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Research report

Central but not peripheral beta-adrenergic antagonism blocks reconsolidation for a morphine place preference

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Abstract

Blocking the process of memory reconsolidation by means of amnestic agents may prove to have therapeutic applications. Here we used a morphine-induced conditioned place preference as an index of drug seeking. After inducing in rats a preference for a distinctive compartment paired with morphine, the memory for drug experience was reactivated by a 20-min test session and saline, the beta-antagonist propranolol, or the peripherally acting beta-antagonist nadolol were administered. Animals which received saline or nadolol upon reactivation, or propanolol without memory reactivation, maintained their preference for the drug-paired compartment 24 h and seven days later. However, animals that received propranolol upon reactivation no longer displayed a morphine preference on either test, although these animals once again expressed a preference when given a morphine-primed retest at 10 days. Our results suggest that beta-blockers may have potential for attenuating the impact of cue-induced craving which is a major cause of relapse in detoxified addicts.

Keywords: Morphine; Place conditioning; Memory; Reconsolidation

1. Introduction

The conditioned associations that arise when an addictive drug is paired with environmental stimuli play an important role in the maintenance of drug self-administration, and in relapse after periods of abstinence [1–4]. If such memories could be eliminated or attenuated it is believed that treatment of drug abuse would be facilitated. According to the current view [5], the physiological substrate of memories becomes labile when the memory is activated in recall, and it is subsequently reconsolidated through biochemical pathways similar to those that led to initial consolidation. Treatments that disrupt these biochemical pathways impair the reactivated memory on a subsequent retest [6–10]. Most of the evidence for the reconsolidation process has been obtained from experiments using conditioned fear paradigms [5]. More recently, reconsolidation has been explored in appetitive paradigms, including paradigms relevant to potential clinical applications for treating drug dependence such as drug-self-administration and conditioned place preference (CPP) [7,8,11–15], but the findings have been inconsistent. Conditioned associations induced by cocaine in the CPP have been shown to be attenuated by several reconsolidation-blocking treatments [8,16] but associations induced by opioids and food appear to be more resistant [12,15,17]. For instance, ICV infusions of the protein synthesis inhibitor anisomycin, which blocked consolidation of a morphine-induced CPP, were nevertheless ineffective in preventing reconsolidation when anisomycin was administered following both a drug-paired and a saline-paired reactivation trial. The morphine CPP seems to be impaired only when anisomycin was administered solely after a morphine pairing in its associated context [7,17,18]. This selective impairment raises the possibility that the apparent block of reconsolidation by anisomycin is due to reinforcer devaluation rather than memory loss [12,17]. It is thought that stimulant and opioid reinforcement are mediated by different neural systems [19–22], and it is possible that these neural systems are not equally sensitive to amnestic agents. Moreover, because of their toxicity, protein synthesis inhibitors are not ideal for studies of drug reinforcement.

An alternative route for disrupting reconsolidation is via the noradrenergic system. The beta-noradrenergic receptor is positively coupled to adenylcyclase-linked G-protein

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receptors, which govern the cAMP cascade [23], and plays a facilitatory role in long-term potentiation (LTP) [24,25]. The beta-adrenergic antagonist propanolol has been found to block reconsolidation of conditioned fear [26], spatial maze learning [10], and to attenuate a CPP induced by cocaine [16]. It has also recently been shown to reduce operant behavior for sucrose reward, although the effect was only reported to occur following a three-week post-training interval with a 20 mn and not a 10 mn reactivation session [11]. However, the impact of beta-adrenergic antagonists on the reconsolidation of appetitive tasks which involve the use of an opioid drug, has not been examined. Here we show that systemic injections of propranolol following reactivation of a morphine-induced CPP block reconsolidation of the memory for up to one week, and that the effect depends on the memory being first reactivated, and is not the result of peripheral effects of beta-adrenergic antagonism.

2. Materials and methods

2.1. Animals

Subjects were male long Evans rats (125–150 g) from Charles River, St Constant, Quebec, Canada, and were given a minimum of three days of handling prior to the beginning of testing. Rats were individually housed in a colony room, maintained on a 12 h light-dark cycle (lights on at 7 am) with a constant temperature of approximately 21 °C, and had food and water available *ad libitum*.

2.2. Apparatus

The CPP apparatus consisted of three compartments made of wood. Compartments A and B were identical in size (36 cm × 34 cm × 26 cm). They were located side by side and had shaded Plexiglass front walls. Compartment C (20 cm × 14 cm × 28 cm) was attached to the rear of compartments A and B and connected them via guillotine doors in the rear wall of compartments A and B. When the doors were lowered, the rat was confined to one of the larger compartments. When the doors were removed, the rat could move freely between compartments A and B via compartment C. The floor of compartment A was painted white and was covered with a large wire mesh flooring (1.2 cm mesh), its ceiling was painted black, and there were black and white vertical stripes on the walls; the floor and ceiling of the other compartment were painted black, with a small wire mesh flooring (0.6 cm mesh), and there were black and white horizontal stripes on the walls. Each large conditioning box contained a passive infrared motion sensor (Radioshack, 49–208A) with a 180-degree horizontal detection field, and there were light beam sensors on the entrance of the third compartment. The sensors were connected to a computer, which calculated the position of the animal at all times.

2.3. Place conditioning procedure

During the place conditioning procedure, all animals were weighed and handled daily. Training days were separated by a 24-h interval. On the first day of training animals were introduced via Box C and allowed to explore freely all three boxes for 20 min. Time spent in each compartment was recorded, and was used to verify that the rats did not exhibit any spontaneous preference for a given compartment.

On each conditioning day the rat was brought to the test room, injected (IP) with the drug (or vehicle), and immediately confined to one conditioning compartment for 20 min. On alternate days, the rat was injected with the vehicle (or drug), and confined for 20 min to the other compartment. The order of injection (drug or vehicle), and the compartment paired with the drug (A or B) was counterbalanced within each group. On test days each rat was introduced via the alley box (Box C) and allowed to move freely in all three boxes for 20 min. Time spent in each compartment was recorded.

2.4. Reconsolidation: Experiment 1

In the first reconsolidation experiment, rats first received three drug pairings and three vehicle pairings without any amnesic treatment followed by a brief 10-min test session, which acted as a memory reactivation session. Following the reactivation session separate groups of rats received a subcutaneous (SC) injection of propranolol, nadolol, or vehicle. All animals were subsequently tested 24 h later to see if the memory for the CPP persisted.

2.5. Reconsolidation: Experiment 2

The second experiment differs from the first in that rats were given four conditioning pairings of drug and vehicle rather than three, and a reactivation control group was added. This group was not given a reactivation trial before a propranolol injection on the day following the last day of conditioning. The reactivation control group were brought to the testing room and weighed but were not introduced into the apparatus before receiving an injection of propranolol.

In addition, the reactivation session consisted of a full 20 min test session. All animals were subsequently tested 24 h and seven days later to see if the memory for the CPP persisted. Seventy-two hours after the one-week test a morphine primed test session was given to examine whether drug exposure could reactivate the CPP. All rats were given 5 mk/kg morphine IP immediately before the test.

2.6. Drugs and injections

Morphine (Sabex, Quebec), diluted to 5 mg/ml, was given IP at a dose of 1 ml/kg. Zero point nine percent sodium chloride was used for control injections in the same volume.

Propranolol (Sigma-Aldrich, USA, Ltd) and nadolol (Sigma-Aldrich, USA, Ltd) were dissolved in 0.9% sodium chloride and administered SC at a dose of 10 and 20 mg/kg, respectively. Controls received an equivalent volume of saline. The volume of injection was 2 ml/kg for Experiment 1 and 1 ml/kg for Experiment 2.

Propranolol has a very high first pass metabolism whereas nadolol does not [27,28]. To reduce possible differences in peak blood concentrations both treatments were given subcutaneously. Nadolol is reported to have equal or higher potency than propranolol as a beta-receptor antagonist [29]. To ensure that any lack of effect from nadolol injections was not simply due to lesser occupancy of peripheral beta-receptors by nadolol, we administered nadolol at twice the dose of propranolol.

2.7. Statistical analysis

Data collected during preexposure and test sessions consisted of time spent in seconds in each of the three chambers in the apparatus.

Since not all groups have scores for the reactivation session, there is no possible complete factorial design. We used two strategies for analysis of reconsolidation effects. We first examined whether each group showed a significant preference for the drug-paired over the vehicle-paired compartment on each trial. The ANOVA (Statistica) was with one repeated measure (the time each animal spent in either compartment). Morphine is known to produce a CPP and the null hypothesis was that all groups would prefer the morphine-paired side. We used *a priori* contrasts (alpha = .05) to test for side preference to maximize power and reduce the risk of a Type II error. Failing to identify a CPP where it was present would increase the probability of reporting a reconsolidation block where none was present.

Second we explored differences between groups over test sessions. For this analysis each animal's score was expressed by a choice index (time on drug-paired side − time on saline-paired side/time on drug-paired side + time on saline-paired side), and submitted to ANOVA followed by Newman–Keuls tests for homogeneous subsets.

An ANOVA comparing the time spent in the left versus the right compartment for each group was run on the preexposure session for each experiment to confirm the apparatus was unbiased.

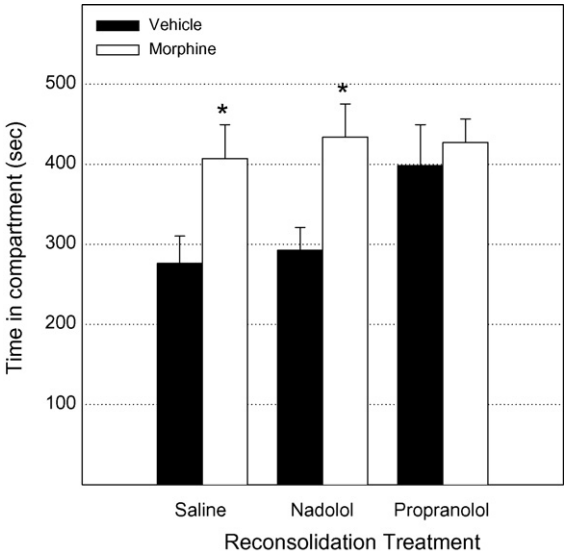

Fig. 1. Effect of propranolol (10 mg/kg; $N=9$), nadolol (20 mg/kg; $N=9$) or saline ($N=9$) given post-reactivation on the expression of a morphine-induced place preference. Data is the time spent in the morphine- and vehicle-paired compartments during the post-reactivation test.
*$p<.05$ for morphine vs. vehicle-paired.

3. Results

3.1. Experiment 1: effect of propranolol SC on reconsolidation of a morphine-induced place preference

When rats were first given an opportunity to explore the apparatus before training the 27 subjects showed no preference for either compartment (F (2,24) = 0.23, NS), confirming the apparatus was unbiased.

The 10 min reactivation scores were not analyzed, as 10 min scores are too variable to reveal a CPP in our apparatus. All groups were tested for their preference 24 h after the propranolol treatment session. As can be seen in Fig. 1, the groups who received saline or nadolol post-reactivation showed a significant preference for the morphine-paired compartment (test: morphine/saline: F (1,24) = 4.22, $p<.05$; morphine/nadolol: F (1,24) = 4.93, $p<.05$), whereas the propranolol group showed no preference for the compartment paired with morphine (test: morphine/propranolol: F (1,24) = 0.21, NS). The control group's preferences for the drug-paired compartment were reliable but weak, raising the possibility that they could be too easily disrupted. In a second experiment the number of cycles of conditioning was increased to four, the size of the CPP was measured at reactivation, and the CPP was retested after one week with and without morphine priming.

3.2. Experiment 2: stability of propranolol block of the reconsolidation of a morphine-induced place preference, and the effect of morphine priming

On the preexposure session, the 40 rats showed no spontaneous bias towards either compartment (F (3,36) = 0.03, NS).

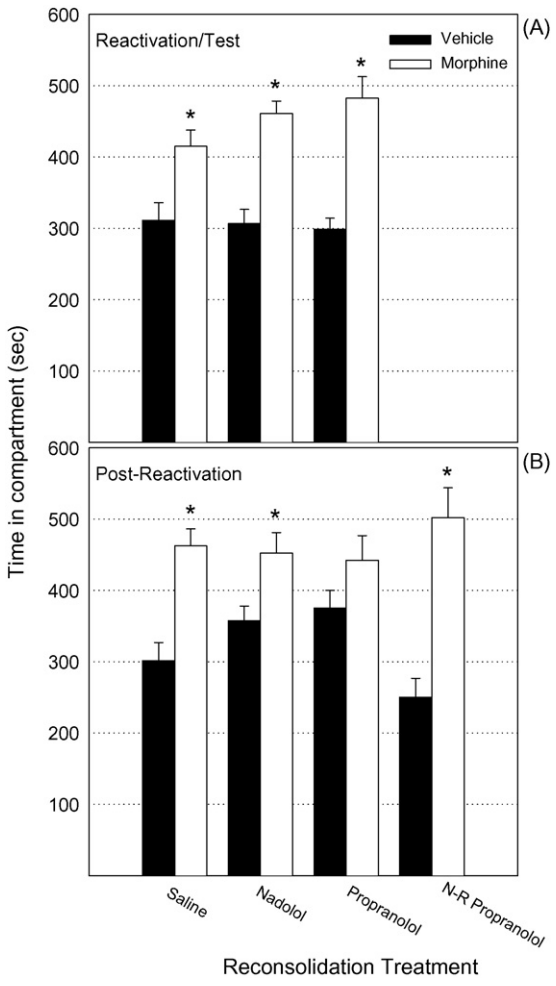

Fig. 2. Morphine-induced conditioned place preference after initial learning/during reactivation (reactivation, panel A) and 24 h after reactivation (post-reactivation, panel B). Data is time spent in the morphine- and vehicle-paired compartments on each test for groups treated with saline ($N=9$), propranolol (10 mg/kg; $N=10$), nadolol (20 mg/kg; $N=11$) or propranolol (10 mg/kg; $N=10$) without reactivation.
*$p<.05$ for morphine vs. vehicle-paired.

Following four cycles of conditioning, three groups of rats were given a test session, which served as a reactivation session, and immediately afterwards given propranolol, nadolol or saline. The remaining subjects served as nonreactivated controls, and received propranolol injections in their home cages. On the reactivation trial the three reactivated groups displayed a significant preference (Fig. 2A) for the morphine-paired compartment (reactivation: saline: F (1,36) = 9.48, $p<.05$; nadolol: F (1,36) = 25.69, $p<.05$; propranolol: F (1,36) = 33.04, $p<.05$). When all groups were tested 24 h after amnestic (or control) treatment (Fig. 2B), the groups given saline, nadolol and propranolol without reactivation (NR-propranolol) showed a CPP (Test 1: saline: F (1,36) = 11.42, $p<.05$; nadolol: F (1,36) = 4.82, $p<.05$; NR-propranolol: F (1,36) = 31.02, $p<.05$). However, the group which received post-reactivation injections of propranolol no longer displayed a significant preference for the morphine-paired compartment (propranolol: F (1,36) = 2.20, NS).

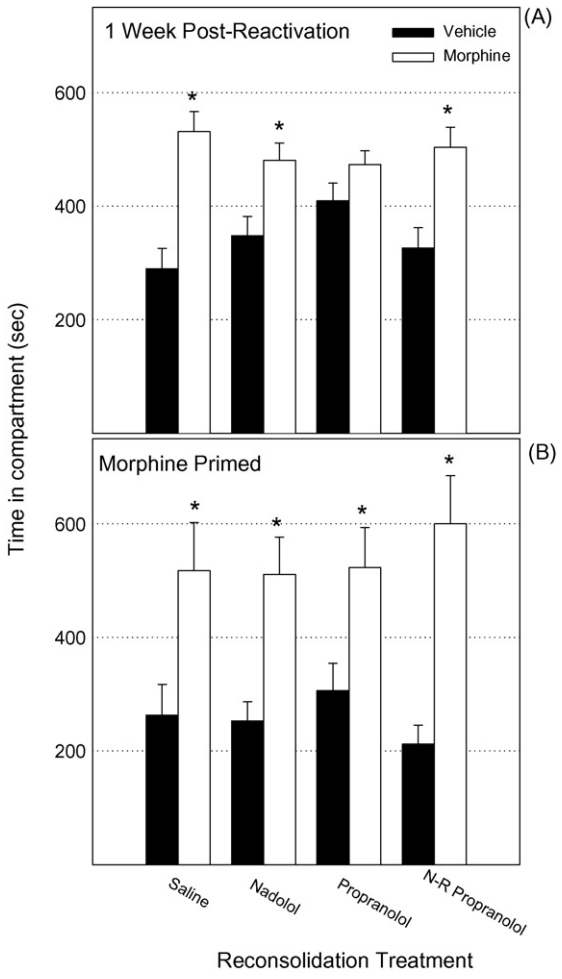

Fig. 3. Morphine-induced conditioned place preference one week following reactivation (panel A) and three days later during a morphine- primed test (morphine primed, panel B). Data is time spent in the morphine- and vehicle-paired compartments on each test for groups treated with saline ($N=9$), propranolol (10 mg/kg; $N=10$), nadolol (20 mg/kg; $N=11$) or propranolol (10 mg/kg; $N=10$) without reactivation.
$^{*}p<.05$ for morphine vs. vehicle-paired.

The overall trend remained the same on a retest one week later (Fig. 3A). All three control groups displayed a significant preference for the drug paired side (Test 2: saline: $F(1,36)=18.83$, $p<.05$; nadolol: $F(1,36)=6.91$, $p<.05$ NR-propranolol: $F(1,36)=11.22$, $p<.05$). However, the propranolol-treated reactivated group did not show a CPP for the morphine-paired compartment (Test 2: propranolol: $F(1,36)=1.45$, NS).

On the morphine primed test three days later (10 days after the initial post-reactivation test), all four groups displayed a strong preference for the morphine-paired compartment, including the propranolol group (Priming: saline: $F(1,36)=5.91$, $p<.05$; nadolol: $F(1,36)=7.41$, $p<.05$; propranolol: $F(1,36)=4.76$, $p<.05$; NR-propranolol: $F(1,36)=15.27$, $p<.05$; Fig. 3B).

Subsequently, an additional control group (nonreactivated saline) was run to confirm that omitting a reactivation trial did not alter the CPP [30]. This group displayed a significant preference (mean 133 s, $t=4.072$, $p<.05$), which was smaller, but not significantly different from that of the nonreactivated propranolol group ($p>.05$). Bernardi et al. have also reported that omitting one reactivation trial has no effect on a cocaine CPP [16].

Between groups analysis of the preference score confirmed that there was a significant difference between groups in the size of the preference for the drug-paired side ($F(3,36)=4.79$, $p<.05$) and this did not change between the 24-h test and the one-week test (effects of tests $F(3,36)=1.34$, NS). There was no interaction. Further analysis of the group effect showed that the reactivated propranolol-treated group had a smaller preference for the drug-paired side than either the saline-treated reactivated group or the propranolol-treated nonreactivated group. The nadolol-treated reactivated group showed an intermediate preference, which could not be distinguished from the other subsets. On the morphine primed test there was no difference between the groups in the size of the CPP ($F(3,36)=0.56$, NS).

4. Discussion

The results from the present study show that following reactivation of morphine-environment associations, reconsolidation of a morphine-induced CPP is blocked by systemic injections of the beta-adrenergic antagonist propranolol, but not the peripheral acting antagonist nadolol. When the memory is not reactivated propranolol has no effect. Thus, the blockade of the CPP is dependent on prior reactivation of the memory. Reactivated animals given the peripheral beta-receptor antagonist nadolol after reactivation retained a CPP, though it seemed to be less robust. Nadolol and propranolol have similar potency as beta-receptor antagonists [29]. Since nadolol was given at twice the dose, the fact that nadolol did not have a significant amnestic effect suggests that the amnestic effect is a result of central rather than peripheral beta-blockade.

Overall our results are consistent with the idea that propranolol blocks reconsolidation, and some alternative interpretations can be eliminated. It has been suggested that propranolol blocks facilitation of memory retrieval caused by stimulation of the noradrenergic system [31], and could interfere with memory expression. However, propranolol has a half-life less than 1.5 h in the rat [32] and would be eliminated before the test at 24 h. Also, any residual propranolol should have impaired memory in the propranolol-treated but not reactivated group, which retained a CPP. Furthermore, this interpretation would not be able to explain why animals given propranolol following reactivation were still impaired when tested after one week. Other possible explanations for our results being a consequence of side effects caused by propranolol can be ruled out on the basis of previous evidence. Sara et al. found no effect of a dose of 10 mg/kg propranolol given IP on spontaneous locomotor activity or exploratory behavior [33] and found that it does not produce its effects due to either taste aversion or reinforcer devaluation [10]. In addition, a study by Roullet and Sara ruled out the possibility that beta-adrenergic block of memory reconsolidation was due to any nonspecific long-term effects on performance, since ICV infusions of timolol were only effective when given 60 min post-reactivation and not 5, 30, or 300 min [34].

In spite of the fact that propranolol blocked reconsolidation of the morphine place preference for at least a week, we found that the CPP was restored by a priming dose of morphine. This recovery of the CPP is not a characteristic of propranolol as an amnestic agent. Debiec and LeDoux showed that post-reactivation systemic injections of propranolol in an auditory fear conditioning task significantly reduced the expression of freezing behavior up to 16 days and three tests after reactivation, and administration of a single unsignaled US (shock) in a different compartment did not restore the memory [26]. Thus, in the case of auditory fear conditioning, reconsolidation block using propranolol produces permanent amnestic effects. One possible explanation for our results is that post-reactivation propranolol treatment only weakened the memory to a sub-threshold level but did not eliminate it. Since morphine priming enhances the morphine-induced CPP and reverses the effect of extinction trials [35–37] it might boost the residual memory above threshold for the CPP. Another possible interpretation is that propranolol did weaken the ability of the apparatus cues [38] to evoke memory of a reinforcing event, and thus blocked the expression of a CPP. However, since reactivation was a drug free session, and morphine also acts as a discriminative cue [39], the reconsolidation procedure may not have affected the memory for morphine cue-apparatus associations and morphine cue-reinforcement associations. During a primed test these morphine discriminative cues might evoke the expression of a place preference. This interpretation suggests that a drug-free test session would be an incomplete reactivation of the memory, and that a more permanent block of the preference might be achieved by using either a primed test or a drug conditioning trial for reactivation.

Finally, these findings confirm that a well-trained appetitive task, reinforced by a strong opioid drug is susceptible to reconsolidation blocking effects through beta-adrenergic blockade. These results, together with those of Bernardi et al. [16] indicate that beta-adrenergic blockade can disrupt reconsolidation of environment-drug associations with two major classes of drugs of abuse [16]–the opioids and psychostimulants. Beta-blockers are already available for clinical use, and there is evidence for the therapeutic use of propranolol as an amnestic to help treat and prevent posttraumatic stress disorder (PTSD) [40–42]. Our results suggest that beta-blockers may be useful for preclinical exploration of blocking reconsolidation of drug-associated memories.

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