Behavioural Brain Research 230 (2012) 69–77

Contents lists available at SciVerse ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Expression and resilience of a cocaine-conditioned locomotor response after brief and extended drug-free periods

Sarah A. Johnson[a], Saadia Sediqzadah[a], Suzanne Erb[a,b,*]

[a] Department of Psychology, University of Toronto at Scarborough, 1265 Military Trail, Toronto, Ontario, M1C 1A4, Canada
[b] Centre for the Neurobiology of Stress, University of Toronto at Scarborough, 1265 Military Trail, Toronto, Ontario, M1C 1A4, Canada

ARTICLE INFO

Article history:
Received 17 November 2011
Received in revised form 17 January 2012
Accepted 24 January 2012
Available online 1 February 2012

Keywords:
Contextual conditioning
Conditioned locomotion
Extinction
Behavioral sensitization
Incubation
Spontaneous recovery
Cocaine

ABSTRACT

Conditioned associations between drug experience and its context are maintained long after drug use ceases, and may contribute to relapse after extended abstinence. These include operantly conditioned associations directed toward seeking drug, but also Pavlovian conditioned associations between drug reward and contextual cues present at the time of drug administration. The present study sought to determine whether expression of a Pavlovian conditioned locomotor (CL) response to a cocaine-associated context increases over time in the same manner observed for instrumental responses, and whether the CL memory is differentially susceptible to extinction and recovery after brief versus extended abstinence. Male rats received injections of cocaine (30 mg/kg, i.p.) or vehicle once per day for 6 days. In Exp. 1, CL activity was measured 1, 7, 21, or 42 days later. Rats that had received cocaine injections displayed robust CL, regardless of when testing occurred. In Exp. 2, extinction and recovery of CL were assessed after 1 or 42 days. The CL response was more readily extinguished in rats tested 1 day after drug exposure, as compared to rats tested 42 days later. Exp. 3 confirmed that conditioning in the testing context was necessary for expression of CL. Overall, our results indicate that Pavlovian associations underlying the CL response are maintained long after drug experience. Although the expression of CL does not change with the passage of time, as has been observed for instrumental drug-related responses, the memory trace does appear to become more resilient over time.

1. Introduction

Relapse is a key challenge faced in recovery from addiction, primarily because risk of recurrence remains high even after extended periods of abstinence [1–3]. One means through which relapse could manifest is return to a context in which drug use had previously occurred, prompting the retrieval of associations formed between contextual cues and drug experience [4,5].

In considering the potential for relapse after prolonged abstinence, it is important to note that susceptibility to craving varies based on the time elapsed since drug intake. In human cocaine users, craving is not typically reported immediately following a binge (i.e. for approximately 1 week), while the likelihood of experiencing craving increases and remains high in the following 10 weeks [6]. Data from animal models suggest a similar progression from low to high risk of craving. Following a period of cocaine self-administration, non-reinforced responding on the drug-associated lever is low for the first 7 days, but increases dramatically over the next 15–60 days [7–9]. A similar, though accelerated time-course is observed after heroin self-administration [10]. Together, these findings suggest that drug seeking follows a pattern of 'incubation' [7,8], whereby a craving-like response is enhanced as time passes after drug exposure.

Drug-seeking responses observed in the aforementioned contexts are ultimately voluntary behaviors that are operantly conditioned. Even so, both operant and Pavlovian associations are formed during drug self-administration training and, while it can be difficult to tease apart the relative contributions of these two forms of memory to subsequent responding, it should be assumed that both types of associations are maintained in the long term. Moreover, it should be considered that both types of associations could contribute to the altered expression of the operant response over time. It is conceivable, for example, that Pavlovian associations formed during training might change in strength on their own over time, or modulate the influence of conditioned stimuli on performance in a time-dependent manner.

Abbreviations: CL, conditioned locomotion; COC, cocaine; CPP, conditioned place preference; DE, drug exposure; HAB, habituation; P, paired; REC, recovery; SENS, sensitization; SpREC, spontaneous recovery; UP, unpaired; VEH, vehicle.

* Corresponding author at: Department of Psychology, University of Toronto at Scarborough, Toronto, Ontario, M1C 1A4, Canada. Tel.: +1 416 287 7454; fax: +1 416 287 7642.
E-mail address: erb@utsc.utoronto.ca (S. Erb).

0166-4328/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbr.2012.01.049

To date, time-dependent effects of prior drug administration on the expression of Pavlovian conditioned associations have been addressed most directly using the conditioned place preference (CPP) procedure. Consistent with findings from self-administration studies, Li et al. [11] demonstrated that expression of morphine CPP is low 1 day after drug-context pairings, but increases in magnitude 7–14 days later. A similar pattern is observed in the expression of nicotine CPP [12].

An alternate paradigm that has been used to study the Pavlovian conditioned associations formed between drug and context is conditioned locomotion (CL). In this procedure, animals are returned to an environment in which they had previously received drug injections, and locomotor activity is assessed in the absence of drug (e.g. [13–19]). Like drug seeking and CPP responses, CL conveys the maintenance of an association between drug experience and the context in which it occurred. In contrast, performance of the CL response does not require that the animal direct its behavior toward or away from a set of contextual cues, or choose a favored location. Accordingly, although all three paradigms are useful for assessing the retention of Pavlovian conditioned associations, it may be argued that expression of the CL response is governed more exclusively by Pavlovian memory systems, and may be differentially affected by variables such as the time elapsed since drug exposure.

Expression of the CL response has been observed at different times after cocaine exposure (e.g. [13,14,20]). However, with respect to examining the time-dependency of the response, studies carried out to date have two limitations. First, CL has mainly been assessed in the first 1–7 days after cocaine exposure [16–19,21,22]. Second, studies measuring CL at more than one time-point have tended to employ within-subjects designs, in which rats or mice undergo repeated testing [13,14,20]. Results from these latter studies suggest, perhaps not surprisingly, that CL is strongest in early test sessions, and then decays with the passage of time and repeated non-reinforced exposures to contextual cues [13,20,23]; though see Ref. [14]. From this perspective, it is reasonable to predict that a between-subjects design, in which separate groups of animals are tested at each time-point after drug exposure, may reveal a different time-dependent pattern of expression of CL, possibly one consistent with the outcome of previous studies employing drug seeking and CPP responses.

Accordingly, the objective of Experiment 1 was to determine the effect of time elapsed after drug exposure on expression of the CL response, using a between-subjects design. Separate groups of rats were tested for CL 1, 7, 21, or 42 days after the final cocaine (or vehicle) exposure in the test context, and the magnitude of the CL response at these time-points was compared. The objective of Experiment 2 was to determine the effect of time after drug exposure on resilience of the CL memory trace, by asking whether the CL response would follow similar patterns of extinction and recovery after a short (1 day) versus long (42 days) post-drug interval. Finally, Experiment 3 was carried out to verify that the CL response observed in Experiments 1 and 2 in fact arose from a learned association between cocaine and the context in which it was administered, rather than from the physiological consequences of repeated exposures to the drug. To this end, CL was compared in rats that were given cocaine injections explicitly paired with the test context, and rats that were given an equal number of cocaine injections in an alternate, non-testing context.

2. Methods

2.1. Subjects

Male Wistar rats (Charles River Canada, St.-Constant, QC) weighing 275–300 g at the time of their arrival to the vivarium were housed individually and maintained on a standard light–dark cycle (lights on 8:00 am–8:00 pm). Food and water were made available ad libitum. Sections of PVC pipe were included in each cage. All rats were handled and weighed at least 4 times per week over the course of the studies. Experimental protocols were approved by the Local Animal Care Committee at the University of Toronto at Scarborough, and were in accordance with the guidelines of the Canadian Council on Animal Care.

2.2. Apparatus

Standard Plexiglas box cages (26 cm × 48 cm × 21 cm) served as activity-monitoring chambers, in which all drug exposure and testing sessions took place (except in Exp. 3, see Section 2.3.3). Locomotor activity was monitored via a CCD camera and infrared sensor mounted 1.5 m overhead. The camera and sensor were connected to an Ethovision tracking system (Noldus, Wageningen, The Netherlands), which recorded the distance traveled (cm) by each rat during sessions. The floor and walls of each chamber were coated with matte black paint to prevent reflections off the Plexiglas surface from being picked up by the camera and sensor. Prior to each drug exposure or testing session, the upper walls of the chambers were treated with peppermint extract to provide a contextual odor cue.

2.3. Behavioral procedures

All experiments included 3 initial phases: (1) habituation, (2) drug exposure, and (3) test for CL. In Experiment 1, the initial test for CL occurred 1, 7, 21, or 42 days after the final drug exposure session, whereas in Experiments 2 and 3, the test for CL was administered 1 or 42 days after drug exposure. Experiment 2 included additional phases following the test for CL (see Fig. 1 and Section 2.3.2).

2.3.1. EXP. 1: assessment of the magnitude of the CL response 1, 7, 21, or 42 days after drug exposure

2.3.1.1. Habituation. After acclimation to the vivarium for 1 week, rats were habituated to the activity chambers in which subsequent cocaine exposures were administered (Fig. 1a; HAB). For this session, rats were handled briefly, weighed, transported to the room housing the activity chambers, and placed individually in a chamber. Activity was recorded for 60 min. Rats were assigned to drug exposure groups according to their baseline activity levels, such that mean baseline activity during the habituation session was equal across groups.

2.3.1.2. Drug exposure. Rats were assigned to one of two drug exposure groups: vehicle (VEH) or cocaine (COC). A total of 6 drug exposure sessions were administered over the subsequent 7 days (Fig. 1a; DE1–DE6). Sessions took place on days 1–3 and 5–7. No manipulations were carried out on day 4 (Fig. 1a). All sessions took place between 10:00 am and 2:00 pm. On each day, rats were briefly handled, weighed, and transported to the room housing the activity chambers. Injections of vehicle (0.9% saline, 1 mL/kg) or cocaine (30 mg/kg cocaine–HCl; Medisca, St.-Laurent, QC) were administered i.p. immediately prior to placement in the activity chambers. Activity was recorded for 30 min, and rats were returned to their home cages. Chambers were scrubbed down and rinsed with tap water between sessions.

2.3.1.3. Test for CL. Testing procedures were identical to drug exposure procedures, except that all rats were given vehicle injections (0.9% saline, 1 mL/kg) prior to placement in the activity monitoring chambers for 60 min (Fig. 1b; CL1). In this experiment, separate