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Research report

Reconsolidation of a morphine place preference: Impact of the strength and age of memory on disruption by propranolol and midazolam

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ABSTRACT

Reactivation of memories may render them labile and subject to disruption by amnestic drugs thus reducing their impact on future behavior, but whether it is possible with well-established memories is not known. Here we examined the effect of two amnestic agents on reconsolidation of a conditioned place preference (CPP) for morphine when memory strength and memory age were varied. In a three-compartment apparatus animals received 4 or 8 experiences of morphine in one compartment and saline in the alternative compartment. The memory was then reactivated drug-free, and immediately afterwards animals received an injection of propranolol (10 mg/kg, SC), midazolam (1 mg/kg, IP), both amnestic agents combined, or saline. Animals conditioned with 4 pairings were re-tested 2 and 7 days after reactivation. After conditioning with 8 drug experiences memories were reactivated and treated 8 times, once every 48 h, beginning 1 or 30 days after training. Propranolol, midazolam and their combination, disrupted reconsolidation for weak memories (4 pairings), but had little effect on stronger memories (8 pairings) reactivated 1 day after training. Extending the reactivation-amnestic treatments to 8 sessions did not disrupt the strong memory. Delaying reactivation sessions by 30 days enabled all three amnestic treatments to disrupt reconsolidation. Repeating amnestic treatment appeared to increase the effect of midazolam, but combining propranolol and midazolam did not enhance the amnestic effect. The amount of training and the age of the memory may be boundary conditions for reconsolidation.

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1. Introduction

Reconsolidation is the process by which previously consolidated memories are rendered labile and susceptible to disruption following recall. It is increasingly recognized as a phenomenon that applies to a broad range of paradigms and species [1]. There are, however, reports that some memories do not undergo reconsolidation, or that there are conditions which protect them from disruption. Factors which appear to determine the lability of a reactivated memory include, memory age [2–5], training strength [6–8], and the content and duration of the reactivation session [2,9,10]. These limiting factors are regarded as boundary conditions for reconsolidation and are becoming a new focus of reconsolidation research [11]. It remains to be determined whether these boundary conditions are rigid or modifiable. Recently some of the requirements for disrupting robust fear memories have been described [5], but whether the same boundary conditions apply to appetitive memories is not known.

The possible application of reconsolidation as a therapeutic treatment for pathological memories requires a detailed understanding of the boundary conditions as well as finding amnestic agents that can be safely administered to humans. Drugs such as propranolol [12–16] and midazolam [2,17] have been reported to disrupt reconsolidation, and are already approved for clinical use in humans. Post-traumatic stress disorder (PTSD) has been the first therapeutic target [18], but an increasing amount of attention is focused on the possibility of blocking appetitive memories that underlie drug seeking [12,16,19,20]. The most widely used models of reward-related memory in animals are the self-administration paradigm and the conditioned place preference (CPP). Both paradigms have revealed reconsolidation effects for drugs [16,20,21] and natural rewards [19,22,23].

Cues associated with addictive drugs have the ability of inducing strong physiological responses and intense craving for many years following recovery and have been linked with high rates of relapse [24–26]. The CPP paradigm tests the impact that contextual cues may have on drug-seeking, and on cue-elicited craving in a drug-free animal. Beta-adrenergic receptors are known to play a role in memory storage [27,28]. Memory reconsolidation for a drug conditioned place preference can be disrupted by post-reactivation injections of the adrenergic beta-receptor antagonist, propranolol, and the effect is dependent on prior memory reactivation [12,16]. Another class of potential amnestics is the GABA(a) agonists [29]. Midazolam has been shown to disrupt reconsolidation of fear

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conditioning [2,17], but it has not been tested on the reconsolidation of a drug-induced CPP. Furthermore, previous research that examined reconsolidation in the CPP focused on memories established by 3–5 drug-context pairings [12,16,30–32]. The strength of such memories is minimal in comparison to the number of associations that occur in the normal course of drug addiction. It is not clear whether stronger, well-trained memories still undergo reactivation-dependent reconsolidation that can be blocked by currently available amnestic agents. If stronger memories are less labile to amnestic treatments it is possible multiple reconsolidation treatments and/or a longer conditioning to reactivation interval, would allow the memories to weaken and become labile.

The use of repeated reactivation treatments has previously been examined for both cocaine [30] and amphetamine [33] CPP. Fricks-Gleason and Marshall showed that post-reactivation propranolol caused a loss of preference for the drug-paired context which was more effective following repeated amnestic treatments [30]. Sadler et al. used the NMDA receptor antagonist MK-801 to disrupt the reconsolidation for an amphetamine place preference. They found that multiple reactivation treatments were required for the memory to be disrupted, and for the effect to last up to 10 days after the last reactivation treatment [33].

The effect of memory age on reconsolidation has been controversial. Several studies have suggested that recent memories are more susceptible to memory reconsolidation effects [3,4], or that older memories may require larger doses of amnestic treatment to block reconsolidation of fear conditioning [2]. On the other hand it has been reported that well-trained memories are labile only after a long training to reactivation interval [5].

In this study we explored the effect of amount of training on the susceptibility of a morphine-induced CPP to reactivation-dependent amnestic effects by two agents—propranolol and midazolam. We also examined whether amnestic effects could be potentiated by combining amnestic agents, administering repeated treatments, or by introducing a delay between conditioning and reactivation [5].

2. Materials and methods

2.1. Animals

Subjects were male Long Evans rats (125–150 g) from Charles River, St Constant, Quebec, Canada. Rats were individually housed in a colony room, maintained on a 12 h light–dark cycle (lights on 7 am) with a constant temperature of approximately 21 °C, and had food and water available ad libitum. This research was reviewed by the Animal Ethics Committee of McGill University and carried out in accordance with the guidelines of the Canadian Council on Animal Care.

2.2. Apparatus

The conditioned place preference (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° 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

Animals were weighed and handled daily, beginning at least 3 days before the first training session. Training sessions were separated by 24 h. On the first day of training animals were introduced to the apparatus via box C and allowed to explore freely all three boxes for 30 min. Time spent in each compartment was recorded, and was used to verify that the rats did not exhibit any spontaneous preference.

On each conditioning day the rat was brought to the test room, injected (SC) with the drug (or vehicle) and immediately confined to one of the large compartments for 30 min. On alternate days, the rat was injected with the vehicle (or drug), and confined for 30 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 30 min. Time spent in each compartment was recorded.

2.4. Experiment 1: the effect of propranolol, midazolam, and their combination on reconsolidation

During training, rats received 4 pairings of morphine with one compartment and 4 pairings of vehicle with the other compartment. The day following the last training session the memory was reactivated by a test for a CPP. Each rat was introduced via the alley box (box C) and allowed to move freely in all three boxes for 30 min. Time spent in each compartment was recorded. Immediately after this reactivation session rats received an injection of propranolol (SC), midazolam (IP), both drugs, or vehicle. An additional group was administered the combination of propranolol plus midazolam without reactivation. The non-reactivated control group was brought to the testing room and weighed, but was not introduced into the apparatus before receiving its injection of propranolol and midazolam. All animals were re-tested 2 and 7 days later to see if the memory for the CPP had reconsolidated. A morphine-primed test session was given 72 h after the 1 week test, to examine whether drug exposure could reactivate the CPP. Rats were given 5 mg/kg morphine (SC) immediately before the test. The design of Experiment 1 is summarized in Fig. 1.

2.5. Experiment 2: reconsolidation of a strong morphine place preference reactivated after 1 day

The second experiment differed from the first in that rats were given 8 (rather than 4) pairings of drug with one compartment and vehicle with the other compartment. Also a non-reactivated group was not included.

The reactivation protocol, as described in Experiment 1 and summarized in Fig. 1, began 1 day after the last conditioning session and was repeated 8 times at 48 h intervals. Each reactivation session doubled as a test of the effect of the previous treatment on reconsolidation of the memory. A morphine-primed (5 mg/kg, SC) test session was given 48 h after the 8th reactivation/test session to examine whether drug exposure could reactivate the CPP.

2.6. Experiment 3: reconsolidation of a strong morphine place preference reactivated after 30 days

The third experiment differed from the second in that rats were returned to their home cage for 30 days after the 8th conditioning session. After 30 days all groups underwent the same reactivation and reconsolidation testing protocol as in Experiment 2. The design is summarized in Fig. 1.

2.7. Experiment 4: the effect of repeated non-reactivated propranolol injections on a morphine place preference

Experiment 4 was a control experiment to confirm that repeated injections of propranolol without reactivation did not disrupt a CPP. Animals received 4 pairings of drug with one large compartment and vehicle with the other. On each of the 4 days after training, animals were brought to the testing room and weighed, but were not introduced into the apparatus before they received an injection of propranolol (10 mg/kg, SC). Animals were then tested drug-free on the fifth day.

2.8. Drugs and injections

Morphine (Sabex, Quebec) was diluted to 5 mg/ml in 0.9% sodium chloride and given (SC) at a dose of 1 ml/kg. Saline was used for control injections in the same volume.

Propranolol (Sigma–Aldrich, USA, Ltd.) was dissolved in 0.9% sodium chloride and given (SC) at a dose of 10 mg/kg. Midazolam (Sandoz, Canada, Inc.) was provided in vials of 5 mg/5 ml and injected (IP) at a dose of 1 mg/kg. Controls received an equivalent volume of saline.

2.9. Statistical analysis

Data collected during pre-exposure and test/reactivation sessions consisted of time spent in seconds in each of the two large chambers in the apparatus. The time spent in the third compartment was not analyzed. Animals which did not display a positive preference (time spent in drug-paired compartment minus time spent in saline-paired > 0) for the drug-paired compartment on initial reactivation were excluded from the analysis (Experiment 1: 2 out of 54; Experiment 2: 5 out of 48; Experiment 3: 9 out of 51).

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