Published in final edited form as:

Drug Alcohol Depend. 2018 January 01; 182: 98–102. doi:10.1016/j.drugalcdep.2017.11.004.

Nicotine as a discriminative stimulus for ethanol use

Brett C. Ginsburg¹, Simon A. Levy^{2,3}, and R.J. Lamb¹

¹Department of Psychiatry, The University of Texas Health Science Center at San Antonio, San Antonio, TX, USA 78229

²Department of Cell & Structural Anatomy, The University of Texas Health Science Center at San Antonio, San Antonio, TX, USA 78229

³Barshop Institute for Longevity and Aging Studies, The University of Texas Health Science Center at San Antonio, San Antonio, TX, USA 78229

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 in 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.

Correspondence: B.C. Ginsburg, Department of Psychiatry, UT Health San Antonio, 7703 Floyd Curl Dr., San Antonio TX 78229, ginsburg@uthscsa.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Contributors

B.Ginsburg was responsible for the experimental design, conduct, and manuscript preparation.

SA Levy helped with experimental design and conduct.

RJ Lamb provided conceptual assistance and helped write and edit the manuscript

All authors approved of the final manuscript before submission.

Conflict of Interest

No conflict declared

Keywords

tobacco; alcohol; cue; recovery; relapse; polysubstance use; smoking; drinking

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 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 320–330g.

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 45mg 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 45mg food pellets. Reinforcement was followed by a 30-sec 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-inappropriate 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 Figure 1, the latency to complete the first five responses depended on the reinforcer available across both groups. Latencies were faster on the food lever than on the ethanol lever for every subject, regardless of group assignment.

3.2 Nicotine Effects

As shown in Figure 2a, 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 Nicotine-Ethanol and Nicotine-Food groups, respectively ($t[5]=1.1$, $p>0.3$). When considered in terms of the behavior occasioned by nicotine, responding on the ethanol lever increased with nicotine dose among rats in the Nicotine-Ethanol group. In contrast, responding on the ethanol lever decreased with nicotine dose among rats in the Nicotine-Food group (Figure 2b).

3.3 Varenicline

Varenicline produced dose-dependent increases in nicotine-appropriate responding in both groups (Figure 3, left panel). This resulted in varenicline occasioning ethanol lever responding in the Nicotine-Ethanol group and food lever responding in the Nicotine-Food group. Again, no difference in the potency of varenicline was detected between the two groups. The minimum dose to produce >50% nicotine-lever responding was (median [IQR]) 0.1 [0.1 – 0.3] mg/kg and 0.03 [0.03 – 0.5] for the Nicotine-Ethanol and Nicotine-Food groups, respectively ($t[6]=1.2$, $p>0.2$).

3.4 Ethanol

Ethanol produced vehicle-appropriate responding in both groups at doses of 250 and 500 mg/kg (Figure 3; right panel). No dose effects were observed. As shown in Figure 3 (right panel) this resulted in ethanol reinstating responding for food in the Nicotine-Ethanol group and reinstating responding for ethanol in the Nicotine-Food group.

4. Discussion

As expected, nicotine came to set the occasion for ethanol use and reinstated ethanol responding (Figure 2, open symbols) when nicotine administration preceded ethanol-reinforced responding. In these rats, varenicline also occasioned ethanol responding while ethanol did not (Figure 3, open symbols). However, nicotine can also come to set the occasion for an alternative behavior to responding for ethanol (Figure 2, closed symbols) when nicotine administration preceded food-reinforced responding. In these rats, varenicline occasioned responding for food but not ethanol, while ethanol occasioned responding for ethanol (Figure 3, closed symbols).

Most problem drinkers smoke, smoking is associated with more dangerous patterns of drinking, and nicotine use may threaten recovery (Van Skike et al., 2016). These effects are often thought to be due to nicotine increasing ethanol seeking and use by directly enhancing the reinforcing effect of ethanol (Doyon et al., 2013). For example after a history of nicotine exposure outside of the context where drinking occurs, nicotine re-exposure increases ethanol consumption and preference, but does not affect cue-induced reinstatement of ethanol responding (Clark et al., 2001; Ericson et al., 2000; Kemppainen et al., 2009; Leão et al., 2015; Madayag et al., 2017; c.f. Sharpe and Samson, 2002).

Smoking and drinking most often co-occur in humans, resulting in conditions where each can come to serve as a discriminative stimulus for use of the other (Higgins and Silverman, 1999; Marlatt and Donovan, 2005). Though the role discriminative stimulus effects may play in polysubstance abuse has not been directly examined, there is some evidence this could occur. For example, when nicotine exposure only occurred during ethanol access (and thus may have come to serve as a discriminative stimulus for ethanol availability), re-exposure to nicotine increases ethanol consumption, preference (versus water), and reinstatement (Lê et al., 2003; Smith et al., 1999). Further, when rats were trained to concurrently self-administer an ethanol solution orally and a nicotine solution intravenously, extinction of responding for ethanol was slower when nicotine remained available versus when both ethanol and nicotine were removed (Lê et al., 2010). Each of these results is consistent with nicotine becoming a discriminative stimulus signaling ethanol availability. Here we demonstrate that nicotine can come to serve as a discriminative stimulus for ethanol responding, and will dose-dependently increase ethanol-seeking. Clearly the role that both direct pharmacological and discriminative stimulus effects may play in polysubstance abuse warrants further investigation.

Varenicline can decrease ethanol self-administration in humans and animals, though these effects are dose- and context-dependent (de Bejczy et al., 2015; Falk et al., 2015; Ginsburg and Lamb, 2013, 2014; Steensland et al., 2007). Varenicline can also reduce ethanol reinstatement, however these results were observed in nicotine-naïve subjects so acute behavioral disruption might explain these results, which could change in nicotine-tolerance subjects (Funk et al., 2016; Wouda et al., 2011). Several groups have shown that varenicline has nicotine-like discriminative effects in rodents and primates (Cunningham et al., 2012; de Moura and McMahon, 2017; Jutkiewicz et al., 2011; LeSage et al., 2009). Results of the present study demonstrate that in subjects with a history where nicotine sets the occasion for drinking, varenicline might prompt reinstatement or relapse, due to this nicotine-like discriminative stimulus effect.

Experimenter ethanol administration in the range we examined (0.2–0.6 g/kg) typically reinstates ethanol responding (Bienkowski et al., 2000; Hay et al., 2013; Lê and Shaham, 2002). Indeed, when rats in the Nicotine-Food group were exposed to ethanol, they responded on the ethanol lever. This possibly resulted from ethanol serving as a discriminative stimulus for its own availability. However, a more parsimonious explanation is that ethanol has distinct pharmacological action from nicotine, and thus prompts responding on the vehicle-appropriate lever, because drug discrimination is more accurately a drug/not drug assay, so drugs with distinct pharmacological action from nicotine (including ethanol) prompt responding on the vehicle-appropriate lever (Swedberg, 2016). Thus, ethanol produced vehicle-appropriate responses in both groups, resulting in ethanol responding in the Nicotine-Food group and food responding in the Nicotine-Ethanol group.

Pharmacological specificity of drug-primed reinstatement is typical in common reinstatement procedures (i.e., the self-administered drug or substantially similar drugs reinstate responding while dissimilar drugs do not), and is often used to support the notion of the drug itself, functioning as a conditioned stimulus for self-administered effects of the drug, prompts a return to drug-seeking. However, there is only limited support for the ability

of conditioned stimuli to prompt a return to drug seeking (Lamb et al., 2016a, 2016b, 2017). Rather, the present result suggest that this specificity might simply result from the self-administered drug coming to set the occasion for subsequent use, and thus functioning as a discriminative stimulus rather than a conditioned stimulus (Lamb et al., 2016b; Slikker et al., 1984). However, the discriminative effect of the self-administered drug appears to be far weaker than a discretely trained, experimenter administered discriminative stimulus (nicotine in the present study). This could be due to the relative discriminability of the dose of nicotine (0.4 mg/kg) administered by the experimenter versus the dose of ethanol (approximately 0.25 g/kg) self-administered by the subject. Reliable discrimination of this dose of nicotine can clearly be obtained (e.g., this study; Jutkiewicz et al., 2011; LeSage et al., 2009). However, we are unaware of anyone training a discrimination based on ethanol doses as low as 0.25 g/kg. This might make some question whether this was a pharmacologically meaningful dose. This self-administered dose is similar to that reported in previous studies in which rats had a similar period of limited access (15–30 min) to a similar ethanol solution (Samson et al., 1988a). Further, this dose was similar to the dose self-administered by rats provided ad libitum food and water (Samson et al., 1988b), suggesting this dose has reinforcing effects that do not depend on the caloric value of ethanol alone. In other studies, we measured breath alcohol levels of rats self-administering similar amounts of ethanol over similar time periods, and these breath alcohol levels indicated that the rats had achieved blood levels of 0.03 – 0.06 g/dl (Ginsburg et al., 2005; Ginsburg and Lamb, 2013). Together, these results strongly suggest that doses consumed by rats in the present study over 20 min are likely to produce pharmacological effects strong enough to maintain behavior. Certainly, there is no reason to suspect that nicotine would be ineffective in setting the occasion for the self-administration of even larger amounts of ethanol, though in such a situation, ethanol might also be effective at reinstating responding for ethanol.

The present results indicate that drugs can come to set the occasion for use of other drugs, just like external environmental stimuli. Re-exposure to the occasion-setting drug may then prompt a return to drug-seeking, regardless of any direct interactions between the drugs. This suggests that the pattern and history of co-abuse should be considered when establishing a treatment strategy for this common pattern of substance use disorder.

Acknowledgments

The experiments reported herein were conducted according to the principles set forth in the National Institute of Health. Publication No. 80-23, Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act of 1966 as amended.

Role of Funding Source

Funded by PHS grants AA12337 and AA023102.

References

- Bienkowski E, Kostowski W, Bogucka-Bonikowska A. Reinstatement of ethanol seeking in rats: behavioral analysis. *Pharmacol Biochem Behav.* 2000; 66:123–128. [PubMed: 10837851]

- Center for Behavioral Health Statistics and Quality. Key substance use and mental health indicators in the United States: Results from the 2015 National Survey on Drug Use and Health. Substance Abuse and Mental Health Services Administration; Rockville, MD: 2016. NSDUH Series H-51
- Clark A, Lindgren S, Brooks SP, Watson WP, Little HJ. Chronic infusion of nicotine can increase operant self-administration of alcohol. *Neuropharmacology*. 2001; 41:108–117. [PubMed: 11445191]
- Cunningham CS, Javors MA, McMahon LR. Pharmacologic characterization of a nicotine-discriminative stimulus in rhesus monkeys. *J Pharmacol Exp Ther*. 2012; 341:840–849. DOI: 10.1124/jpet.112.193078 [PubMed: 22438471]
- de Bejczy A, Löf E, Walther L, Guterstam J, Hammarberg A, Asanovska G, Franck J, Isaksson A, Söderpalm B. Varenicline for treatment of alcohol dependence: A randomized, placebo-controlled trial. *Alcohol Clin Exp Res*. 2015; 39:2189–2199. DOI: 10.1111/acer.12854 [PubMed: 26414337]
- de Moura FB, McMahon LR. The contribution of $\alpha 4\beta 2$ and non- $\alpha 4\beta 2$ nicotinic acetylcholine receptors to the discriminative stimulus effects of nicotine and varenicline in mice. *Psychopharmacology (Berl)*. 2017; 234:781–792. DOI: 10.1007/s00213-016-4514-4 [PubMed: 28028600]
- Doyon WM, Thomas AM, Ostroumov A, Dong Y, Dani JA. Potential substrates for nicotine and alcohol interactions: A focus on the mesocorticolimbic dopamine system. *Biochem Pharmacol*. 2013.
- Ericson M, Engel JA, Söderpalm B. Peripheral involvement in nicotine-induced enhancement of ethanol intake. *Alcohol*. 2000; 21:37–47. DOI: 10.1016/S0741-8329(99)00099-3 [PubMed: 10946156]
- Falk DE, Castle IJP, Ryan M, Fertig J, Litten RZ. Moderators of varenicline treatment effects in a double-blind, placebo-controlled trial for alcohol dependence: An exploratory analysis. *J Addict Med*. 2015; 9:296–303. DOI: 10.1097/ADM.000000000000133 [PubMed: 26083958]
- Ferster CB, Skinner BF. *Schedules of Reinforcement*. Appleton-Century-Crofts; NY: 1957.
- Funk D, Lo S, Coen K, Lê AD. Effects of varenicline on operant self-administration of alcohol and/or nicotine in a rat model of co-abuse. *Behav Brain Res*. 2016; 296:157–162. DOI: 10.1016/j.bbr.2015.09.009 [PubMed: 26365457]
- Galanter M, Kleber HD, editors *The American Psychiatric Publishing textbook of substance abuse treatment*. 4th. American Psychiatric Pub; Washington, DC: 2008.
- Ginsburg BC, Koek W, Javors MA, Lamb RJ. Effects of fluvoxamine on a multiple schedule of ethanol- and food-maintained behavior in two rat strains. *Psychopharmacology (Berl)*. 2005; 180:249–57. DOI: 10.1007/s00213-005-2156-z [PubMed: 15682293]
- Ginsburg BC, Lamb RJ. Relative potency of varenicline or fluvoxamine to reduce responding for ethanol versus food depends on the presence or absence of concurrently earned food. *Alcohol Clin Exp Res*. 2014; 38:860–870. DOI: 10.1111/acer.12285 [PubMed: 25396255]
- Ginsburg BC, Lamb RJ. Effects of varenicline on ethanol- and food-maintained responding in a concurrent access procedure. *Alcohol Clin Exp Res*. 2013; 37:1228–1233. DOI: 10.1111/acer.12085 [PubMed: 23413834]
- Hay RA, Jennings JH, Zitzman DL, Hodge CW, Robinson DL. Specific and nonspecific effects of naltrexone on goal-directed and habitual models of alcohol seeking and drinking. *Alcohol Clin Exp Res*. 2013; 37:1100–1110. DOI: 10.1111/acer.12081 [PubMed: 23398292]
- Higgins ST, Silverman K, editors *Motivating behavior change among illicit drug abusers: research on contingency management interventions*. 1st. American Psychological Association; Washington, DC: 1999.
- Jutkiewicz EM, Brooks EA, Kynaston AD, Rice KC, Woods JH. Patterns of nicotinic receptor antagonism: Nicotine discrimination studies. *J Pharmacol Exp Ther*. 2011; 339:194–202. DOI: 10.1124/jpet.111.182170 [PubMed: 21730011]
- Kempainen H, Hyytiä P, Kiianmaa K. Behavioral consequences of repeated nicotine during adolescence in alcohol-preferring AA and alcohol-avoiding ANA rats. *Alcohol Clin Exp Res*. 2009; 33:340–349. DOI: 10.1111/j.1530-0277.2008.00838.x [PubMed: 19032573]

- Lamb RJ, Ginsburg BC, Schindler CW. Conditioned stimulus form does not explain failures to see pavlovian-instrumental-transfer with ethanol-paired conditioned stimuli. *Alcohol Clin Exp Res*. 2017; 41:1063–1071. DOI: 10.1111/acer.13376 [PubMed: 28294355]
- Lamb RJ, Ginsburg BC, Schindler CW. Effects of an ethanol-paired CS on responding for ethanol and food: Comparisons with a stimulus in a Truly-Random-Control group and to a food-paired CS on responding for food. *Alcohol Fayettev N*. 2016a; 57:15–27. DOI: 10.1016/j.alcohol.2016.10.009
- Lamb RJ, Schindler CW, Pinkston JW. Conditioned stimuli's role in relapse: Preclinical research on Pavlovian-Instrumental-Transfer. *Psychopharmacology (Berl)*. 2016b; 233:1933–1944. DOI: 10.1007/s00213-016-4216-y [PubMed: 26800688]
- Lê A, Shaham Y. Neurobiology of relapse to alcohol in rats. *Pharmacol Ther*. 2002; 94:137–156. [PubMed: 12191599]
- Lê AD, Lo S, Harding S, Juzysch W, Marinelli PW, Funk D. Coadministration of intravenous nicotine and oral alcohol in rats. *Psychopharmacology (Berl)*. 2010; 208:475–486. DOI: 10.1007/s00213-009-1746-6 [PubMed: 20013113]
- Lê AD, Wang A, Harding S, Juzysch W, Shaham Y. Nicotine increases alcohol self-administration and reinstates alcohol seeking in rats. *Psychopharmacology (Berl)*. 2003; 168:216–221. DOI: 10.1007/s00213-002-1330-9 [PubMed: 12536264]
- Leão RM, Cruz FC, Vendruscolo LF, de Guglielmo G, Logrip ML, Planeta CS, Hope BT, Koob GF, George O. Chronic nicotine activates stress/reward-related brain regions and facilitates the transition to compulsive alcohol drinking. *J Neurosci Off J Soc Neurosci*. 2015; 35:6241–6253. DOI: 10.1523/JNEUROSCI.3302-14.2015
- LeSage MG, Shelley D, Ross JT, Carroll FI, Corrigan WA. Effects of the nicotinic receptor partial agonists varenicline and cytisine on the discriminative stimulus effects of nicotine in rats. *Pharmacol Biochem Behav*. 2009; 91:461–467. DOI: 10.1016/j.pbb.2008.08.024 [PubMed: 18817808]
- Madayag AC, Czarnecki KS, Wangler LM, Robinson DL. Chronic nicotine exposure initiated in adolescence and unpaired to behavioral context fails to enhance sweetened ethanol seeking. *Front Behav Neurosci*. 2017; 11:153.doi: 10.3389/fnbeh.2017.00153 [PubMed: 28860980]
- Marlatt GA, Donovan DM, editors. *Relapse prevention: maintenance strategies in the treatment of addictive behaviors*. 2nd. Guilford Press; New York: 2005.
- Samson HH, Pfeffer AO, Tolliver GA. Oral ethanol self-administration in rats: Models of alcohol-seeking behavior. *Alcohol Clin Exp Res*. 1988a; 12:591–598. [PubMed: 3067600]
- Samson HH, Tolliver GA, Pfeffer AO, Sadeghi K, Haraguchi M. Relation of ethanol self-administration to feeding and drinking in a nonrestricted access situation in rats initiated to self-administer ethanol using the sucrose-fading technique. *Alcohol Fayettev N*. 1988b; 5:375–385.
- Schuster CR, Thompson T. Self administration of and behavioral dependence on drugs. *Annu Rev Pharmacol*. 1969; 9:483–502. DOI: 10.1146/annurev.pa.09.040169.002411 [PubMed: 4978013]
- Sharpe AL, Samson HH. Repeated nicotine injections decrease operant ethanol self-administration. *Alcohol*. 2002; 28:1–7. DOI: 10.1016/S0741-8329(02)00238-0 [PubMed: 12377355]
- Slikker W, Brocco MJ, Killam KF. Reinstatement of responding maintained by cocaine or thiamylal. *J Pharmacol Exp Ther*. 1984; 228:43–52. [PubMed: 6537976]
- Smith BR, Horan JT, Gaskin S, Amit Z. Exposure to nicotine enhances acquisition of ethanol drinking by laboratory rats in a limited access paradigm. *Psychopharmacology (Berl)*. 1999; 142:408–412. DOI: 10.1007/s002130050906 [PubMed: 10229066]
- Steensland P, Simms JA, Holgate J, Richards JK, Bartlett SE. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, selectively decreases ethanol consumption and seeking. *Proc Natl Acad Sci USA*. 2007; 104:12518–12523. DOI: 10.1073/pnas.0705368104 [PubMed: 17626178]
- Stolerman IP. Components of drug dependence: Reinforcement, discrimination and adaptation. *Biochem Soc Symp*. 1993; 59:1–12.
- Stolerman IP, Kumar R, Reavill C. Discriminative stimulus effects of cholinergic agonists and the actions of their antagonists. *Psychopharmacol Ser*. 1988; 4:32–43. [PubMed: 3293044]

- Swedberg MDB. Drug discrimination: A versatile tool for characterization of CNS safety pharmacology and potential for drug abuse. *J Pharmacol Toxicol Methods*. 2016; 81:295–305. DOI: 10.1016/j.vascn.2016.05.011 [PubMed: 27235786]
- Van Skike CE, Maggio SE, Reynolds AR, Casey EM, Bardo MT, Dwoskin LP, Prendergast MA, Nixon K. Critical needs in drug discovery for cessation of alcohol and nicotine polysubstance abuse. *Prog Neuropsychopharmacol Biol Psychiatry*. 2016; 65:269–287. DOI: 10.1016/j.pnpbp.2015.11.004 [PubMed: 26582145]
- Wouda JA, Riga D, De Vries W, Stegeman M, van Mourik Y, Schetters D, Schoffelmeer ANM, Pattij T, De Vries TJ. Varenicline attenuates cue-induced relapse to alcohol, but not nicotine seeking, while reducing inhibitory response control. *Psychopharmacology (Berl)*. 2011; 216:267–277. DOI: 10.1007/s00213-011-221 [PubMed: 21331520]

Highlights

- Nicotine can serve as a discriminative stimulus for ethanol-maintained responding.
- In this case, nicotine and varenicline prompt ethanol responding; ethanol doesn't.
- Nicotine can also serve as a discriminative stimulus for an alternative to ethanol.
- In this case, nicotine and varenicline decrease ethanol responding.
- One drug can function as discriminative stimuli to enhance use of another.

Figure 1.

Latency to complete the first five responses during training sessions. The first five responses were completed faster on the food lever than on the ethanol lever for every subject, regardless of group assignment. Thus, response rate was lower on the ethanol lever regardless of whether the discriminative stimulus for ethanol was nicotine (Nicotine-Ethanol group) or saline (Nicotine-Food group).

Figure 2.

Nicotine discrimination. Points represent the mean (S.E.M.) number of drug-appropriate responses expressed as a percentage of total responses for each rat. Nicotine produced dose-dependent increases nicotine-appropriate responding (left panel). One group of rats ($n=5$) was trained such that nicotine treatment indicated ethanol availability and vehicle indicated food availability (open symbols). In this group, nicotine treatment resulted in responding on the lever that produced ethanol access. Another group of rats ($n=3$) was trained such that nicotine treatment indicated food availability and vehicle indicated ethanol availability (closed symbols). In this group, nicotine treatment dose-dependently decreased ethanol-lever responding.

Figure 3.

Varenicline and ethanol effects in nicotine discriminations. Points represent the mean (S.E.M.) number of drug-appropriate responses expressed as a percentage of total responses for each rat. Varenicline dose-dependently increased nicotine-appropriate responding, and ethanol produced vehicle-appropriate responding. In rats trained such that nicotine indicated ethanol availability ($n=5$, open symbols), varenicline dose-dependently increased responding on the ethanol lever, while ethanol treatment resulted in responding on the food lever at both doses tested. In contrast, in rats trained such that nicotine indicated food availability ($n=3$, closed symbols), varenicline produced dose-dependent decreases in ethanol lever responding and ethanol produced ethanol lever responding at both doses tested.