Drug and Alcohol Dependence 129 (2013) 94–101

Contents lists available at SciVerse ScienceDirect

Drug and Alcohol Dependence

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

A history of alternative reinforcement reduces stimulus generalization of ethanol-seeking in a rat recovery model

Brett C. Ginsburg[a,b,*], R.J. Lamb[a,b]

[a] The University of Texas Health Science Center at San Antonio, Department of Psychiatry, 7703 Floyd Curl Dr., San Antonio, TX 78229, USA
[b] The University of Texas Health Science Center at San Antonio, Department of Pharmacology, 7703 Floyd Curl Dr., San Antonio, TX 78229, USA

ARTICLE INFO

Article history:
Received 10 July 2012
Received in revised form
11 September 2012
Accepted 21 September 2012
Available online 31 October 2012

Keywords:
Addiction
Stimulus control
Choice
Discrimination

ABSTRACT

Background: Longer periods of recovery reduce the likelihood of relapse, which may be due to a reduced ability of various stimuli to occasion alcohol or drug seeking. However, this hypothesis remains largely uninvestigated.
Methods: Here we assessed the ability of intermediate stimuli to occasion responding for ethanol in rats trained to discriminate an 8 kHz tone signaling a food fixed-ratio (FR) of 5 and an ethanol FR5, from a 16 kHz tone signaling a food FR150 and ethanol FR5. In the presence of the 8 kHz tone responding for food predominates, and in the presence of the 16 kHz tone, responding for ethanol predominates.
Results: In the context of alternation between these conditions, varying the tone from 8 to 16 kHz produces a graded increase in ethanol (versus food) responding, consistent with a stimulus generalization function. A recent history of responding under food-predominant choice conditions, either during the test session or in the four sessions that precede it shifts the generalization function downwards. Extending this history to nine sessions shifts the curve further downwards. The stimulus generalization function was similar in a separate group, trained with different relative ratios for food and ethanol, but with similar behavioral allocation under each discriminative stimulus. Finally, withholding access to food and ethanol for 4 or 16 sessions did not affect the stimulus generalization gradient.
Conclusion: These results suggest that longer histories of reinforced alternative behavior might reduce the likelihood of relapse by decreasing the control exerted over alcohol- or drug-seeking by stimuli similar to those that previously occasioned alcohol- or drug-seeking.

1. Introduction

Alcoholism and other addictions are often characterized as a loss of control over drinking or drug use. This can be interpreted in two different ways (Keller, 1972). Loss of control can describe an inability to refrain from initiating a drinking bout when confronted with stimuli that have come to occasion drinking. The sight of a preferred bar or socializing with a particular group of friends can come to occasion initiation of drinking. It follows then, that there is likely a range of stimuli or situations that might occasion initiation of a drinking bout, and over time the range of such stimuli might broaden beyond those that initially occasioned drinking (Schuster, 1986). Loss of control can also mean that once drinking starts, it does not stop until intoxication is so severe drinking cannot continue.

Recovery can be viewed as the converse of loss of control, so drinking may be moderate after initiation of a drinking bout. Likewise, a person in recovery may be able to abstain even in the presence of stimuli that had previously occasioned drinking (Bickel and Kelley, 1997). We postulate that as alternative behavior supplants drinking, the range of stimuli that occasion drinking diminishes. This may, in part, explain why, for a variety of addictions including alcoholism (Gilpin et al., 1997; Gossop et al., 1990; Hunt et al., 1971; McKay et al., 2001), the probability of relapse diminishes as recovery lengthens.

Presumably, as stimuli that had occasioned heavy drinking lose their effectiveness, other, similar stimuli also lose their ability to occasion drinking. For example, early in recovery, walking by a bar may occasion a relapse to drinking, even if it is not the same bar where most of the problematic drinking had occurred. This is called stimulus generalization. Over time, the ability of such similar stimuli to occasion drinking may decline so that walking by a bar is no longer likely to precipitate relapse. Although this has been posited as a crucial mechanism in successful recovery, there is little data regarding this notion (Bickel and Kelley, 1997; Schuster, 1986). Procedures to study stimulus generalization are well-established

* Corresponding author at: The University of Texas Health Science Center at San Antonio, Department of Psychiatry, MC 7792, 7703 Floyd Curl Dr., San Antonio, TX 78229, USA. Tel.: +1 210 567 0871; fax: +1 210 567 5381.
E-mail address: ginsburg@uthscsa.edu (B.C. Ginsburg).

0376-8716/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.drugalcdep.2012.09.017

in experimental psychology (Honig and Urcuioli, 1981). Subjects are trained to make different responses in the presence of distinct stimuli, A and B. Once this behavior is established, responding is assessed in the presence of varying stimuli that are intermediate between A and B. Typically, intermediate stimuli more similar to A result in responses that were trained in the presence of A, while those more similar to B result in responses that were trained in the presence of B. Experimental manipulations can then be performed and their effects on the stimulus generalization gradient observed.

Despite the conceptualization of addiction as a broadening of the stimuli that occasion drug use (Bickel and Kelley, 1997; Schuster, 1986), stimulus generalization has not been used to study stimulus control over drug-reinforced behavior. Further, stimulus generalization has not been used in situations where a choice between two different commodities (such as food and drug) is made.

Here, we provide concurrently available food and ethanol and, by changing the response requirement for food, produce food-predominant or ethanol-predominant responding. We then examine stimulus generalization in a situation where one stimulus occasions food-predominant responding and another occasions ethanol-predominant responding. With this baseline, we examine if a history of responding in only the food-predominant situation can decrease the ability of a range of stimuli to occasion responding for ethanol. First, we determine stimulus generalization functions in test sessions in which alternating or only food-predominant conditions are presented during reinforced components. We then test whether a history of four or nine preceding sessions in which only the food-predominant response conditions were presented affects the stimulus generalization function. We further determine whether changing the relative response requirements for food versus ethanol affect stimulus generalization. Finally, we examine whether a history of not responding for ethanol (or food, by removing the rats from the operant apparatus for the equivalent of 16 sessions) has a similar impact on the stimulus generalization function. Our choice of four, nine, and sixteen sessions was based on other studies using a similar procedure. In those studies, four and sixteen preceding sessions in which only food-predominant conditions are presented increased the amount of responding for food when rats were re-exposed to a stimulus signaling ethanol-predominant responding (Ginsburg and Lamb, in press).

If longer periods of recovery reduce the risk of relapse by decreasing the range of stimuli that result in problematic use, we might expect that longer periods in which responding for ethanol does not occur will decrease the effectiveness of intermediate stimuli to occasion responding for ethanol. If this is due to an increase in the frequency of alternative behavior in the same context in which drug-use had occurred, a history of responding predominately for food should shift the stimulus generalization function. If, however, this is simply due to time spent not responding for ethanol, a similar shift should be seen after a period in which rats are prevented from responding for ethanol.

2. Methods and materials

2.1. General materials and methods

2.1.1. Subjects. Male, adult, singly housed Lewis rats (Harlan, Frederick, MD) served as subjects. All experiments included data from $n = 5$ rats, except as indicated in Experiments 3 and 6 (Sections 2.4 and 2.7). Separate groups of rats were used for Experiments 1–4 and Experiments 5–6. Rats used in Experiments 1–4 had previously been involved in studies related to resumption of responding for ethanol following extended periods of food-predominant responding under the same procedure (Ginsburg and Lamb, in press). Upon arrival, rats weighed 260–265 g and spent one week habituating to our facilities with food and water provided ad libitum. Subsequently, water was always available in the rats' cages, however food was restricted to maintain body weights of 280–320 g for the remainder of the study (approximately 12–15 g/day).

2.1.2. Apparatus. Training and testing occurred in a commercially available apparatus (Standard Rat Chamber, Med Associates, St. Albans, VT). On one wall of the chamber, two response levers were arranged horizontally, one on each side of the wall. Equidistant between the levers was a receptacle that provided access to 45 mg food pellets (Bio-Serve, Frenchtown, NJ) via a pellet dispenser and to a solution via a 0.1-ml dipper. Chambers also had a speaker connected to a tone generator (ANL-926, Med Associates, St. Albans, VT) which produced pure tones that served as stimuli. Stimuli presentation and reinforcement delivery as well as data collection were accomplished by custom software written using a commercially available programming language (Med-PC, Med Associates, St. Albans, VT). Computer-generated pink noise was broadcast in the procedure room to mask ambient noise. Ethanol (190 proof) was obtained from Decon Labs Inc. (King of Prussia, PA) and mixed with tap water to obtain a 10% (w/v) solution. Solutions were made fresh daily, and allowed to reach room temperature before being presented to the rats.

2.1.3. Training. Sessions were conducted on weekdays and were 30-min in duration. Rats were first trained to respond on the left lever for 8% sucrose solution in the presence of a 16 kHz, 80 dB tone. Upon completion of the response requirement, a dipper containing 0.1 ml of solution was raised and the 16 kHz tone was replaced with white noise at 80 dB. The dipper remained accessible for 15-s, at which point it returned to the inaccessible position, and white noise was replaced with the 16 kHz tone. During this 1-s period, responses had no programmed consequences. During this portion of training, responses on the right lever had no programmed consequences. Once rats earned over 80 sucrose deliveries in a 30-min session (typically 2–7 sessions), the fixed-ratio (FR) was increased over a few sessions until rats were required to respond five times for a sucrose delivery. Subsequently, ethanol was introduced into the solution at 10% (w/v), then sucrose was removed from the solution over the next 10–25 sessions so rats responded for 10% (w/v) ethanol solution in tap water.

Responding for food was trained in a subsequent 30-min session during presentation of a 8 kHz tone at 80 dB. Under this stimulus condition, responses on the right lever resulted in the delivery of a 45 mg food pellet, and the tone changed to 0.1 kHz. Over the next several sessions, the FR was increased to 25, then rats were introduced to the multiple concurrent schedule.

Rats were trained to respond under a multiple concurrent schedule of food and ethanol reinforcement. In this schedule, components alternated randomly between a 16 kHz tone and associated contingencies (food FR150, ethanol FR5 for Experiments 1–4 and food FR75, ethanol FR5 for Experiments 5 and 6) and an 8 kHz tone and associated contingencies (food FR5, ethanol FR5 for Experiments 1–4 and food FR25, ethanol FR5 for Experiments 5 and 6). The order of components was randomized within each block of two components. Delivery of reinforcement was accompanied by a change in stimuli present in the chamber for 15-s, which was followed by the next component. Sessions were 30-min in length.

2.1.4. Stimulus generalization test. Stimulus generalization functions were determined within a single session. These sessions consisted of a multiple schedule in which components included probe trials as well as reinforced components. During probe trials, a tone (6, 8, 10, 12, 14, 16, or 18 kHz) was presented. The first five responses on either lever ended the trial. The tone was silenced, and a 15-s timeout in which responses had no programmed consequences ensued. The next trial began after this timeout. Probe trials were interspersed with reinforced components in which either an 8 or 16 kHz tone was presented and the appropriate contingencies were active. Presentation of either a probe trial or reinforced component followed random selection without replacement from a block of 8 possibilities where 2 of the 8 possibilities were probe trials and the rest were reinforced components. Thus, during the test sessions, contingent reinforcement was not delivered in 1/4 of the trials. If a probe trial was selected, the tone presented was randomly selected without replacement from a list of the possible tones, so that each tone was presented before the list was refreshed. This allowed rats to respond in the presence of each probe tone at least two times per session in almost every test session.

2.1.5. Analysis. Ethanol responses expressed as a percentage of total responses during each probe trial was calculated and averaged for each subject and served as the measure for each comparison. Comparisons were made using a repeated measures analysis of variance (ANOVA). First and second baseline function determinations were compared with tone and determination order as factors. The impact of a preceding history of food-predominant responding for 4 or 9 sessions were also compared with the baseline function using a repeated measures ANOVA with tone and preceding session conditions (alternating, four or nine food-predominant condition only sessions) as factors. Another repeated-measures ANOVA was performed to compare stimulus generalization functions obtained during test sessions in which reinforced components alternated or only consisted of food-predominant response conditions. The effect of conditions present during reinforced components of the test session (alternating versus food-predominant) was assessed with a repeated-measures ANOVA following matched histories of preceding sessions with tone and test session conditions as factors. Stimulus generalization functions generated in rats trained with food fixed ratios of 5 and 150 were compared against the function generated in a separate group of rats trained with corresponding food fixed-ratios of 25 and 75 (ethanol fixed-ratios were 5 in every case) using a mixed ANOVA (tone as within-subject, and group as between-subjects). Finally, the stimulus generalization