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Effects of varenicline on ethanol- and food-maintained responding in a concurrent access procedure

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Abstract

Background—Varenicline has been reported to reduce drinking in smokers, and to selectively decrease responding for ethanol versus alternatives in preclinical studies. Such selectivity may reflect potential therapeutic effects and the involvement of nicotinic receptors in ethanol reinforcement. However, these studies have been conducted with ethanol and an alternative available in isolation or in separate groups, and selectivity can depend on the context in which reinforcement occurs. Whether varenicline selectivity is maintained when ethanol and an alternative are concurrently available has not been reported. To examine the effects of varenicline on ethanol self-administration when an alternative is concurrently available, male Lewis rats ($n=5$) were trained to respond for ethanol and food under a concurrent FR5 FRX schedule where the fixed-ratio for food was adjusted ($FR=25$ or 35) for each subject to provide matched numbers of ethanol and food deliveries during a 30-min session.

Methods—Doses of varenicline ($0.56 - 5.6$ mg/kg) or vehicle were administered 30-min before sessions. Effects of varenicline on responding across the session and during each tenth of the session were compared to responding following vehicle treatment.

Results—Lower doses ($0.56 - 1.0$ mg/kg) of varenicline increased responding for ethanol without affecting responding for food. Higher doses disrupted responding for ethanol and food similarly.

Conclusions—Previous reports of varenicline selectivity on ethanol-maintained responding may not generalize to other experimental conditions. The increase in responding for ethanol following lower doses might be due to enhanced ethanol reinforcement, rate-dependency, or greater perseverance on the initial, ethanol response.

Keywords

operant; alcoholism; nicotine; alcohol

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Introduction

Recent reports suggest that varenicline can reduce drinking both in humans who also smoke and in animal models of alcohol use. In heavy drinking smokers, varenicline reduced ethanol self-administration in a laboratory procedure (McKee et al., 2009). A subsequent placebo-controlled, double-blinded study extended this finding to 64 heavy drinking smokers who were not seeking treatment for their drinking (Mitchell et al., 2012). These studies suggest that varenicline might be an effective treatment for drinking, at least among those who smoke. The utility of varenicline among non-smokers with alcohol dependence or among those wishing to reduce or eliminate drinking has yet to be reported.

Preclinical experiments have provided complimentary results. In mice, a dose of varenicline that reduces ethanol consumption in a two-bottle choice procedure did not affect saccharin consumption (Kamens et al., 2010a). Similarly, doses of varenicline that reduced responding for ethanol did not affect responding for sucrose in a separate group of rats (Steensland et al., 2007). This effect on responding for ethanol was long-lasting, persisting across 6 days of repeated treatment.

However, in light of similar results from studies of selective serotonin reuptake inhibitors (SSRI) for the treatment of alcoholism, some caution interpreting these varenicline results is warranted. Early results with SSRIs were promising, however these studies were conducted in subjects with no intent to reducing drinking (Naranjo et al., 1994; Tiitonen et al., 1996), similar to subjects in the varenicline reports. Later studies with people who wished to reduce or stop drinking showed more modest benefit, and only in particular subtypes of alcoholism (Pettinati, 2001; Chick et al., 2004). Also similar to results obtained with varenicline, early preclinical studies showed selective effects of SSRIs on ethanol- versus alternative-maintained responding in separate groups or when ethanol or the alternative was available in isolation (Lamb and Järbe, 2001; Ginsburg et al., 2005). This selectivity vanished or even reversed in subsequent studies using procedures where ethanol and food were concurrently available (Ginsburg and Lamb, 2006; Ginsburg et al., 2012).

Preclinical reports of selective effects of varenicline on ethanol- versus alternative-maintained behavior could reflect specific effects of varenicline on the reinforcing actions of ethanol, however other explanations are also possible. Due to the nature of the inverted-U shaped curve typical of self-administration studies, higher concentrations of ethanol maintain lower levels of responding than moderate concentrations, even though more ethanol is earned (Lamb and Järbe, 2001). Thus, decreases in responding for ethanol following varenicline treatment could actually reflect a potentiation of ethanol reinforcement rather than blunting of it. Indeed, in mice, varenicline enhances the motoric effects of ethanol (Kamens et al., 2010b). Alternatively, the selective effect seen in separate groups may be due to different ethanol exposure and behavioral histories. Varenicline may be more effective in animals with a history of ethanol self-administration. A procedure in which both ethanol and an alternative are concurrently available is one way to address these issues.

Because the same subject is used to evaluate effects on responding for ethanol and the alternative, the ethanol exposure and behavioral history is matched within the subject. If

varenicline increases the reinforcing effects of ethanol, it should strengthen responding for ethanol versus food. If varenicline decreases ethanol reinforcement, it should weaken responding for ethanol versus food. If varenicline exerts a general disruptive effect, responding for ethanol and food will be similarly affected. However, to date, there are no published reports on the effects of varenicline in a concurrent schedule, where ethanol and an alternative are both available. Here, we examine the effects of varenicline on responding maintained by ethanol or food under a concurrent schedule in which rats earn equal numbers of ethanol and food deliveries during a 30-min session.

Methods

Subjects

Five male Lewis rats (Harlan, Frederick, MD) were trained under the concurrent schedule. Rats weighed ~275g upon arrival, and were allowed at least 1 week to habituate to our facility. Subsequently, daily feeding occurred after the operant session and was limited to maintain their weights at 300-330g throughout the study. Water was always available in rats' home cage.

Apparatus and lever assignment

Five operant conditioning chambers were used (MedAssociates, Georgia, VT), each equipped with an overhead house light, a rear stimulus light, two response levers, two lever lights (one above each lever), a dipper mechanism capable of delivering 0.1 ml of ethanol solution, and a pellet magazine capable of delivering 45 mg food pellets. Dipper presentation and food delivery occurred in a bin between the two levers. Each chamber was housed in a light and sound-attenuating cubicle (MedAssociates, Georgia, VT). Chambers were interfaced with a computer. Commercially available software was programmed to coordinate light presentations, deliver reinforcers, and record lever responses (MedAssociates, Georgia, VT).

Training

Subjects were trained to respond for ethanol using a method originally described by Samson (Samson et al., 1988). Briefly, rats were trained to press the ethanol-associated lever for a sucrose solution. Sucrose was gradually faded out of and ethanol gradually faded into the solution, and the response requirement was increased. Eventually, rats were responding for 8% (w/v) ethanol in water (no sucrose) on a fixed-ratio five (FR5) schedule of reinforcement during a 30-min session. Illumination of the left lever light indicated ethanol availability and completion of the ratio requirement turned off the lever light, illuminated the rear stimulus light, and provided access to the dipper for 30-sec. Once this behavior was stable, a second 30-min session was introduced immediately after ethanol availability in which rats were trained to press the other lever for food pellets (45 mg, Bio-Serv, New Brunswick, NJ). Under this condition, the right lever light was illuminated; indicating food availability and completion of the ratio requirement turned off the lever light and illuminated the overhead house light for 30-sec, and released two food pellets into the hopper. Training proceeded until rats were performing stably on a FR5 schedule during each of two consecutive 30-min sessions (ethanol then food).

Finally, rats were introduced to the terminal schedule: a single 30-min session in which both lever lights were illuminated to signal concurrent availability of food and ethanol. Completion of the ratio requirement on the ethanol-associated lever turned both lever lights off, illuminated the rear stimulus light, and provided dipper access for 30-sec. Completion of the ratio requirement on the food-associated lever turned both lever lights off, illuminated the overhead house light, and provided two food pellets. Following completion of a ratio for food or ethanol, a 30-sec post-reinforcement timeout was present during which lever lights were turned off, and responses had no programmed consequences. There was no penalty for switching levers before the completion of a ratio, and completion of a ratio on one lever did not reset the ratio on the alternative lever. Initially, the response requirement was FR5 for both food and ethanol. Subsequently, FR requirements for food were increased for each rat so that the difference between the number of food and ethanol deliveries was less than 20% of the total number of deliveries earned. Once this criterion was consistently met in a subject for five consecutive days, testing began. The final fixed-ratios for food and ethanol for each rat are shown in Table 1. Training took 4.5 ± 0.7 months (mean $\pm$ SEM).

To assess whether baseline response rate and presentations earned did not change over the duration of the study, paired t-tests were performed on each subject's data from the Thursday that immediately preceded initiation of drug studies and the Thursday that immediately preceded the final determination. No significant changes in food or ethanol presentations nor in response rates for food or ethanol were observed across the duration of the study following vehicle treatment.

Testing

Doses of varenicline (0.56 – 5.6 mg/kg) or saline vehicle were administered on Tuesdays and Fridays. Each dose of varenicline or vehicle was administered 30-min before the subject was removed from his home cage and placed in the operant chamber and the session initiated. Two separate dose effect curves (including vehicle) were established in mixed order. Because an ANOVA revealed no effect of replicate number on total responses for food ($F[1, 44] = 0.1, p > 0.05$) or ethanol ($F[1, 44] = 0.1, p > 0.05$), replicates were averaged for each subject. Saline vehicle was also administered 30-min before sessions on Thursday. Responding during these sessions served as a control for total responses per session following varenicline (or vehicle) administration on Tuesdays and Fridays.

Analysis

For each subject, the number of responses completed on each lever following each dose of varenicline was expressed as a percentage of control responses following vehicle on Thursdays. Effects of varenicline on responding for food versus ethanol were assessed by repeated-measures ANOVA with dose and reinforcement (food or ethanol) as factors. Because an interaction between these factors was present, additional analyses were conducted for each behavior. Effects of each dose on total responses for food and ethanol per session were compared with responding following vehicle using paired t-tests corrected for multiple comparisons with the method of Benjamini and Hochberg (1995).

To assess varenicline effects within the session, responses on each lever during the session were pooled across tenths of each session and averaged across subjects. The 95% confidence interval for responses during each tenth of the session was determined for food and ethanol after vehicle injections on Tuesdays and Fridays, and points that fell outside of these intervals following varenicline administration were considered significantly different from control.

Drugs

Ethanol solutions were made by mixing ethanol (95%, Decon Labs, Inc., King of Prussia, PA) with tap water to achieve a 8% w/v solution. Varenicline was provided by Pfizer, Inc (Groton, CN) and was dissolved in 0.9% saline to provide 1 ml/kg solutions for each dose tested.

Ethanol Consumption

To ensure that rats were consuming the ethanol provided during the session, blood ethanol concentrations were calculated using the method of Javors, et al. (2005) immediately after a 30-min session with no pretreatment. During this session, rats earned 10.3 ± 0.7 (mean $\pm$ S.E.M.) ethanol deliveries, or approximately 0.25 ± 0.02 g/kg ethanol. This resulted in blood ethanol levels of 0.06 ± 0.005 g/dL after this session.

Results

As shown in Table 1, following vehicle administration, the number of deliveries of ethanol and food earned during the session was not significantly different. However, to achieve this, the FR for food was set at either FR25 or FR35. This resulted in a significantly greater number of responses for food versus ethanol during the session.

An ANOVA on the number of fixed-ratios completed (deliveries earned) revealed a main effect of varenicline dose ($F[5, 44] = 21.7, p < 0.05$), but not of reinforcer type ($F[1, 44] = 0.1, p > 0.05$) nor an interaction ($F[5, 44] = 1.2, p > 0.05$). An ANOVA on percent control responding revealed main effects of varenicline dose ($F[5, 44] = 40.1, p < 0.05$) and an interaction between dose and reinforcement ($F[5, 44] = 2.9, p < 0.05$). A main effect of reinforcement was not present ($F[1, 44] = 3.4, p > 0.05$). As shown in Figure 1, the interaction was due to an increase in responding for ethanol following 0.56 and 1.0 mg/kg varenicline. These same doses had no effect on responding for food. Higher doses decreased responding for ethanol and food similarly.

As shown in Figure 2, following vehicle administration, responding in the first tenth of the session was predominately on the ethanol lever. Over the next several tenths of the session, responding switched to the food lever, and responding on the ethanol lever remained at low levels for the remainder of the session. As described in the preceding paragraph and shown for 1.0 mg/kg varenicline in Figure 2, lower doses of varenicline increased responding for ethanol and had no effect on responding for food. These increases in responding for ethanol were due to increased persistence of responding on the ethanol lever during the first half of the session, as shown in Figure 2 (top panel). A trend toward decreased responding on the food lever during the first half of these sessions was also apparent, but these decreases were

not significantly different from responding following vehicle (except for the fourth tenth of the session, top panel). As shown in the lower panel of Figure 2 for 1.78 mg/kg varenicline, responding on the ethanol lever was significantly reduced during the first tenth of the session and several of the subsequent tenths of the session, while decreases in responding for food were apparent throughout the session after the first tenth of the session. Higher doses (3.2 and 5.6 mg/kg) similarly decreased responding for both ethanol and food, and this decrease persisted throughout the session.

Discussion

At lower doses, varenicline increased responding for ethanol without affecting responding for food; higher doses disrupted responding for ethanol and food similarly. The increase in responding for ethanol at lower doses resulted from increased persistence of responding for ethanol early in the session. This responding eventually returned to control levels later in the session. There are several potential explanations for the increase in responding for ethanol following doses of varenicline that do not disrupt responding for food: low doses of varenicline may enhance ethanol reinforcement, varenicline may exert rate-dependent effects, or varenicline may slow response switching, leading to perseveration on the lever where the first response was made. These results indicate that the generality of previously reported selective effects of varenicline on responding for ethanol may depend on the conditions under which the experiments were conducted.

Following vehicle administration, the number of ethanol and food deliveries earned during a session were not significantly different for the group. In order to achieve this, the food FR was set at 5 or 7 times that for ethanol. Thus, the amount of responding for food over the session was substantially higher than for ethanol. However, by adjusting the FR values for ethanol and food in this manner, the number of deliveries of each under control conditions were matched. Moreover, similar proportional changes in responding for food and ethanol resulted in similar proportional changes in the number of deliveries of food and ethanol.

Lower doses of varenicline (0.56 or 1.0 mg/kg) increased responding for ethanol, but had no effect on responding for food. Higher doses (1.78, 3.2, and 5.6 mg/kg) decreased food- and ethanol-maintained responding similarly. This is somewhat inconsistent with other published reports. Kamens et al. (2010a) showed that 2 mg/kg varenicline decreased consumption of 20% (v/v) ethanol, but had no effect on saccharin consumption. This study used a two bottle choice procedure in which either ethanol or saccharin solution was concurrently available with water. Mice in this study were first tested with ethanol available, and then with saccharin available. A 1.0 mg/kg dose of varenicline increased consumption of saccharin and slightly decreased consumption of ethanol, though these effects were not statistically different from consumption following vehicle.

Bito-Onan et al. (2011) showed that 2 mg/kg varenicline decreased operant self-administration of 20% (v/v) ethanol in rats, while 0.8 mg/kg nicotine increased it. Nicotine and varenicline have similar potency in rats and mice (Cunningham and McMahon, 2011; Jutkiewicz et al., 2011) so this might suggest that lower doses of varenicline would have

increased ethanol self-administration had they been tested. Earlier, Steensland (2007) showed that doses of 1 and 2 mg/kg varenicline significantly reduced responding for ethanol, but not sucrose in separate groups of rats. An increase in responding for both ethanol and sucrose was apparent following 0.3 mg/kg varenicline, though this increase failed to reach statistical significance in either group. Effects of 0.56 mg/kg varenicline (which produced significant increases in responding for ethanol but not food in the present study) were not reported.

The lack of a selective effect observed under a concurrent schedule in the present study might reveal limitations of conducting such studies in separate groups like Steensland et al. (2007) or in isolated sessions like Kamens et al. (2010a). For example, we have shown that fluvoxamine (a selective serotonin reuptake inhibitor, SSRI) exerts selectivity similar to that reported for varenicline in separate groups of rats responding for ethanol or food (Lamb and Järbe, 2001) and in rats responding for ethanol or food in separate components of a multiple schedule (Ginsburg et al., 2005). However, this selectivity vanishes or even reverses in rats responding under a concurrent schedule like the one used in the present study (Ginsburg and Lamb, 2006; Ginsburg et al., 2012). Thus, the selective effects reported for drugs like fluvoxamine and varenicline may be limited to particular assay conditions. Better understanding the determinates of selective treatment effects on drinking could help to target treatment to those more likely to benefit and may explain why clinical studies have shown that fluvoxamine and other SSRIs may benefit some, but not all patients wishing to reduce or stop drinking (Pettinati, 2001; Chick et al., 2004).

The increase in responding for ethanol at lower doses of varenicline could be due to an enhancement of ethanol reinforcement. There are reports that suggest a direct role of nicotinic acetylcholine receptors in ethanol reinforcement (Kamens et al., 2010a; Löf et al., 2010). Further, selective decreases in responding for ethanol following drug administration are considered to indicate specific attenuation of ethanol reinforcement (Camarini et al., 2010). For example, Bito-Onan et al. (2011) conclude that increases in operant ethanol self-administration following 0.8 mg/kg nicotine and the reversal of these increases by pretreatment with 2 mg/kg of the putative partial agonist varenicline suggest a specific role of the nicotinic acetylcholine receptors these drugs target in ethanol. However, it should be noted that this same varenicline dose reduced responding by a similar amount in rats that received no nicotine, which suggests that the reversal of the stimulating effect of nicotine could be due to general behavioral disruption by 2 mg/kg varenicline.

Other explanations are also possible for the present results. Because responding for ethanol was maintained at lower rates than food, rate-dependency could explain our findings. Rate-dependent effects have been observed for many drugs, whereby the same dose of a drug can increase responding maintained at lower rates while not affecting behavior maintained at higher rates (Kelleher and Morse, 1968). While rate-dependent effects of varenicline have not been reported, rate dependent effects of nicotine (0.3 and 0.56 mg/kg) have been reported (Raiff and Dallery, 2008), and the present results are entirely consistent with this possibility.

Alternatively (but perhaps not exclusively), varenicline might impair response switching, leading to perseveration on the first response made, which was typically on the ethanol lever in the present procedure. Eventually, rats switched to the food lever, but this switch occurred later in the session following 0.56 and 1.0 mg/kg varenicline, as shown in Figure 2. Because other studies of varenicline on ethanol-maintained behavior occurred in the absence of an explicit alternative reinforced response, such an effect would not have been observed. Additional studies are thus necessary to better understand the reason for the increase in responding for ethanol observed here, but perhaps not in other experimental situations.

Together, these data suggest that the conditions under which responding for ethanol is maintained may influence the apparent selectivity of varenicline effects. This may reflect that conditions under which varenicline exerts a selective effects on responding for ethanol are limited. This may also reflect limitations to the methods currently in use to study potential medications for alcoholism. Certainly preliminary evidence suggests that varenicline is effective in heavy drinkers who smoke with no intention to change their drinking patterns. However, additional studies are required to determine the benefit provided by varenicline to non-smoking drinkers, or to those entering a study with the intent to reduce or stop drinking. The increase in responding for ethanol following lower doses of varenicline is potentially troubling, and may suggest that lower doses of varenicline could exacerbate drinking. These increases may simply reflect the same sort of enhancement of responding for ethanol seen following similar doses of nicotine (Potthoff et al., 1983; Blomqvist et al., 1996; Olausson et al., 2001; Lê et al., 2003). Alternatively, these results may indicate that experimental conditions determine whether selective effects on ethanol- versus alternative-maintained behavior are observed, regardless of the pharmacological targets of the treatment.

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Varenicline provided by Pfizer, Inc.

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Figure 1.

Effects of varenicline on responding for ethanol (○) and food (▲), expressed as a percentage of the total responses for each following vehicle administration on Thursdays in each subject. Points represent mean $\pm$ S.E.M. for five rats. * indicates a significant change from responding following vehicle after Benjamini-Hochberg correction for multiple comparisons ($p < 0.05$).

Figure 2.

Effects of varenicline (1.0 or 1.78 mg/kg) on responding for ethanol (○) and food (▲) during the session. Each point represents the mean number of responses for five rats for each tenth of the session. The filled area represents the 95% confidence interval for responses for food during each tenth of the session after vehicle injections on Tuesdays and Fridays. The hashed area represents the 95% confidence interval for responses for ethanol during each

tenth of the 30-min session after vehicle injections on Tuesdays and Fridays. Points that fall outside of these intervals are considered significantly different ($p < 0.05$).

Table 1
Performance of each subject following vehicle treatment on Thursdays

Subject	Food FR	Ethanol FR	Food Deliveries	Ethanol Deliveries	Total Food Responses	Total Ethanol Responses
1	35	5	22.7	10.8	805.2	54.2
2	25	5	13.0	15.0	325.7	75.0
3	35	5	8.3	9.3	299.0	46.4
4	35	5	15.9	11.0	559.4	55.0
5	25	5	6.8	15.1	171.9	75.5
Average			13.3	12.2	432.2	61.2
95% C.I.			[7.8 – 18.9]	[9.9 – 14.6]	[212.2 – 652.3]	[49.6 – 72.8]