Full length article

Frustration stress (unexpected loss of alternative reinforcement) increases opioid self-administration in a model of recovery

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ABSTRACT

Purpose: Engaging in alternative activities in the context where opioid use had occurred can constrain opioid use and helps to maintain recovery. However, "frustration stress" that occurs when contingencies on these alternative activities unexpectedly change (e.g., job loss or divorce) is thought to threaten recovery by prompting a return to drug use. Yet it remains unclear whether frustration stress can result in a return to drug use, and if so, whether it returns to prior levels or to even greater levels.

Procedures: We examine the impact of unsignaled extinction of alternative reinforcement on opioid use. Rats were trained to respond for an etonitazene solution (5 µg/ml, p.o.), then for food in alternating daily sessions. Subsequently, food and etonitazene were made concurrently available. Under concurrent availability conditions, rats were exposed to 1, 2, or 4 sessions of unsignaled food extinction, and effects on responding for etonitazene and food measured.

Findings: When etonitazene was the only reinforcer available, rats earned 58.3 ± 20.3 µg/kg/session (mean $\pm$ S.E.M.). When food was available in alternating sessions, etonitazene earned was unchanged (65.3 ± 19.2 µg/kg/session). Concurrent food availability decreased etonitazene earned (13.5 ± 4.5 µg/kg/session). Unsignaled food extinction returned etonitazene earned to levels similar to (60.5 ± 18.4 µg/kg/session), but not greater than, those observed previously when etonitazene alone was available.

Conclusions: Unsignaled extinction of alternative behavior controlling opioid use can result in increased opioid use, but this use does not rise beyond previous levels observed when opioid use is unconstrained by alternative reinforced behavior.

1. Introduction

Opioid addiction remains a persistent public health problem. For those in recovery who successfully reduce or eliminate opioid use, relapse remains a threat, though the likelihood of relapse declines as time in recovery increases (e.g., Gossop et al., 1990). Thus, preventing relapse is particularly crucial early in recovery before alternatives to drug use become habitual and less susceptible to disruption by precipitants of relapse (Ginsburg and Lamb, 2013a,b,c; Lamb et al., 2016; Lamb and Ginsburg, 2017). Psychosocial stress is thought to be an important precipitant of relapse (Dawes et al., 2000; Kosten et al., 1986; McLellan et al., 1983). It is believed that stress produces a dysphoric response which might prompt drug use and increase it to abnormally high levels (Koob, 2009). Although momentary stress exposure can produce reports of drug craving and increase attention to drug-associated cues, clinical evidence that stress exposure increases drug use is weak (Brown et al., 2015; Preston and Epstein, 2011). Yet such relationships are difficult to

determine due to the complex nature of clinical studies, especially in naturalistic settings; thus, researchers have attempted to address this issue using preclinical techniques. Preclinical research on the role stress plays in relapse has largely involved studies using the reinstatement procedure in which drug-maintained responding is extinguished and then reinstated in extinction by exposing subjects to stressors including inescapable foot-shock or cold exposure (Crombag et al., 2008; Epstein et al., 2006; Mantsch et al., 2016). There is also some evidence that social isolation might precipitate reinstatement, though this has received relatively limited examination (Chauvet et al., 2009; Mantsch et al., 2016).

A limitation of the reinstatement procedure is the necessity of extinction and the lack of measures of drug-taking or alternative behavior after exposure to stressors (Katz and Higgins, 2003). Extinction is difficult to impose clinically, and its relevance to clinical situations has been challenged (Bouton et al., 2017). Instead, humans in recovery often reduce drug-seeking and consumption even in the presence of

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continuing drug availability − e.g., the dealer still lives down the block and has the same supply for sale at the same price as before recovery. Further, reinstatement is assessed under extinction, thus any effect on drug-taking is not possible to determine. As noted above, there is clinical evidence that stress exposure can increase self-reported craving, but the link between self-reported craving and resumption of drug use is, at best, weak (Furnari et al., 2015; Preston and Epstein, 2011; Wray et al., 2013). Therefore, it remains unclear whether reinstated drug use would rise to lower, greater, or similar levels as those observed before extinction. Finally, alternative behavior is neither reinforced nor measured in the reinstatement procedure, which prevents assessments of changes in other behavior upon exposure to relapse precipitants (Ginsburg and Lamb, 2013a).

While a case can be made for the clinical relevance of reinstated responding precipitated by exposure to drug-related stimuli, the relevance of the stressors typically used in this procedure is less apparent (Crombag et al., 2008; Epstein et al., 2006). Clinical studies linking stress exposure to relapse tend to identify psychosocial stress as the most important type of stress (Dawes et al., 2000; Kosten et al., 1986; McLellan et al., 1983; Pilowsky et al., 2013). Thus, the validity of exposure to inescapable foot-shock or cold, and the role such exposure might play in relapse in humans is not clear. Instead, relapse is more likely to follow from more common, daily life stressors, e.g., job loss, familial disruption, or financial difficulty (Gallo et al., 2001; Temple et al., 1991). These types of events have alternatively been classified as frustrations, where historical contingencies no longer produce expected reinforcement. Substance use and likelihood of relapse has been linked to diminished tolerance to this type of frustration stress in adolescents and adults (Baars et al., 2013; Miller, 1991).

Few preclinical studies have addressed the role frustration stress might play in relapse. In a study in mice, restricting access to an exercise wheel increased voluntary ethanol consumption in female mice with genetic manipulations that reduce β-endorphin levels (McGonigle et al., 2016). In rat studies, others have observed the resurgence of extinguished responding for ethanol or cocaine upon unsignaled extinction of food (Podlesnik et al., 2006; Pyszczynski and Shahan, 2013; Quick et al., 2011). However, it remains unclear whether a return to substance use in the face of unanticipated loss of alternative reinforcement results in a return to levels of drug use seen prior to the introduction of the alternative reinforcer or if drug use exceeds prior levels in response to the dysphoric effect of frustration. Further, it remains unclear whether restoring the alternative reinforcement can return drug use to pre-frustration levels.

Here we address these questions by examining first how providing alternative reinforcement (food) in the context where an opioid is available affects opioid self-administration; first when food is available in alternating sessions, and then when it is available concurrently with the opioid. We then examine the impact of unsignaled extinction of food on opioid self-administration. These results support the notion that frustration stress can increase opioid use and might increase the likelihood of relapse.

2. Methods

2.1. Subjects

Male Lewis rats (Envigo, Inc., Indianapolis, IN, n = 8) arrived at 6 weeks of age weighing approximately 275 g. Rats were individually housed and allowed to habituate to vivarium routines for at least 2 weeks. During this time, rats had ad libitum access to food and water in their cages. Once rats weighed 300 g, food was restricted to 12–15 g/day to maintain rats' weights at approximately 330 g (median: 329 g; range: 302–364 g) for the rest of the study. Water remained available in the home cage at all times. All studies were approved by the Institutional Animal Care and Use Committee as well as by the United States Air Force AFMSA/SGE-C Animal Use Program, and were

conducted in accordance with the Guide for Care and Use of Laboratory Animals (National Research Council, 2011). Animals were housed under a 14/10-h light/dark cycle and tests were conducted during the light cycle.

2.2. Apparatus

Training and testing occurred in standard rodent operant chambers from a commercial vendor (Med-Associates, Georgia, VT). Chambers were equipped with a liquid dipper that delivered 0.1 ml of a solution into an accessible location in the center of one chamber wall. A food dispenser was also present which delivered 45 mg rodent chow flavored pellets (BioServ, Flemington, NJ) to the same receptacle. Two response levers were present on either side of the receptacle and a stimulus light was located above each lever. A house light was present at the top of the opposite wall. Chambers were enclosed in ventilated, sound and light-attenuating enclosures.

2.3. Etonitazene

Etonitazene HCl was obtained from a commercial supplier (Sigma, Inc., St. Louis, MO). Etonitazene was dissolved in drinking water at a concentration of 1000 μg/ml to produce a stock solution. This stock solution was then diluted to the working concentrations (described below) in drinking water. Etonitazene working solutions were made fresh every 2-5 days, as needed. Sucrose was purchased from a local grocery store and dissolved to the appropriate concentration in drinking water.

2.4. Training

After the two-week habituation period, rats were trained to respond on a lever when the light above it was illuminated for 10-s access to 0.1 ml of a sucrose solution (8% w/v) during a two-hour session. Initially a single response produced 10-s dipper access, turned off the stimulus light above the lever, and turned on the house light. During the initial three sessions, the number of deliveries earned increased from 87 ± 35 to 204 ± 17 (mean ± S.E.M.). For the next session, etonitazene (0.625 μg/ml) was added to the sucrose solution. This concentration was maintained for the next 8 sessions, then the etonitazene concentration was increased to 1.25 μg/ml for the next five sessions and then to 2.5 μg/ml for the next six sessions, and then to the final concentration of 5.0 μg/ml. This sequence was based off of earlier reports in which rats were trained to respond for an orally available etonitazene solution (Meisch and Kliner, 1979; Meisch and Stark, 1977). Over the next 4 sessions, the response requirement was increased from fixed-ratio 1–5 (FR1 to FR5). This condition was maintained for the next 13 sessions, then sucrose was gradually removed from the solution over the next 27 sessions, until rats were responding for deliveries of 0.1 ml of 5.0 μg/ml etonitazene in drinking water. Altogether, this process took 67 sessions. Once responding was maintained by etonitazene in water alone, rats continued training until responding stabilized; i.e. amount earned over four consecutive sessions varied by less than 30% of the mean for each subject. Sessions occurred on weekdays.

2.5. Alternating sessions of etonitazene and food reinforcement

Subsequently, rats were placed in the operant chamber and the light above the other lever was illuminated. Responses on this lever resulted in delivery of a food pellet (45 mg "rodent chow" flavor, Bioserv, CAT#F0165), turned off the stimulus light, and turned on the house light. During the next three sessions (Sessions 103–106), the response requirement for food was increased to FR5. Sessions then alternated between food and etonitazene for the next 12 sessions (Sessions 107–118), with each session lasting two hours.