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Short communication

Nicotine as a discriminative stimulus for ethanol use

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ABSTRACT

Abused drugs reinforce behavior; i.e., they increase the probability of the behavior preceding their administration. Abused drugs can also act as discriminative stimuli; i.e., they can set the occasion for responding reinforced by another event. Thus, one abused drug could come to set the occasion for the use of another and this functional relationship may play a role in polysubstance abuse, where common patterns of use could result in this relationship. Here we establish nicotine (0.4 mg/kg, ip 5-min pre-session) as a discriminative stimulus for behavior reinforced by ethanol (0.1 ml 8% w/v po, versus food) and determine the ability of nicotine (0.02-0.4 mg/kg), varenicline (0.1-3.0 mg/kg), and ethanol (250 and 500 mg/kg) to control responding for ethanol. We compare these results to those from rats where nicotine signaled food was available (and ethanol was not). Nicotine came to function as a discriminative stimulus. Nicotine and varenicline produced dose-dependent increases in responding on the nicotine-appropriate lever while ethanol produced responding on the vehicle-appropriate lever. Whether this responding occurred on the lever that produced ethanol or food access depended on the training condition. These results demonstrate that a drug can come to set the occasion for use of another and suggest that this behavioral mechanism could play an important role in the maintenance of and recovery from polysubstance abuse, depending on the pattern of use.

1. Introduction

Substance use rarely involves only a single drug. Instead, most substance users consume two or more substances, often simultaneously (Galanter and Kleber, 2008). This could result in situations where one drug comes to set the occasion for use of another, leading to a situation where use of the former increases the likelihood of use of the latter (Higgins and Silverman, 1999). This has potentially important implications in the treatment of and recovery from addiction (Higgins and Silverman, 1999). If a drug becomes established as a discriminative stimulus for the problematic substance, ceasing use of the former might improve treatment outcomes regardless of its direct pharmacological effects, while use of the former might prompt a relapse to the latter.

The notion that an abused drug can set the occasion for use of another is based on several well-established lines of evidence. Abused drugs reinforce behavior; i.e., they increase the likelihood of subsequent use (Schuster and Thompson, 1969). Discriminative stimuli can come to set the occasion for, and thus control behavior (Stolerman, 1993). In many experimental situations, external tones or lights are established as discriminative stimuli (Ferster and Skinner, 1957), however abused drugs can also become discriminative stimuli, setting the occasion for a particular behavior (Swedberg, 2016). Thus, it is likely that in situations where drugs are used in concert, one drug can come to set the occasion for use of the other, though this has not yet been demonstrated.

Ethanol is the most widely used recreational drug (Center for Behavioral Health Statistics and Quality, 2016). Ethanol consumption increases the likelihood of subsequent use; i.e., ethanol reinforces behavior (Samson et al., 1988a). Like other reinforced behavior, ethanol use can come to be controlled by discriminative stimuli that indicate prevailing contingencies (Ginsburg et al., 2005). For example, lights can come to control whether rats respond on one lever for ethanol or on another lever for food. In the presence of one light, responses on the ethanol lever result in ethanol delivery, while in the presence of another light, responses on the lever do not produce ethanol access (but responses on another lever produce food). Under these conditions, presentation of the first light results in ethanol lever responding, while presentation of the other light does not (e.g., Ginsburg et al., 2005). Thus, discriminative stimuli (here the lights) can control ethanol use.

Nicotine can also reinforce behavior and additionally, can serve as a discriminative stimulus (Stolerman et al., 1988). Such drug discriminations are typically established when nicotine administration

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precedes sessions in which responses on one lever produce food, while vehicle administration precedes sessions in which responses on another lever produce food. After repeated exposure to these conditions, subsequent exposure to nicotine or similar drugs reliably results in responding on the former lever while vehicle administration results in responding on the latter lever.

The purpose of this study was to establish nicotine as a discriminative stimulus for ethanol versus food reinforcement, to determine if the nicotinic agonist varenicline produced similar effects, and whether this history influenced the ability of ethanol to reinstate responding for ethanol.

2. Methods

2.1. Subjects

Male Lewis rats were obtained from Charles River (Hollister, CA). Five rats (Subjects 1–5) were trained with nicotine as a discriminative stimulus for ethanol (Nicotine-Ethanol group), and three others (Subjects 6–8) were trained with nicotine as a discriminative stimulus for food (Nicotine-Food group), as described below. Previously, these rats had been trained to respond for ethanol (8% w/v in water) under a random-interval schedule using a postprandial induction procedure (see Lamb et al., 2017 for further information). Subjects 1–6 were trained under a random-interval schedule in which the overhead houselight served as a discriminative stimulus (Lamb et al., 2017; Experiment 2), while subjects 7–8 were trained with a tone serving as a discriminative stimulus (Lamb et al., 2017; Experiment 1). For additional details about the training and history of these rats, see Lamb et al. (2017). Subjects were fed a daily ration of food after operant sessions to maintain body weights ranging from 320 to 330 g.

2.2. Apparatus

Training and testing occurred in standard operant chambers from a commercial vendor (Med-Associates, Georgia, VT). Chambers were equipped with a dipper that delivered 0.1 ml of a solution to 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 located on either side of the receptacle and a stimulus light was located above each. A house light was located at the top of the opposite wall. Chambers were enclosed in ventilated, sound and light-attenuating enclosures.

2.3. Discrimination training

Rats were trained using a double-alternating pattern of nicotine or vehicle treatment. Treatment was administered (i.p.) 5-min before sessions began. During sessions, stimulus lights above both levers were illuminated and responses on the treatment-appropriate lever were reinforced. Responses on the left lever were reinforced with delivery of 0.1 ml ethanol solution (8% w/v in water); responses on the right lever were reinforced with delivery of two 45 mg food pellets. Reinforcement was followed by a 30-s time-out in which all lights were darkened and responses had no programmed consequence. Responses on the treatment-inappropriate lever had no programmed consequence. Initially, sessions in which ethanol was the reinforcer lasted for 20-min, while food sessions lasted 15-min. Eventually, food session length was increased to 20-min and the response requirement was increased to five (FR5). Training continued until all subjects met stability criteria: > 80% of all responses on the treatment-appropriate lever and completion of five responses on the treatment-appropriate lever occurred before five or more responses on the inappropriate lever.

2.4. Training conditions

Nicotine (0.4 mg/kg) or matched volume of vehicle (1 ml/kg) was administered (i.p.) 5-min before each session. Five rats (Nicotine-Ethanol group) were trained such that nicotine administration signaled that responses on the ethanol-associated lever were reinforced and vehicle signaled that responses on the food lever were reinforced. The remaining three rats (Nicotine-Food group) were trained under the converse conditions (nicotine signaled food, vehicle signaled ethanol).

2.5. Test sessions

Nicotine (0.02–0.4 mg/kg), varenicline (0.3–3.0 mg/kg), ethanol (0.25 or 0.5 g/kg), or vehicle were administered 5-min before test sessions. Test sessions ended after the first five responses on either lever. Responding on the drug-appropriate lever was expressed as a percentage of responses on both levers during the test session for analysis for each rat.

2.6. Drugs

Nicotine (25 mg base/ml propylene glycol) was obtained from a commercial source (NicVape, Spartanburg, SC). This solution was diluted in saline to produce the training solution of 0.4 mg/ml (expressed as weight of the base). Test solutions included this concentration, as well as concentrations ranging from 0.02–0.2 mg/ml. Nicotine solutions were titrated to pH 7 using acetic acid (glacial, Fisher, Inc, Fair Lawn, NJ). Varenicline was generously provided Pfizer Inc. (Groton, CT) and was dissolved in 0.9% saline to make 1 ml/kg solutions for each dose. Ethanol (200 proof) was obtained from Decon Labs (King of Prussia, PA). Ethanol was diluted to 8% (w/v) in drinking water.

2.7. Analysis

Due to the limited sample size, we compared nicotine and varenicline potency in each group by determining in each rat the lowest dose tested that produced > 50% nicotine-lever responding, and for which the next higher dose also produced > 50% nicotine-lever responding. Thus, we determined the minimum dose that resulted in > 50% nicotine-appropriate responding for each subject. These potency values were compared between groups with a Student's *t*-test for nicotine and varenicline (ethanol did not produce intermediate levels of responding in either group, see Results).

3. Results

3.1. Training

Rats required a median of 79 sessions to meet stability criteria (range: 65–85). Once trained, rats in the Nicotine-Ethanol group earned 0.25 ± 0.09 g/kg ethanol during sessions when ethanol was available and 81 ± 10 food pellet deliveries when food was available. Rats in the Nicotine-Food group earned 0.21 ± 0.07 g/kg during sessions when ethanol was available and 71 ± 11 food pellet deliveries when food was available. As shown in Fig. 1, the latency to complete the first five responses depended on the reinforcer available across both groups. Latencies were shorter on the food lever than on the ethanol lever for every subject, regardless of group assignment.

3.2. Nicotine effects

As shown in Fig. 2 (left panel), Nicotine produced dose-dependent increases in responding on the nicotine-appropriate lever in both groups. No differences were observed between the two training conditions; the minimum dose to produce > 50% nicotine-lever responding was (median [IQR]) 0.1 [0.04–0.2] mg/kg and 0.1 [0.06–0.1] for the