



Environmental enrichment induces early heroin abstinence in an animal conflict model



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ARTICLE INFO

Article history:

Received 18 May 2015

Received in revised form 21 August 2015

Accepted 10 September 2015

Available online 12 September 2015

Keywords:

Heroin addiction

Abstinence

Environmental enrichment

Conflict model

ABSTRACT

Rationale and objectives: Heroin addiction is a significant health and societal problem for which there is no highly effective long-term behavioral or pharmacological treatment. Therefore, strategies that support heroin abstinence should be a primary focus of heroin treatment research. To this end, the current study used an animal conflict model that captures the aversive consequences of drug seeking (as are typical in humans, e.g., incarceration and job loss) to induce abstinence. Using this abstinence model, we examined the capacity of environmental enrichment (EE) to facilitate abstinence in heroin seeking rats.

Methods: The procedure consisted of two phases: drug self-administration (phase 1) and electric barrier application (phase 2) that resulted in abstinence. For phase 1, male rats were trained to self-administer intravenous heroin under a fixed-ratio schedule of reinforcement. After self-administration was acquired, animals were housed either in EE or standard cages (non-EE control). During abstinence in phase 2, the electric barrier was introduced in the operant conditioning chambers by electrifying the floor area near the levers.

Results: We found that EE rats achieved abstinence (zero active lever presses for 3 consecutive sessions) in significantly fewer sessions than NEE rats. Further, EE rats abstained at significantly lower electric currents than NEE rats.

Conclusions: EE facilitated abstinence in the conflict model. The current use of the abstinence–conflict model to investigate EE as a behavioral strategy to facilitate abstinence will help in the development of effective treatments for human addicts by bringing together the positive consequences of abstinent behavior in an enriched environment with the aversive consequences of drug seeking.

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1. Introduction

Although pharmacotherapies for heroin addiction (e.g., buprenorphine and methadone) show promise compared to no treatment in reducing heroin use, they continue to fall short of being highly effective when the goal is long-term abstinence and relapse prevention (Koob et al., 2009; Kreek et al., 2002; Peck and Ranaldi, 2014). Therefore, strategies that support heroin abstinence should be a primary focus of heroin treatment research. Further, a successful drug-treatment program will likely be one that focuses on both the neurological mechanisms within the addicted individual and the environmental contingencies that mediate drug use. For example, research shows that combining treatment medications with behavioral therapy is a more effective way to help sustain abstinence (Carroll and Onken, 2005; Silverman et al., 1996; Higgins et al., 2005; Haug et al., 2004). Therefore,

increasing our understanding about which behavioral factors determine successful long-term heroin abstinence will lead to more efficient treatment strategies in heroin addiction.

In humans, drug abstinence often results from the aversive consequences that coincide with drug use (Epstein and Preston, 2003; Panlilio et al., 2003, 2005; Cooper et al., 2007). There are some earlier studies that have presented aversive consequences during drug taking and drug seeking with animals. For example, punishment-based relapse models (Panlilio et al., 2003, 2005) have been developed in which drug-reinforced lever pressing is suppressed by the delivery of an electric shock immediately after drug infusions. The punishment model relates to the human condition, where the aversive consequences of drug taking outweigh the hedonic (i.e., rewarding) effects (Panlilio et al., 2005). However, in humans, some of the aversive consequences related to drug use are those that occur during drug seeking, such as hiding from law enforcement, family and friends, or securing the funds for obtaining the drug (Epstein and Preston, 2003; Cooper et al., 2007). That is, human drug-seeking episodes during abstinence often involve a ‘conflict’ situation, which usually involves a choice between experiencing the positive effects of the drug and the aversive consequences of drug seeking.

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Cooper et al. (2007) developed a conflict-based abstinence model wherein aversive consequences occur during cocaine seeking. In the Cooper et al. (2007) study, rats were trained to lever press for cocaine infusions paired with a discrete light stimulus. An electric barrier was then introduced by electrifying the floor area near the levers, while the drug continued to be available; thus, the animals could continue to self-administer the drug but doing so necessitated enduring electric shock. Then the researchers increased the electric shock intensities daily until the rats stopped emitting the drug-taking response (i.e., lever pressing), an outcome operationally defining abstinence. In a subsequent relapse test with the electric barrier remaining activated, the effect of non-contingent cocaine cue presentations led to the resumption of drug seeking (relapse).

Recently, we (Peck et al., 2013) used a similar abstinence conflict model with heroin self-administration. We found that abstinence was achieved for all heroin-seeking rats by increasing the electric shock intensity. Our results, as well as previous research (Cooper et al., 2007, Barnea-Ygaël et al., 2012), suggest that the abstinence conflict model may represent important features where aversive consequences are present during drug seeking. Further, the model demonstrates how the aversive consequences of drug use play an integral part in the initiation and maintenance of drug abstinence. Therefore, investigating the effects of behavioral treatments such as environmental enrichment in an abstinence conflict model could support abstinence by bringing together both the positive consequences of abstinent behavior (e.g., enrichment) with the aversive consequences of drug seeking (e.g., electric barrier) (Peck and Ranaldi, 2014).

Chauvet et al. (2009); Thiel et al. (2009) and Ranaldi et al. (2011) found that, in animals already trained to self-administer drug, introduction to enriched housing conditions reduced responding in extinction and attenuated cue-induced relapse to cocaine seeking. What these studies demonstrate is that when rewarding stimulation is provided from enriched environments outside the drug context there is an apparent reduction in the incentive motivational effects of the drug(s) and/or drug-associated stimuli. These studies tested the capacity of EE to facilitate extinction of drug-seeking. However, extinction is different from abstinence (Peck and Ranaldi, 2014). It is of particular interest to know how EE affects abstinence – the omission of drug seeking and taking while drug is available.

In the current study, our primary focus was to use the abstinence conflict model that captures the aversive consequences of drug seeking to induce abstinence. Also, under these same abstinence conditions, to investigate environmental enrichment (EE) as a potential treatment strategy of facilitating abstinence in heroin-seeking rats.

In Phase 1, male rats were trained to self-administer intravenous heroin under a fixed ratio schedule of reinforcement. Then after self-administration was acquired, enriched animals (EE) were housed in environmental enrichment boxes while control rats (NEE) remained in standard cages (Phase 2). Each rat continued to reside in its respective EE or NEE housing condition until the end of subsequent abstinence. During abstinence, all rats were introduced to an electric barrier by electrifying the floor area near the levers in order to model the aversive consequences of continued drug seeking. Shock intensities were increased over sessions until no active lever responses occurred for three consecutive sessions (abstinence achieved). It was hypothesized that EE rats would achieve abstinence in significantly fewer sessions than NEE rats. If these results were to be observed then this would lend more support for the implementation of environmental enrichment as a strategy to facilitate heroin abstinence in rats.

2. Methods and materials

2.1. Subjects

Subjects consisted of male Long Evans rats weighing between 350 and 400 g at the time of surgery. Each rat was individually housed

under a reversed 12 h light:dark cycle (lights on at 1900 h). All rats had access to food (Purina rat chow) and water at all times except when in operant conditioning chambers.

2.2. Intravenous surgery

Each rat was anesthetized using sodium pentobarbital (65 mg/ml, i.p.). An incision was made in the neck area and the jugular vein was isolated and opened. A silastic intravenous catheter (Dow Corning, Midland, MI) was inserted into the vein so that the tip penetrated to the position just before the right atrium. The other end of the catheter was fed subcutaneously to the back of the neck and exited through an opening on the scalp. A 22-gauge stainless steel tube was inserted into the catheter and secured to the skull by dental acrylic and 4 stainless steel screws. This tube served as a connector between the catheter and the drug infusion line. The catheter was flushed with heparin solution (200 U/ml) immediately after surgery and every day thereafter.

2.3. Apparatus

Each animal was placed in a 26 × 26 × 30-cm operant conditioning chamber equipped with two levers positioned 10 cm from the floor. One lever was designated as active and the other as inactive. Each chamber had a white cue light 3 cm above each lever. Polyethylene tubing connected each animal's catheter assembly, through a fluid swivel, to a heroin-filled syringe in a pump (Razel, 3.33 rpm). The electric barrier was provided by constant-current aversive stimulators that were connected to two thirds of the floor adjacent to the levers. The stimulators produced a constant voltage, and the rats received a shock by touching any two of the activated rods. The remaining one third of the chamber with no current served as a no-shock zone.

2.4. Procedure

The procedure consisted of two phases: drug self-administration and the electric barrier application. After self-administration was established (operationally defined as 15 sessions of stable drug intake), enriched animals (EE) were housed in environmental enrichment boxes (large bins with running wheels, tubes, and various toys) while control rats (NEE) remained in standard cages. Each rat continued to reside in its respective EE or NEE housing condition until the end of the experiment.

2.5. Heroin self-administration

Three days after surgery each animal began self-administration training in operant conditioning chambers in daily 3-h sessions. All self-administration sessions were conducted during the dark phase of the light:dark cycle. Each press on the active lever illuminated the cue light above it for 20 s and activated the pump delivering an injection of 0.05 mg/kg of heroin in a 0.125 ml volume of saline over 4.5 s. A time-out of 20 s began at the start of each infusion. Presses on the inactive lever produced no consequences during both phases. Each rat was trained to self-administer drug on a fixed-ratio one (FR1) schedule of reinforcement until attainment of 15 consecutive stable sessions. Stable responding was defined as follows: 15 consecutive sessions where the total number of rewards obtained per session was greater than 12 and where the total number of rewards per session for the last three consecutive sessions was within ± 10% of the mean for these three sessions.

2.6. Environmental enrichment

For each rat, after stable FR1 responding for 15 sessions was established, they were randomly assigned to either the environmental enrichment (EE) or no-environmental enrichment (NEE) group. There was 48 h in which rats remained in their respective housing conditions

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