabant, impaired the consolidation, retrieval, and reconsolidation of METH CCP. Rimonabant may be a promising therapeutic agent to affect drug-related reward memories and ultimately can be developed to prevent/treat relapse to drug use.

Acknowledgments This work was supported in part by the National Basic Research Program of China (Nos. 2007CB512302 and 2009CB522004), the National High Technology Research and Development Program of China (863 Program, 2006AA02Z4D1), and the Natural Science Foundation of China (Nos. 30670713 and 30725016).

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