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Effects of Prior Cocaine Versus Morphine or Heroin Self-Administration on Extinction Learning Driven by Overexpectation Versus Omission of Reward

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ABSTRACT

BACKGROUND: Addiction is characterized by an inability to stop using drugs, despite adverse consequences. One contributing factor to this compulsive drug taking could be the impact of drug use on the ability to extinguish drug seeking after changes in expected outcomes. Here, we compared effects of cocaine, morphine, and heroin self-administration on two forms of extinction learning: standard extinction driven by reward omission and extinction driven by reward overexpectation.

METHODS: In experiment 1, we trained rats to self-administer cocaine, morphine, or sucrose for 3 hours per day (limited access). In experiment 2, we trained rats to self-administer heroin or sucrose for 12 hours per day (extended access). Three weeks later, we trained the rats to associate several cues with palatable food reward, after which we assessed extinction of the learned Pavlovian response, first by pairing two cues together in the overexpectation procedure and later by omitting the food reward.

RESULTS: Rats trained under limited access conditions to self-administer sucrose or morphine demonstrated normal extinction in response to both overexpectation and reward omission, whereas cocaine-experienced rats or rats trained to self-administer heroin under extended access conditions exhibited normal extinction in response to reward omission but failed to show extinction in response to overexpectation.

CONCLUSIONS: Here we show that cocaine and heroin can induce long-lasting deficits in the ability to extinguish reward seeking. These deficits were not observed in a standard extinction procedure but instead only affected extinction learning driven by a more complex phenomenon of overexpectation.

Keywords: Addiction, Cocaine, Extinction, Heroin, Morphine, Orbitofrontal, Rat, Self-administration

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Drug addiction is characterized by an inability to stop using drugs, often despite a reported lack of enjoyment of the drugs and a high probability of adverse consequences. Drug-seeking behavior is even resistant to extinction-based treatments specifically designed to extinguish the addict's response to drug-associated cues (1,2) that often provoke relapse during abstinence (3,4).

According to theoretical accounts, extinction depends on new memories formed when outcomes predicted by cues and events in the environment fail to materialize (5,6). The mismatch between expected and actual outcomes results in teaching signals—prediction errors—that are thought to drive this new learning, which then suppresses or modulates expression of the original learned behaviors (7). A critical part of this process is appropriate signaling of the expectations regarding likely outcomes. Failure to appropriately signal outcome expectancies results in impaired extinction learning, since such a failure can weaken (or even reverse) the sign of the resultant error signal. Thus, drug-induced dysfunction in the signaling of these outcome expectancies can result in impaired extinction learning in some settings. This hypothesis is supported by recent findings showing that exposure to cocaine causes long-lasting structural and functional changes in the orbitofrontal cortex (OFC), a region critical to signaling information about expected outcomes (8–14). Accordingly, exposure to psychostimulants, particularly cocaine, often impairs OFC-dependent behaviors (8,9,12,15–21). The list of impaired behaviors includes Pavlovian overexpectation (22), a task in which learning depends directly upon signaling of outcome expectancies (23). We have found that these deficits are associated with disrupted signaling of outcome expectancies in OFC (22,24).

To further address this hypothesis—the specificity of the extinction learning deficit—and whether effects on OFC function might be observed for drugs other than cocaine, we trained rats to self-administer cocaine, morphine, or heroin

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versus an oral sucrose solution. Three weeks after the end of this training, we tested these same rats in a Pavlovian overexpectation task (23). This task independently assesses extinction of conditioned responses driven by summation and overexpectation, an OFC-dependent learning process, versus that induced by simple reward omission, which we have found to be independent of OFC (25,26). As previously reported (22), we found that rats trained to self-administer cocaine under limited access conditions were unable to extinguish a previously learned behavior in response to overexpectation but showed normal extinction of the same behavior in response to reward omission. Rats trained to self-administer heroin under extended access conditions showed a similar pattern of behavior. However, morphine-experienced rats with limited access showed no deficit in the ability to extinguish in response to overexpectation or omission of reward. These results have implications for understanding how drug exposure disrupts fundamental nonexperiential mechanisms that normal subjects access to modulate behavior and learning.

METHODS AND MATERIALS

Subjects

Rats (experiment 1: 43 Long-Evans rats; experiment 2: 23 Sprague-Dawley rats) (Charles River Labs, Frederick, Maryland) weighing 250 g to 275 g upon arrival were housed individually and placed on a 12-hour light/dark schedule. During testing, rats were food deprived to 85% of their baseline weight. All testing followed the guidelines outlined in the Guide for the Care and Use of Laboratory Animals (8th edition; http://grants.nih.gov/grants/olaw/Guide-for-the-Care-and-Use-of-Laboratory-Animals.pdf).

Drugs

Cocaine hydrochloride, morphine sulfate, and heroin (diacetylmorphine hydrochloride) (National Institute on Drug Abuse, Bethesda, Maryland) were dissolved in sterile .9% saline.

Surgery

Rats were anesthetized with ketamine (100 mg/kg, intraperitoneal) (Sigma-Aldrich, St. Louis, Missouri) and xylazine (10 mg/kg, intraperitoneal) (Sigma-Aldrich) and catheters were implanted in the right jugular vein, passed subcutaneously to the top of the skull, attached to a 22-gauge cannula (Plastics One, Roanoke, Virginia), and mounted to the rat's skull. Carprofen (.1 mg/kg, subcutaneous) (Pfizer, New York, New York) was given after surgery as an analgesic (8). Catheters were flushed every day with sterile .9% saline plus the antibiotic Gentamicin (.08 mg/mL) (BioSource International, Carlsbad, California).

Self-Administration

In experiment 1, rats self-administered cocaine (.75 mg/kg per infusion; $n = 16$), morphine (1 mg/kg per infusion; $n = 15$), or sucrose (10% wt/vol; $n = 11$) 3 hours per day for 14 consecutive days. In experiment 2, rats self-administered heroin (.1 mg/kg per infusion; $n = 13$) or sucrose (10% wt/vol; $n = 10$) 12 hours per day for 14 days. A fixed ratio 1 schedule of reinforcement was used: presses on the active lever delivered a 4-second (experiment 1) or 3.5-second (experiment 2) infusion of the drug. Each chamber was equipped with two levers located 8 cm to 9 cm above the floor. Presses on the retractable (active) lever activated the infusion pump to deliver drug or sucrose; presses on the stationary (inactive) lever were not reinforced.

For cocaine and morphine self-administration (SA) in experiment 1, sessions lasted 3 hours, with 15-minute time-out periods after each hour. Each session began with the insertion of the active lever. Each infusion was accompanied by the retraction of the active lever, followed by a 40-second time-out period. Pressing on the inactive lever had no programmed consequences. At the end of each session, the active lever was retracted. The number of cocaine or morphine infusions was limited to 20 per hour to prevent overdose. After 20 infusions, the active lever was retracted for the remainder of the hour. For heroin SA in experiment 2, procedures were the same as those for cocaine or morphine SA, except that daily sessions lasted 12 hours and the number of heroin infusions was limited to 100 per day.

Overexpectation

Three weeks after the end of SA training, all rats underwent Pavlovian overexpectation training. Food reinforcers (45 mg sucrose pellets: plain, banana flavored, or grape flavored) (Bio-Serv, Flemington, New Jersey) were delivered to a food cup recessed in the center of one wall. White noise or a tone, each measuring approximately 76 dB, was delivered via a wall speaker. Also mounted on that wall were a clicker (2 Hz) and a 6-W bulb that could be illuminated to provide a light stimulus during the otherwise dark session. Procedures were identical to those described previously (25).

Training began with simple conditioning. Rats were shaped to retrieve food pellets and then they underwent 10 conditioning sessions. In each session, the rats received eight 30-second presentations of three different auditory cues (A1, A2, and A3) and a visual cue (V1). Cues were presented in a blocked design (counterbalanced); V1 consisted of a cue light, and cues A1, A2, and A3 consisted of a tone, clicker, or white noise (counterbalanced). Two differently flavored sucrose pellets (banana [O1] and grape, counterbalanced) were used as rewards. V1 and A1 terminated with delivery of three pellets of O1, and A2 terminated with delivery three pellets of grape. A3 was not paired with food.

After completion of conditioning, rats received 4 consecutive days of compound training in which A1 and V1 were presented together as a 30-second compound cue terminating with three pellets of O1 and V1, A2, and A3 continued to be presented as before. Cues were again presented in a blocked design (counterbalanced). For each cue, there were 12 trials on the first 3 days of compound conditioning and 6 trials on the last day of compound conditioning.

One day after the last compound training session, rats received an extinction probe test session consisting of eight nonreinforced presentations (extinction conditions) of the three auditory cues (A1, A2, A3), with the order mixed and counterbalanced.

Behavioral Measures

The primary measure of conditioning to cues was the percentage of time that each rat spent with its head in the food