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Reinstatement of Both a Conditioned Place Preference and a Conditioned Place Aversion with Drug Primes

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PARKER, L. A. AND R. V. MCDONALD. *Reinstatement of both a conditioned place preference and a conditioned place aversion with drug primes.* PHARMACOL. BIOCHEM. BEHAV **66**(3) 559–561, 2000.—In two experiments, we report that the place-conditioning paradigm can be used to demonstrate reinstatement of place preference/aversion by a drug prime following extinction training. In Experiment 1, rats were trained to prefer a chamber paired with morphine. Following extinction training, a morphine drug prime reinstated the morphine place preference. In Experiment 2, a lithium-induced conditioned place aversion was reinstated following extinction training by a lithium prime prior to testing. These results indicate that not only do rewarding drug primes produce reinstatement of learned responses (as demonstrated in the drug self-administration paradigm), but also aversive drug primes reinstate aversive learned responses. © 2000 Elsevier Science Inc.

Morphine lithium reward aversion place preference place aversion reinstatement memory learning relapse

IN humans, exposure to a formerly abused drug can reinstate compulsive drug seeking even after long periods of abstinence. This effect has been described for a number of classes of drugs of abuse such as alcohol, nicotine, psychostimulants, and opioids (1,3,5–7). Animal models of relapse also demonstrate that drug primes can effectively reinstate previously extinguished self-administration (4,11,12), and that shock primes can effectively reinstate previously extinguished conditioned fear (2).

Drug-induced reinstatement of responding has been primarily demonstrated in the instrumental conditioning paradigm of drug self-administration. In animals that have been trained to self-administer drugs such as heroin or cocaine, and that are exposed to a period of extinction, presentation of noncontingent priming injections of the self-administered drug leads to reinstatement of responding (11).

Another measure of the reinforcing properties of drugs is that of place conditioning. In contrast to the self-administration paradigm, in the place conditioning paradigm the primary motivational properties of a drug treatment serves as an unconditioned stimulus (UCS) that is repeatedly paired with a previously neutral set of environmental stimuli. During the course of conditioning, these cues acquire secondary motivational properties such that they elicit approach when the animal is exposed to the stimuli. The potential of drug primes to reinstate previously extinguished place-preference learning has not been reported in the literature.

In the following experiments, we demonstrate that the place-conditioning paradigm can also be used to evaluate the effect of drug primes on relapse following extinction training. When assessed in the place-conditioning paradigm, morphine produces a place preference (8) but lithium chloride produces a place aversion (8). The potential of a morphine prime to reinstate a conditioned morphine place preference following extinction training was evaluated in Experiment 1. Furthermore, in Experiment 2, we evaluated the potential of a lithium prime to reinstate a lithium-induced conditioned place aversion following extinction training.

EXPERIMENT 1

Method

Subjects. The subjects were 20 male Sprague–Dawley rats weighing between 291 and 330 g on the first conditioning trial. They were purchased from Charles River Laboratories, St.

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Constant, Quebec. The rats were maintained on ad-lib food and water throughout the experiment, and were housed in pairs in polyethylene cages with woodchip bedding in a room on a 12 L:12 D cycle. The rats were always tested in the light phase of the cycle.

Apparatus. The place-conditioning apparatus, previously described (9), included two chambers separated during conditioning trials by a wooden divider. The wooden walls of each chamber (35 by 25 by 30 cm) were painted flat black. The conditioning cues consisted of the textural floors in the chambers: One floor was covered with mesh (0.625 cm) and the other floor was covered with sandpaper strips (5 cm) located 5 cm apart. When assessed for their preference for each of these cues, rats did not display a significant preference for a specific floor measured by group averages.

During testing, the divider between the chambers was removed, allowing the rats to explore both chambers. The activity of the rats during testing was monitored by a videotracking apparatus (Videomex-V, Columbus Instruments, Columbus, OH) from a video camera mounted to the ceiling. This provided a measure of the amount of time that the rat spent in each chamber.

Procedure

Conditioning. The rats arrived in the laboratory 1 week prior to the initiation of experimental manipulations, and were handled on each of 5 days prior to the first conditioning trial. The rats received a total of four differential conditioning trial cycles, with the first conditioning day of each cycle consisting of a CS− trial and the second conditioning day of a cycle (24 h later) consisting of a CS+ trial; 2 days intervened between each cycle of trials. On the CS− trial, the rats were injected intraperitoneally (IP) with saline 5 min prior to placement in the chamber with the sandpaper ($n = 10$) or mesh ($n = 10$) floor for 30 min. On the CS+ trial, the rats were injected IP with morphine (10 mg/kg), 5 min prior to placement in the opposite chamber from that paired with saline on the previous day. The morphine sulfate (obtained from the National Institute on Drug Abuse, Research Triangle, NC), was prepared in saline solution at a concentration of 10 mg/ml. Immediately after each rat's trial, the apparatus was cleaned with soapy water and was thoroughly dried prior to the next run of rats.

Extinction training. Two days after the final CS+ trial, the rats were given extinction training. The rats received three extinction trials with 24 h between each trial. On each trial, the rat was placed at the intersection between the two chambers with the divider removed and was allowed to explore both chambers for 15 min. The amount of time spent in each chamber was automatically recorded by the videotracking apparatus.

Reinstatement. On each of the next 2 days, the ability of morphine primes to reinstate the place preference was assessed. In a within-subject design, the rats were tested following a morphine (10 mg/kg) prime and a saline prime on each day; for half of the rats in each condition, the morphine prime occurred on day 1, and for half of the rats it occurred on day 2. On each day, the rats were injected IP with the appropriate solution at a volume of 1 ml/kg, 5 min prior to placement in the apparatus for 15 min. The amount of time that rats spent in each chamber was automatically recorded by the videotracking apparatus.

Results and Discussion

Figure 1 presents the mean number of seconds spent on the morphine-paired minus the saline-paired floor during the extinction tests and the reinstatement tests of Experiment 1. Across extinction tests, the strength of the morphine-induced place preference declined, as revealed by a significant linear trend in difference scores across tests, $F(1, 19) = 4.0$, $p < 0.05$.

The final data points present the mean difference score during the reinstatement tests when rats were given a morphine prime or a saline prime. As is apparent, a morphine prime reinstated the place preference. Following a morphine prime, rats displayed larger mean difference scores than following a saline prime, $t(19) = 2.5$, $p < 0.025$.

EXPERIMENT 2

Experiment 1 demonstrated that a morphine prime reinstated a morphine place preference. In Experiment 2 we examine whether a similar phenomenon would be evident with a lithium place aversion. Like shock-based avoidance learning (10), place-aversion learning is extremely resistant to extinction (unpublished findings). Therefore, we examined the ability of a lithium prime to reinstate a place aversion that was weakened, but not eliminated by extinction training.

Method

The subjects were 24 male Sprague–Dawley rats weighing 272–313 g on the first conditioning trial. During conditioning, the rats were treated identically to those in Experiment 1, except that the drug administered on the CS+ trials was lithium chloride (LiCl). LiCl was prepared in distilled water in a 0.15 M solution, and administered at a volume of 12 ml/kg (75 mg/kg).

The rats received place-preference extinction trials until there was evidence of decreased aversion (seven consecutive extinction trials). Twenty-four hours after the final extinction trial, the rats were given a single reinstatement trial. In contrast to Experiment 1, a between-subjects design was used to prevent carryover effects between the tests to assess reinstatement. In the reinstatement test, half of the rats ($n = 12$) were injected with LiCl at the same dose given during conditioning, and half were injected with saline, 5 min prior to placement in the place conditioning apparatus for 15 min.

Results and Discussion

Figure 2 presents the mean time (seconds) spent on the lithium-paired floor minus the saline-paired floor on each of seven extinction tests and during the reinstatement test of Experiment 2. Across extinction tests, the strength of the lith-

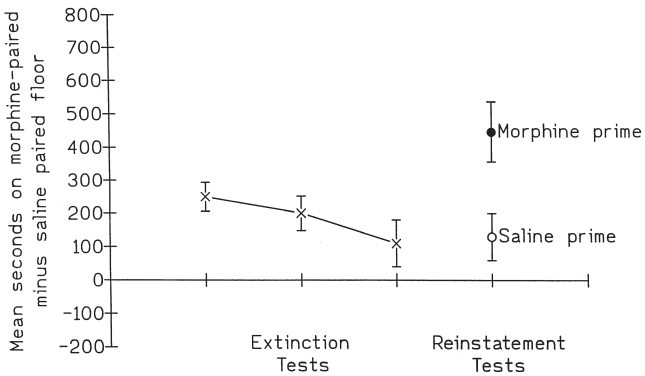

FIG. 1. Mean seconds (±SEM) on morphine-paired minus saline-paired floor during each extinction test and reinstatement test in Experiment 1.

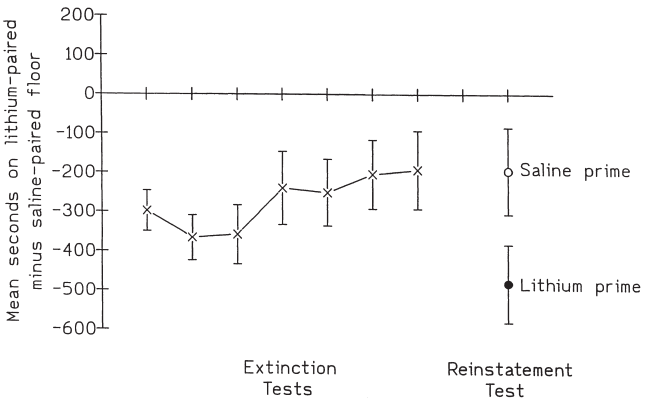

FIG. 2. Mean seconds (±SEM) on lithium-paired minus saline-paired floor during each extinction test and the reinstatement test in Experiment 2.

ium-induced place aversion declined as revealed by a significant linear trend in difference scores across tests, $F(1, 23) = 5.0$, $p < 0.05$. Rats spent significantly less time on the lithium-paired floor during the first three trials (mean = −341 ± 39 s) than during the final three extinction trials (mean = −216 ± 74 s).

Following the final extinction trial, rats administered the lithium prime during the reinstatement test displayed a stronger place aversion than those rats administered the saline prime, $t(22) = 2.1$, $p < 0.05$. Therefore, the lithium prime prior to a preference test reinstated a weakened place aversion. Reinstatement of place conditioning was, therefore, not limited to that produced by a positively reinforcing drug.

GENERAL DISCUSSION

As in the self-administration paradigm (11), a morphine prime reinstated a morphine place preference. Furthermore, a lithium prime following extinction training reinstated a weakened lithium-induced place aversion. Therefore, unlike the self-administration paradigm, the place-conditioning paradigm can demonstrate reinstatement of conditioning based on both positively reinforcing drugs and aversive drugs.

Clearly, our results suggest that when tested in the drug state, rats display both a stronger place preference or place aversion than when tested in the saline state. This effect parallels that displayed in the self-administration paradigm when rats are exposed to the drug following a period of extinction training. In the self-administration paradigm, the reinstatement effect is attributed to the hedonic properties of the drug, which produce a central motivational state that reinstates the preference and/or aversion [e.g., (4,11,12)]. It is also possible that this explanation accounts for the reinstatement of place conditioning following drug primes.

However, the results of our experiments can also be explained as a state-dependent retrieval deficit. The stimulus properties of the drug are present during conditioning, but are absent during extinction training. If the display of place conditioning were state dependent, then the rats would be expected to display a stronger effect in the presence of the drug than in the absence of the drug. This is exactly what we found during the reinstatement test. That is, although the rats showed a weakened association between the context and the drug during extinction training, the stimulus properties of the drug restored the approach or avoidance response during the reinstatement test.

Although the present results cannot unambiguously identify the mechanism responsible for the effect, they do demonstrate that the place-conditioning paradigm, like the self-administration paradigm, can be used to demonstrate that reexposure to a drug cue following extinction training to the context reinstates the conditioned effect.

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