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Effects of chronic fluvoxamine on ethanol- and food-maintained behaviors

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Abstract

Acute treatment with fluvoxamine reduces responding for ethanol more than responding for food. However, pharmacotherapy for alcoholism is likely to require chronic treatment. These experiments were performed to assess the effects of chronic fluvoxamine on ethanol- and food-maintained behaviors. Effects of chronic fluvoxamine (10 and 17.8 mg/kg/day $\times$ 30 days) on ethanol- and food-maintained responding were compared to responding during saline treatment in four Sprague-Dawley rats responding for ethanol and food under a multiple fixed-ratio 5, fixed-ratio 5 schedule. In two subjects, chronic fluvoxamine reduced ethanol-maintained responding more than food-maintained responding; however this effect was transient. In another subject, treatment persistently decreased food-maintained responding relative to ethanol-maintained responding. Finally, in one subject, fluvoxamine nonspecifically disrupted responding for food and ethanol. Similar to results in humans, outbred Sprague-Dawley rats had differential responses to chronic fluvoxamine. The effect was transient in rats that responded favorably (greater reduction of ethanol relative to food responding), while response reductions persisted throughout treatment in rats that responded unfavorably (greater reduction of food relative to ethanol or nonspecific reductions).

Key Terms

alcohol; self-administration; serotonin; selective serotonin reuptake inhibitor; operant; 5-HT

Introduction

Work from several laboratories, including our own, suggests that ethanol-maintained behavior is more sensitive to the effects of selective serotonin reuptake inhibitors (SSRI) than behaviors maintained by alternative reinforcers (Ginsburg et al., 2005; Lamb and Järbe, 2001; Maurel, et al., 1999; Murphy et al., 1985). These effects are not likely due to differences in baseline response-rates, drug history, or training history (Ginsburg et al. 2005;

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Lamb and MacMillan, 1986). Most of the studies performed to examine the effects of SSRIs on ethanol-maintained behavior have used acute treatments. However, the effects of SSRIs over time are of interest as this is a more similar to treatment regimen for alcoholism (Naranjo and Knoke, 2001; Pettinati, 2001).

In one study, several SSRIs were administered via osmotic minipump to C57BL/6 mice and ethanol-maintained responding was monitored over a two week period (Gulley et al., 1995). In this study, these SSRIs each decreased responding for ethanol by approximately 20–50% (Gulley et al., 1995). This effect was transient, however, and responding for ethanol returned to baseline levels after 2–5 days of treatment (Gulley et al., 1995).

Several studies have examined the effects of long-term treatment with SSRIs on human alcohol consumption, often with mixed results. Treatment outcomes in alcoholics are more likely to be favorable when the alcoholism is late in onset, and the baseline rate of ethanol intake is relatively low (Naranjo and Knoke, 2001). In subjects that respond to SSRI treatment, reductions of 15–30% in measures related to alcohol consumption were seen early, but the effect dissipated over the course of the first week (Naranjo and Knoke, 2001). In some patients, SSRIs appear to worsen outcomes (Naranjo and Knoke, 2001; Chick et al., 2004). Thus, in some alcoholics SSRIs are beneficial, but these effects may be fleeting. In other patients, SSRIs worsen the alcoholic condition. Understanding the determinants of SSRI effects on alcohol intake may help improve treatment outcomes in patients.

The present study provides a within-subjects comparison of chronic fluvoxamine effects on responding maintained by food and ethanol. Response rates for each reinforcer have been matched to provide similar behavioral baselines, a known determinant of drug effects on behavior. In previous work from our laboratory, 10 mg/kg fluvoxamine reduced ethanol-maintained responding to a greater extent than food-maintained responding under some conditions; however this effect did not reach statistical significance (Ginsburg et al., 2005). Further, 17.8 mg/kg fluvoxamine reduced ethanol-maintained behavior significantly more than corresponding food-maintained behavior under most conditions examined (Ginsburg et al. 2005). Such selective effects of SSRIs on behavior reinforced by ethanol relative to food have been interpreted to demonstrate a relatively greater role for the serotonergic system in ethanol reinforcement relative to food. To determine if preferential effects on ethanol-maintained responding developed during treatment with 10 mg/kg fluvoxamine and persisted during treatment with 17.8 mg/kg fluvoxamine, the effects of chronic treatment with each of these doses of fluvoxamine on ethanol- and food-maintained responding were compared with effects seen during matched saline treatment.

Methods

Subjects

Four adult male Sprague-Dawley rats, previously used to determine acute effects of fluvoxamine on food and ethanol-maintained responding (Ginsburg et al., 2005), were housed in our institutional animal facility. The room was maintained on a 14/10-hour light/dark cycle and maintained at 20° C. Experiments were conducted during the light cycle. Subjects had access to water *ad libitum* while in their home cages. Subjects were fed approximately 12g of rat chow (Purina, St. Louis, MO) each day following experimental sessions and maintained at a body weight of 300–350g. All experiments were conducted in accordance with the guidelines of the NAS-NRC.

Apparatus

Four operant conditioning chambers were used (Gerbrands, Alderston, MA), each equipped with a house light overhead, 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. Each chamber was housed in a light and sound-attenuating cubicle (Gerbrands, Alderston, MA). The dipper mechanism was directly opposite the ethanol-associated lever, and the pellet magazine was directly opposite the food-associated lever. Chambers were interfaced with an IBM-PC compatible computer. Commercially available software was used to coordinate light presentations, deliver reinforcers, and record lever responses (MedPC, MedAssociates, Georgia, VT).

Training

The training of these subjects has been described elsewhere (Ginsburg et al., 2005). Briefly, rats were trained to press the ethanol-associated lever for a sucrose solution. At first, each lever response resulted in access to the sucrose solution. This response requirement was gradually increased until rats were required to respond five times for each dipper access (fixed-ratio 5). Sucrose was then gradually faded out of and ethanol gradually faded into the solution. Eventually, rats were responding for 8% (w/v) ethanol in water (no sucrose) on a fixed-ratio five (FR5) schedule of reinforcement with a 30-sec post-reinforcer timeout during 5-min sessions. Once this behavior was stable, rats were trained to press the other lever for food pellets (Research Diets, Inc., New Brunswick, NJ). Training proceeded until rats were performing stably on a FR5 schedule with a 30-sec post-reinforcer timeout during a 5-min session. Finally, rats were introduced to the terminal schedule: a 5-min component of Food availability (Food1) followed immediately by a 5-min period of ethanol availability (Ethanol), followed immediately by a second 5-min period of food availability (Food2). Parameters were the same during each component, FR5 response requirement, and a 30-sec post-reinforcer timeout. When the associated reinforcer was not available including the post-reinforcer timeout and other components, lever responses were recorded but not included in calculations and had no programmed consequence,

Treatments

Each subject was treated with fluvoxamine or saline for 30 consecutive days, including weekends and holidays. However, experimental sessions were conducted only on weekdays and non-holidays. Subjects were administered fluvoxamine (i.p) at 10 mg/kg/day 30-min before the start of the experimental session. After 30 days of treatment, fluvoxamine administration was stopped for one month. Subsequently, subjects received 17.8 mg/kg/day fluvoxamine for 30 days as described above. Following a second one month washout period, subjects received daily injections of volume-matched saline for 30 days.

Dose order was chosen based on previous results of acute pretreatment effects of fluvoxamine in the same subjects (Ginsburg et al., 2005). We had some concern about the accumulation of fluvoxamine during daily dosing, so a fixed-order of dosing was implemented, beginning with the minimally effective dose in acute studies, 10 mg/kg. This dose was tested first to determine if selective effects developed over chronic treatment. Acute administration of 17.8 mg/kg fluvoxamine reduced ethanol- and food-maintained responding in these subjects, so this dose was tested second to determine if the acute effects persisted or changed. Finally, a matched volume of saline was administered daily over the same time period to provide a within-subject control for chronic injections.

Analysis

Treatment effects on responding in each component for each subject were compared with a two-way ANOVA with treatment (saline, 10 mg/kg/d, 17.8 mg/kg/d) and component (Food1, Ethanol, Food2) considered as factors. In each case, an interaction between treatment and component was present, allowing analysis of the effects of each treatment on each component, relative to control. Tukey-corrected (TukeyHSD) tests were conducted on

treatment $\times$ component terms to compare treatment effects within each component with the appropriate control condition. Differences were considered significant at $p < 0.05$. Statistics were performed using R for Mac OS X v. 1.14 (The R Foundation for Statistical Computing; <http://www.R-project.org>)

The mean and standard deviation of responding during each component were determined for each subject over the 30 days period of saline treatments. During fluvoxamine treatment, responding during a component that was at least two standard deviations different from the mean for that component during saline treatment was considered significant. The number of days in which responding under each component was different from control was tallied for each subject as a measure of selectivity.

Amount of ethanol earned was determined for each treatment day. The average amount earned was calculated for each treatment, and compared to the 95% confidence interval during chronic saline administration.

Drugs

Fluvoxamine maleate (a gift from Solvay Pharmaceuticals, Weesp, The Netherlands) was dissolved in 0.9% saline and administered (i.p., 1 ml/kg) 30-min prior to start of the first food component. Fluvoxamine doses are expressed as the salt. Sucrose was dissolved in tap water and ethanol (95% (v/v), Aaper Alcohol and Chemical Co., Shelbyville, KY) was added (when appropriate) to obtain a solution with the desired concentration.

Results

Significant interaction effects (treatment $\times$ component) were present for each subject. F-values for interactions were as follows: SD10, $F[4,234]=2.54$; SD8, $F[4, 234]=3.58$; SD9, $F[4,234]=6.24$; SD11, $F[4,225]=3.11$ (all p 's < 0.05). Due to the interaction between treatment and component in each subject, Tukey-corrected t-tests were conducted to compare the effects of each treatment on responding during each component with the respective control.

Subjects responding favorably to treatment

In two rats, chronic fluvoxamine produced reductions in ethanol-maintained responding relative to food-maintained responding; a favorable response to treatment. These effects were transient and largely dissipated over the second week of treatment in both subjects that responded to fluvoxamine favorably (Fig. 1A and 1B).

Subject SD10

In subject SD10, fluvoxamine (10 mg/kg) significantly disrupted responding reinforced by ethanol ($p < 0.0001$), but not responding reinforced by food (Food1 and Food2: p 's > 0.5), when compared with saline treatment. Seven of the eleven days where ethanol responding was significantly reduced were before study day 10. Fluvoxamine (17.8 mg/kg) significantly disrupted responding reinforced by ethanol ($p < 0.005$), but not food (Food1 and Food2: p 's > 0.5) when compared with saline treatment. Ten of the sixteen days where ethanol responding was significantly reduced were before study day 10. As shown in Fig. 1A, both doses of fluvoxamine disrupted responding for food and ethanol during the first two weeks. However, during this period, responding for ethanol was substantially lower than responding for food, with the exception of the first day of treatment with 10 mg/kg when responding in the second food component (Food2) was lower than responding for ethanol.

Subject SD10 earned an average of 0.217 g/kg/day (95% CI: ± 0.003). Average ethanol doses earned during treatment with 10 mg/kg/day and 17 mg/kg/day fluvoxamine were 0.167 and 0.176 g/kg/day, respectively. Both of these average doses fall below the 95% confidence interval for ethanol earned during chronic saline treatment.

Subject SD8

In subject SD8, fluvoxamine (10 mg/kg) significantly disrupted responding reinforced by ethanol ($p < 0.01$), but not responding reinforced by food (Food1 and Food2: p 's > 0.9), when compared with saline treatment. Two of the three days where ethanol responding was significantly reduced were before study day 10. The higher fluvoxamine dose (17.8 mg/kg) did not produce significant effects on any component when compared with saline treatment; however the trend was similar (Fig. 1B). Both days where ethanol responding was significantly reduced were after study day 10, however, there was a tendency for ethanol, but not food, responding to be reduced during the first week.

Subject SD8 earned an average of 0.208 g/kg/day (95% CI: ± 0.014). Average ethanol doses earned during treatment with 10 mg/kg/day and 17 mg/kg/day fluvoxamine were 0.172 and 0.195 g/kg/day, respectively. Average ethanol dose earned during treatment with 10 mg/kg, but not 17.8 mg/kg fluvoxamine fell below the 95% confidence interval for ethanol earned during chronic saline treatment.

Subjects responding unfavorably to treatment

In two rats, chronic fluvoxamine produced either a greater decrease in food-maintained responding relative to ethanol-maintained responding or nonspecific disruption of both behaviors; an unfavorable outcome. These effects persisted throughout the course of treatment (Fig. 1A and 1B).

Subject SD9

In subject SD9, responding for food, but not ethanol was consistently decreased below control levels over the entire month of treatment with 10 and 17.8 mg/kg fluvoxamine (Fig. 1C). Fluvoxamine (10 mg/kg) significantly disrupted responding reinforced by food (Food1 and Food2: p 's < 0.00001) but not responding reinforced by ethanol ($p > 0.9$), when compared with saline treatment. Seven of the twelve days where food responding in the first food component was significantly reduced were after study day 10. Fluvoxamine (17.8 mg/kg) significantly disrupted responding reinforced by food (Food1 and Food2: p 's < 0.00001) but not ethanol ($p > 0.9$), when compared with saline treatment. Thirteen of the eighteen days where food responding in the first food component was significantly reduced were after study day 10.

Subject SD9 earned an average of 0.199 g/kg/day (95% CI: ± 0.016). Average ethanol doses earned during treatment with 10 mg/kg/day and 17 mg/kg/day fluvoxamine were 0.196 and 0.197 g/kg/day, respectively. Neither of these average doses fall outside of the 95% confidence interval for ethanol earned during chronic saline treatment.

Subject SD11

In subject SD11, responding for both food and ethanol was disrupted during treatment with both doses of fluvoxamine (10 mg/kg and 17.8 mg/kg). this non-specific disruption persisted throughout the treatment period with no diminution (Fig. 1D). Fluvoxamine (10 mg/kg) significantly disrupted responding reinforced by food and ethanol (p 's < 0.00001), when compared with saline treatment. Fluvoxamine (17.8 mg/kg) also significantly disrupted responding reinforced by food and ethanol (p 's < 0.00001), when compared with saline

treatment. Responding for ethanol and food was disrupted throughout the study at both fluvoxamine doses, with no obvious change in effect over time.

Subject SD11 earned an average of 0.204 g/kg/day (95%CI: ± 0.011). Average ethanol doses earned during treatment with 10 mg/kg/day and 17 mg/kg/day fluvoxamine were 0.088 and 0.031 g/kg/day, respectively. Both of these average doses fall below the 95% confidence interval for ethanol earned during chronic saline treatment.

Discussion

In the present study, fluvoxamine reduced ethanol-maintained behavior to a greater extent than food-maintained behavior in two of four rats, but these effects dissipated during the second week as responding returned to baseline levels. In another rat, fluvoxamine reduced food-maintained behavior relative to ethanol-maintained behavior, and this effect persisted throughout the duration of treatment. In the fourth rat, fluvoxamine nonspecifically disrupted responding maintained by both ethanol and food throughout treatment, although responding returned to baseline levels immediately upon discontinuation (data not shown). The results of the present study are generally in agreement with previous studies conducted in animals and humans, indicating that chronic SSRI treatment may transiently reduce ethanol intake in some animal subjects and alcoholics, while some may derive no benefit or even detrimental effects (Chick et al., 2004; Gulley et al., 1995; Naranjo and Knocke, 2001).

Sprague-Dawley rats (an outbred strain) displayed three distinct responses to chronic fluvoxamine treatment in the present study. Half of the rats tested displayed reduced ethanol responding compared with food. This is similar to our previous observations (Ginsburg et al., 2005). This is also similar to outcomes in some human studies (Naranjo and Knocke, 2001; Pettanati, 2001). In one subject, fluvoxamine reduced food responding more than ethanol responding. In this subject, ethanol responding was relatively higher than food responding (SD9, Fig. 1C). Similarly, alcoholics with relatively high baseline ethanol intake respond less favorably to SSRI treatment than those with lower baseline rates (Chick et al., 2004; Naranjo and Knocke, 2001). Finally, fluvoxamine nonspecifically disrupted responding for both food and ethanol in one subject (SD11, Fig. 1D). In some alcoholics, SSRI treatment is neither beneficial nor detrimental (Naranjo and Knocke, 2001).

Subjects in this study earned an average of 0.207 (± 0.004) g/kg/day. While this may appear to be a low dose at first blush, it is important to consider that that ethanol was earned and available only during a 5-min component. Thus, when the unit dose of ethanol is considered over time, the dose earned per minute equals or exceeds that reported in previous studies of ethanol self-administration in rats (Maurel et al., 1999). Further, blood ethanol levels achieved after 5-min of responding for ethanol under this procedure have been reported to produce behavioral effects and maintain responding (Ginsburg et al., 2005).

Ethanol-maintained responding was reduced 11–44% more than food-maintained responding in subjects SD10 and SD8 during the first nine days of chronic fluvoxamine treatment compared to corresponding control (Fig. 1A, 1B). This is very similar to the effect size we reported following acute fluvoxamine treatments (Ginsburg et al., 2005). Gulley et al., (1995) also reported similar results during the first 2–3 days of chronic SSRI treatment in mice. Further, this is similar to the degree of ethanol intake reduction during the first week (15–30%) seen in humans that respond to SSRI treatment (Naranjo and Knocke, 2001).

The preferential effect of fluvoxamine on ethanol-maintained responding was transient in both subjects that had this response. In these subjects, responding for both food and ethanol returned to baseline levels after nine days of treatment. The time course of the development

of this behavioral tolerance is similar to results in mice and humans (Gulley et al., 1995; Naranjo and Knocke, 2001). However, no tolerance developed in one subject whose responding for food was more sensitive to fluvoxamine than responding for ethanol, nor in another subject whose responding was non-selectively disrupted by fluvoxamine treatment. Thus, preferential effects of fluvoxamine on ethanol-maintained behaviors appear short-lived, while selective disruption of responding for food or non-selective disruption of responding for food and ethanol (which may represent less-favorable outcomes) appear to persist throughout 30 days of treatment. This appears to be the case in humans, as well (Chick et al., 2004; Naranjo and Knocke, 2001). Although one must be cautious when extrapolating from animal to human data, the similarities in the magnitude and duration of the preferential effect of fluvoxamine on ethanol-maintained behavior could reflect common mechanisms in rats and humans.

Conclusion

This report, in agreement with human studies, suggests that the effects of fluvoxamine on ethanol-maintained behaviors can differ among individuals (Naranjo and Knocke, 2001). Further investigations into the determinants of the response to fluvoxamine could be instructive in understanding the mixed human data (Naranjo and Knocke, 2001; Pettanati 2001). Although differences due to different relative baseline levels of ethanol intake cannot be ruled out (Naranjo and Knocke, 2001), biological factors may also be important, as demonstrated in studies in rodents, primates, and humans (Barr et al. 2003; Elkins et al., 2000; Mantere et al., 2002). Thus, future studies designed to investigate potential behavioral and biological differences that influence the response to chronic SSRI treatment could yield valuable insight into human treatment outcomes. Further, future studies could provide a better understanding of the differential tolerance that appears to develop during chronic fluvoxamine treatment.

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Figure 1.

The effect of chronic fluvoxamine (10 mg/kg/day or 17.8 mg/kg/day) in four subjects responding for ethanol (□) and food (Food1:Δ Food2:▽) under the mult FR FR schedule. Mean ($\pm$ 95% confidence limits) for one month of saline treatment for each component is graphed on the left abscissa. Days following initiation of treatment (7 treatment days/week, 5 experimental days/week) with fluvoxamine are graphed on the right abscissa. Closed symbols represent data points that are at least two standard deviations below the respective control.