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Cannabinoid CB_1 receptor antagonist rimonabant disrupts nicotine reward-associated memory in rats

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ABSTRACT

Exposure to cues previously associated with drug intake leads to relapse by activating previously acquired memories. Based on previous findings, in which cannabinoid CB_1 receptors were found to be critically involved in specific aspects of learning and memory, we investigated the role of CB_1 receptors in nicotine reward memory using a rat conditioned place preference (CPP) model. In Experiment 1, rats were trained for CPP with alternating injections of nicotine (0.5 mg/kg, s.c.) and saline to acquire the nicotine-conditioned memory. To examine the effects of rimonabant on the reconsolidation of nicotine reward memory, rats were administered rimonabant (0, 0.3, and 3.0 mg/kg, i.p.) immediately after reexposure to the drug-paired context. In Experiment 2, rats were trained for CPP similarly to Experiment 1. To examine the effects of rimonabant on the reinstatement of nicotine reward memory, rimonabant (0, 0.3, and 3.0 mg/kg, i.p.) was administered before the test of nicotine-induced CPP reinstatement. In Experiment 3, to evaluate whether rimonabant itself produces a reward memory, rats were trained for CPP with alternating injections of different doses of rimonabant (0, 0.3, and 3.0 mg/kg) and saline. Rimonabant at a dose of 3.0 mg/kg significantly disrupted the reconsolidation of nicotine memory and significantly blocked the reinstatement of nicotine-induced CPP. However, rimonabant itself did not produce CPP. These findings provide clear evidence that CB_1 receptors play a role in nicotine reward memory, suggesting that CB_1 receptor antagonists may be a potential target for managing nicotine addiction.

1. Introduction

Tobacco use through cigarette smoking is the world's leading cause of preventable death, responsible for almost 5 million deaths per year, especially in economically disadvantaged countries and populations (Yach and Wipfli, 2006). Tobacco is highly addictive, making it difficult to quit smoking. A key aspect of tobacco withdrawal is conditioned craving in response to cues and environments associated with tobacco use (Yach and Wipfli, 2006). Nicotine, a psychoactive component of tobacco, appears to play a major role in tobacco dependence. Similar to other drugs of abuse, after repeated use over a prolonged period, nicotine reinforces drug-seeking and drug-taking behavior through its action on nicotinic acetylcholine receptors (nAChR) in the mesolimbic dopamine system of the brain (Stolerman and Shoaib, 1991; Corrigall et al., 1992; Fung and Lau, 1992). Nicotine is self-administered not only by humans (Henningfield et al., 1983), but also by rodents (Corrigall and Coen, 1989; Donny et al., 1995; Tessari et al., 1995) and primates (Goldberg et al., 1981; Sannerud et al., 1994). Nicotine also produces a conditioned place preference (CPP) in rats (Horan et al., 1997; Dewey et al., 1999; Biala, 2003).

Learning and memory processes and drug dependence share molecular signaling mechanisms associated with similar long-term changes in synaptic plasticity (Hyman, 2005; Hyman et al., 2006). Indeed, repeated drug administration induces adaptations in neuronal mechanisms that control normal learning and memory (Shaham et al., 2003; Lu et al., 2006; Valjent et al., 2006a,b). Reactivation of a consolidated memory returns this memory to a labile, sensitive state, in which it can be modified, changed, or even erased (Nader, 2003) in a process called reconsolidation (Nader et al., 2000; Sara, 2000; Tronson and Taylor, 2007). Memory reconsolidation can be influenced in many ways, including pharmacological intervention (Tronson et al., 2006; Tronson and Taylor, 2007).

Many neurotransmitter systems have been hypothesized to be neural substrates of the motivational and reinforcing properties of nicotine, including the dopaminergic, opioidergic, and cannabinoid systems. These substrates might be also involved in nicotine's behavioral effects (Isola et al., 2002; Valjent et al., 2002; Biala and Weglinska, 2006). Animal studies revealed that nicotine and Δ^9-tetrahydrocannabinol interact in producing CPP (Valjent et al., 2002). Furthermore, the rewarding properties of nicotine, assessed in a

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place-conditioning or self-administration paradigm, were absent in cannabinoid CB_1 receptor knockout mice (Cossu et al., 2001; Castane et al., 2002). This research demonstrates the functional interactions between brain cannabinoid CB_1 receptors and nAChRs. Studies using the CB_1 antagonist rimonabant have shown the involvement of CB_1 receptors in operant nicotine self-administration (Cohen et al., 2002) and nicotine-induced CPP in rats (Le Foll and Goldberg, 2004). Furthermore, rimonabant attenuates nicotine relapse induced by associated environmental stimuli (Cohen et al., 2005). Phase III clinical trials have revealed that rimonabant is significantly effective in achieving smoking cessation (Fernandez and Allison, 2004). Although this previous research suggests that cannabinoid receptor antagonists are an effective treatment for cigarette smoking, no study has explored whether cannabinoid CB_1 receptors are involved in nicotine reward-associated memory. Thus, we used a CPP procedure to determine whether CB_1 receptors play a role in nicotine reward-related memory.

2. Materials and methods

2.1. Animals and drugs

A total of 150 male Sprague–Dawley rats (280–320 g) were obtained from the animal laboratory of Peking Medical University. The animals were housed at a room temperature of 22 ± 2 °C with a 12 h/12 h light/dark cycle and were allowed to adapt to this environment for a period of 7 days before the experiments. All experiments were performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985). The procedures were approved by the local Committee of Animal Use and Protection.

The drugs used in the present study were nicotine tartrate and rimonabant (Xinxiang Crude Medicinal Drugs Co., Jiangsu, China). Nicotine tartrate was diluted to 0.5 mg/ml with saline. Rimonabant was prepared in saline containing 0.5% Tween 80 and 0.5% ethanol in three different concentrations (0 [vehicle], 0.3, and 3.0 mg/ml).

2.2. Conditioned place preference

The apparatus for CPP training and testing consisted of five identical three-chamber polyvinyl chloride (PVC) boxes. Two of these boxes were large side chambers (27.9 cm long × 21.0 cm wide × 20.9 cm high), separated by a smaller chamber (12.1 cm long × 21.0 cm wide × 20.9 cm high, with a smooth PVC floor). The side chambers had different floor textures (bar or grid), and the three chambers were separated by manual guillotine doors.

To determine baseline place preference, the rats were initially placed in the middle chamber and permitted to move freely for a period of 15 min (pre-conditioning [Pre-C]) on the day before first conditioning (Lu et al., 2000; Wang et al., 2001). A computer measured the time spent in the designated saline- or nicotine-paired chambers during the 15 min session by counting the number of times the animals interrupted infrared beams. Most rats spent approximately one-third of the time in each chamber ($p > 0.05$). Approximately 2% of the rats were discarded because of a strong unconditioned preference (>540 s in one chamber).

Conditioning was performed using an unbiased, balanced protocol. To train nicotine CPP, rats were treated for six consecutive sessions with alternating injections of nicotine (0.5 mg/kg, s.c.) and saline (1 ml/kg, s.c.) during the training period. To train rimonabant CPP or CPA, rat was treated for six consecutive sessions with alternating injections of rimonabant (0.3 mg/kg, s.c. or 3 mg/kg, s.c.) and saline (1 ml/kg, s.c.) during the training period. The rats were confined to one compartment for 45 min immediately after the injection of nicotine or rimonabant and to the other compartment after the saline injection. On the day after six consecutive sessions, the rats were tested for nicotine or rimonabant (post-conditioning [Post-C])-induced CPP. During the post-training test, the rats were allowed free access to the three chambers for 15 min, and the time spent in each chamber was recorded. The control rats underwent the same CPP testing procedure described above, although they always received saline injections before being placed in both environments. The detailed procedure in each experiment was described in the section of experimental design. The CPP score was defined as the time spent in the nicotine or rimonabant-paired chamber minus the time spent in the saline-paired chamber (Harris et al., 2005; Zhai et al., 2008).

2.3. Drug memory reactivation

Rats were confined to the nicotine-paired chamber for 10 min to selectively reactivate nicotine reward memory (Milekic et al., 2006; Wang et al., 2008) and then given the different experimental treatments.

2.4. Retesting of nicotine-induced conditioned place preference

Rats were retested for nicotine-induced CPP 1 and 7 days after treatment. If the rats did not demonstrate nicotine-induced CPP 1 week after reactivation, then they were given a priming injection of nicotine (0.25 mg/kg, s.c) and immediately tested again (priming test).

2.5. Extinction and reinstatement of nicotine-induced conditioned place preference

During the extinction phase of CPP, the rats underwent extinction training for 6 days. On the day following this period of extinction, the rats were injected with nicotine (0.25 mg/kg) to reinstate the extinguished CPP. The CPP test was performed after extinction (post-extinction) and after the nicotine injection (priming test). To investigate the effects of rimonabant on the reinstatement of nicotine-induced CPP, the rats with extinguished nicotine-induced CPP were primed with nicotine (0.25 mg/kg). Different doses of rimonabant (0, 0.3, and 3.0 mg/kg) were administered 30 min prior to these priming injections of nicotine (Li et al., 2008).

2.6. Training for rimonabant-induced conditioned place preference

To exclude the possibility that rimonabant elicits rewarding or aversive memory, three separate groups of rats were trained for CPP with different doses of rimonabant (0, 0.3, and 3.0 mg/kg) by using the same procedure described above. After Pre-C, the animals were treated for six consecutive sessions with alternating injections of rimonabant (0, 0.3, and 3.0 mg/kg, i.p.) and saline (1 ml/kg, i.p.) (De Vries et al., 2001). The rats were confined to the compartment for 45 min immediately after the drug injection and to the other compartment after the saline injection. After six consecutive sessions, the rats were tested for rimonabant (Post-C)-induced CPP or conditioned place aversion (CPA).

2.7. Experimental design

2.7.1. Experiment 1: effect of rimonabant on the reconsolidation of nicotine reward memory

Experiment 1 was performed to determine the effect of rimonabant on the reconsolidation of nicotine conditioned memory. Rats were trained for nicotine-induced CPP (Pre-C and Post-C) and then randomly assigned to three groups, which received one of the following treatments after drug memory reactivation: vehicle, rimonabant (0.3 mg/kg, i.p), or rimonabant (3.0 mg/kg, i.p). Retesting of nicotine-induced conditioned place preference (day1 test, day7 test

and priming test) was performed on following days. The experimental design for Experiment 1 is illustrated in Fig. 1A.

2.7.2. Experiment 2: Effect of rimonabant on the reinstatement of nicotine reward memory

Experiment 2 was performed to explore whether rimonabant impairs the reinstatement of nicotine conditioned memory induced by a nicotine injection. When nicotine-induced CPP memory was extinguished after extinction training, the rats were randomly assigned to three groups, in which they received one of the following treatments 30 min prior to nicotine priming (0.25 mg/kg, s.c.): vehicle, rimonabant (0.3 mg/kg, i.p.), or rimonabant (3.0 mg/kg, i.p). The experimental design for Experiment 2 is illustrated in Fig. 2A.

2.7.3. Experiment 3: effect of rimonabant on the reinstatement of nicotine reward memory

To determine whether rimonabant itself produces CPP or CPA, naive rats were trained with different doses of rimonabant (0, 0.3, and 3.0 mg/kg) during the conditioning phase as described above.

2.8. Statistical analysis

The CPP score was defined as the time spent in the drug-paired chamber minus the time spent in the drug-unpaired chamber. The data are expressed as mean ± SEM. The statistical analysis was performed using two-way analysis of variance (ANOVA), with CPP score as the dependent factor. *Post hoc* comparisons of means were performed with the Tukey test for multiple comparisons when appropriate. The level of statistical significance was set at $p<0.05$.

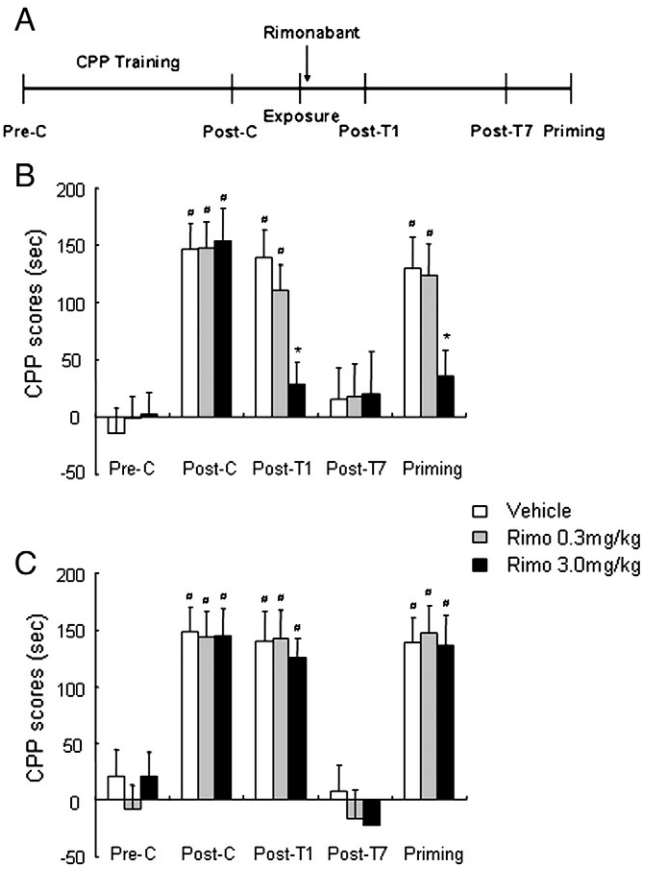

Fig. 1. Effect of rimonabant on the reconsolidation of nicotine reward memory. (A) Experimental timeline. (B) Rimonabant disrupted the reconsolidation of nicotine reward memory. Data are expressed as CPP scores. A significant difference was found in Post-T1 and priming test CPP scores between the vehicle group and 3 mg/kg group. $^{*}p<0.05$, compared with vehicle group in the same phase; $^{\#}p<0.05$, compared with pre-conditioning within the same group. (C) Rimonabant had no effect on nicotine-induced CPP without reactivation. $^{\#}p<0.05$, compared with pre-conditioning within the same group. $n=8$ per group.

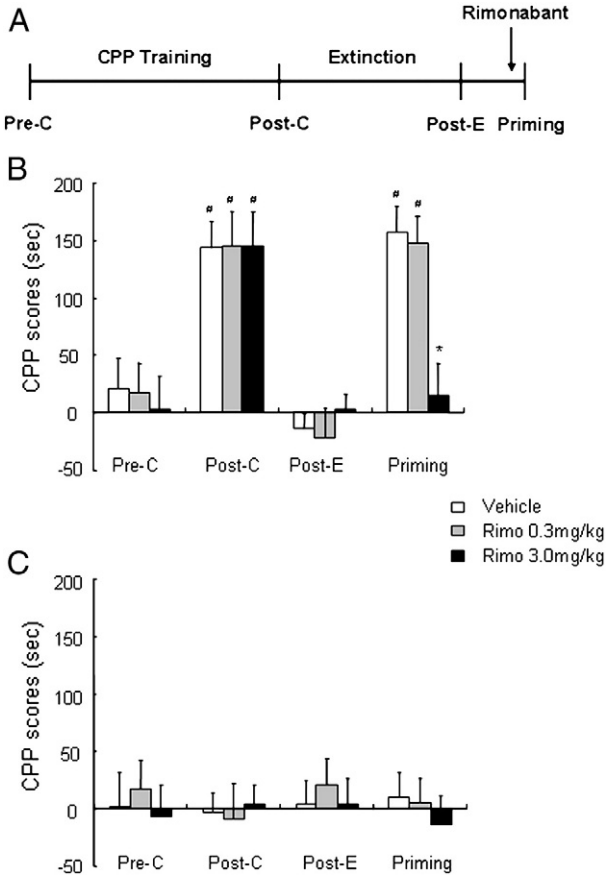

Fig. 2. Effect of rimonabant on the reinstatement of nicotine reward memory. (A) Experimental timeline. (B) Rimonabant disrupted the nicotine-induced reinstatement of nicotine reward memory. Data are expressed as CPP scores. A significant difference was found in Post-E and priming test CPP scores between the vehicle group and 3 mg/kg group. $^{*}p<0.05$, compared with vehicle group in the same phase; $^{\#}p<0.05$, compared with pre-conditioning within the same group. (C) Rimonabant had no effect on saline-induced CPP. $n=8$ per group.

3. Results

3.1. Effect of rimonabant on the reconsolidation of nicotine reward memory

As shown in Fig. 1B, two-way ANOVA revealed significant effects of different doses of rimonabant; $F_{2,119}=4.41$, $p<0.05$) and phase ($F_{4,119}=20.91$, $p<0.001$) on CPP scores and a significant treatment × phase interaction ($F_{8,119}=2.45$, $p<0.05$). *Post hoc* analyses revealed that after nicotine training, all groups acquired CPP ($p<0.001$), with no significant differences in CPP scores between any two groups during Post-C. Compared with the vehicle and 0.3 mg/kg groups, the 3 mg/kg group showed significantly decreased CPP scores at testing 1 day after treatment ($p<0.05$). To examine the long-term effects of rimonabant on the reconsolidation of nicotine-induced CPP, the rats were tested for the expression of nicotine-induced CPP on day 7 (Post-T7) after rimonabant administration. All groups failed to show a nicotine-induced CPP. In the priming test, no significant differences in CPP scores were found in the 3 mg/kg group between the priming test and baseline, indicating that a priming injection of nicotine did not reinstate nicotine-induced CPP.

To determine whether the effect of rimonabant on nicotine memory is reactivation-dependent, the other three groups were

given the same doses of rimonabant or vehicle and reexposed to the previous drug context. As shown in Fig. 1C, the two-way ANOVA revealed a significant effect of phase ($F_{4,119}=33.46$, $p<0.001$) but not different doses of rimonabant; $F_{2,119}=0.32$, $p=0.73$) on CPP scores and no phase × treatment interaction ($F_{8,119}=0.22$, $p=0.98$). The CPP scores (absence of memory retrieval) did not significantly change in the different groups, indicating that rimonabant did not disrupt nicotine-induced CPP in the absence of nicotine-induced CPP reactivation.

3.2. Effect of rimonabant on the reinstatement of nicotine reward memory

As shown in Fig. 2B, the ANOVA revealed significant effects of different doses of rimonabant; $F_{2,95}=3.48$, $p<0.05$) and phase ($F_{3,95}=31.12$, $p<0.001$) on CPP scores and a significant treatment × phase interaction ($F_{6,95}=2.90$, $p<0.05$). Nicotine-induced reinstatement of extinguished CPP memory was significantly attenuated by the administration of rimonabant at a dose of 3.0 mg/kg ($p<0.001$), but not at a dose of 0.3 mg/kg.

As shown in Fig. 2C, in the control groups that underwent saline training, the ANOVA revealed no significant effect of different doses of rimonabant; $F_{2,95}=0.26$, $p=0.77$) or phase ($F_{3,95}=0.12$, $p=0.92$) on CPP scores and no treatment × phase interaction ($F_{6,95}=0.18$, $p=0.981$). These findings indicate that the CPP scores in all control groups did not significantly change during the different phases, demonstrating that rimonabant did not have effects on CPP in the saline control groups.

3.3. Acquisition of rimonabant-induced conditioned place preference or aversion

As shown in Fig. 3, no significant differences in CPP scores were found for the different rimonabant doses (0, 0.3, and 3.0 mg/kg, $p>0.05$), indicating that rimonabant itself did not produce CPP or CPA.

4. Discussion

The present study was designed to investigate the role of the cannabinoid CB_1 receptor antagonist rimonabant in nicotine reward-associated memory using the CPP paradigm. The main findings of present study were the following: (1) rats acquired nicotine-induced CPP memory after conditioned training, and the reconsolidation of nicotine reward memory was impaired by the administration of rimonabant (3.0 mg/kg) immediately after reexposure to the drug-paired context; (2) extinguished CPP memory was reinstated by a priming injection of nicotine, an effect attenuated by rimonabant (3.0 mg/kg); and (3) rimonabant itself did not produce CPP or CPA. Altogether, these findings demonstrate that cannabinoid CB_1 receptors may play an important role in nicotine reward memory.

Conditioned place preference procedures have been widely used to measure the reward-associated memory of many different psychoactive drugs (Bardo et al., 1995; Tzschentke, 1998; Bardo and Bevins, 2000). In the CPP procedure, a distinctive environment is repeatedly paired with drug administration, and a different environment is repeatedly associated with vehicle administration. Conditioned place preference occurs when the repeated administration of a drug in this particular environment results in the ability of that environment to elicit approach behavior and increased place preference in the absence of the previously administered drug.

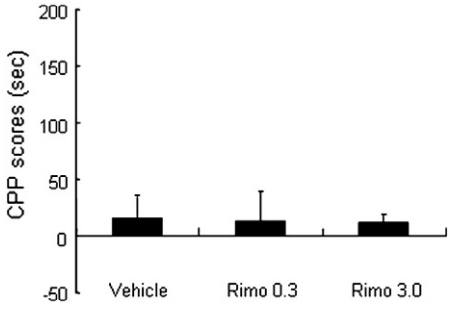

Fig. 3. Acquisition of rimonabant-induced CPP or CPA. Data are expressed as CPP scores. No significant difference was found in CPP scores between the vehicle group, 0.3 mg/kg group, and 3 mg/kg group ($p>0.05$). $n=7$–9 per group.

Using the CPP paradigm, we studied the effects of cannabinoid receptor blockade on nicotine reward-associated memory in different stages of nicotine-induced CPP. Rimonabant at a dose of 3 mg/kg effectively impaired the reconsolidation of nicotine reward memory after reexposure to the drug-paired context. The rimonabant-induced impairment of nicotine-induced CPP was not reinstated by a priming injection of nicotine, indicating that the effects of postretrieval rimonabant are long lasting. Rimonabant itself did not induce reward or aversion memory, suggesting that the CB_1 antagonist disrupts both cue-induced memory reconsolidation and the drug-induced reinstatement of extinguished memory.

In other behavioral tasks, such as inhibitory avoidance and contextual fear conditioning, learning and memory have been shown to be disrupted by the blockade of CB_1 receptors (de Oliveira Alvares et al., 2005, 2006; Arenos et al., 2006). For example, memory consolidation was impaired in an inhibitory avoidance paradigm by the CB_1 antagonist AM251 (de Oliveira Alvares et al., 2005, 2006, 2008). This suppressive effect of AM251 was also demonstrated in the open-field habituation task (de Oliveira Alvares et al., 2006). Moreover, rimonabant at a dose of 3 mg/kg disrupted extinction learning in both the conditioned freezing and passive avoidance tasks (Niyuhire et al., 2007). Altogether, these findings demonstrate that CB_1 receptors play a critical role in learning and memory.

High levels of CB_1 receptors are present in many brain regions (Tsou et al., 1998), including the prefrontal cortex, amygdala, nucleus accumbens, striatum, and hippocampus, which are involved in addiction-associated behaviors (Everitt et al., 1999; Vorel et al., 2001; Kalivas and McFarland, 2003). In these brain regions, CB_1 receptor activation modulates the release of a variety of neurotransmitters, including dopamine, γ-aminobutyric acid, and glutamate, all of which have been implicated in drug dependence (De Vries et al., 1999; Kalivas and McFarland, 2003; Shaham et al., 2003). Previous studies have shown that cocaine's primary reinforcing effects, measured in the self-administration procedure, are not altered by the blockade or absence of CB_1 receptors (Tanda et al., 2000; Cossu et al., 2001). Thus, environmental stimuli associated with drug administration appear to be particularly important in the disruptive effects of CB_1 receptor antagonists. Endocannabinoids mediate memory in several brain areas that are critically involved in addiction, including the nucleus accumbens, prefrontal cortex, amygdala, and hippocampus (Ohno-Shosaku et al., 2001; Wilson and Nicoll, 2002). Further studies are needed on the molecular mechanisms by which CB_1 receptors mediate relapse to drug addiction by affecting reward-associated memory.

In summary, the cannabinoid CB_1 receptor antagonist rimonabant impaired the reconsolidation and reinstatement of nicotine reward-related memory, supporting the existence of interactions between the cannabinoid and nicotinic systems and providing pharmacological evidence for the involvement of CB_1 receptors in the mediation of nicotine-related memory. Our findings suggest that the CB_1 receptor antagonist rimonabant could become a new pharmacological target in the treatment of nicotine addiction.

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