Published in final edited form as:

Exp Clin Psychopharmacol. 2006 November ; 14(4): 483–492. doi:10.1037/1064-1297.14.4.483.

Fluvoxamine effects on concurrent ethanol- and food-maintained behaviors

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Abstract

In previous studies, the selective serotonin reuptake inhibitor fluvoxamine preferentially reduced responding for ethanol compared with responding for food under conditions in which each was available alone in separate groups or in the same subjects under a multiple schedule in which baseline response rates were matched. The impact of providing concurrent access to food on pharmacological effects on ethanol self-administration remains largely unexplored. In this study, acute doses of fluvoxamine (3.0–17.8 mg/kg) were administered 30-min before the experimental session to Lewis rats responding under a concurrent fixed-ratio, fixed-ratio schedule of ethanol and food presentation. Ratios for food were adjusted for each subject to provide matched rates of food and ethanol reinforcement across the 30-min session. Although the number of ethanol and food deliveries did not significantly differ under baseline conditions, response rates did differ. Following fluvoxamine administration, responding for food was decreased more than responding for ethanol. This differential effect did not appear to be related to response rate or fixed-ratio size. Thus, the selectivity of fluvoxamine on ethanol- versus food-maintained responding depends upon the context in which the behavior occurs. Such results may help explain inconsistencies between preclinical results and those in humans, and could provide insight into the behavioral determinants of pharmacological effects on ethanol self-administration.

Keywords

operant; alcoholism; alcohol; SSRI; lever-press; Lewis rat; concurrent schedule; food

The development of methods to study ethanol-maintained behavior has led to a greater understanding of the neurobiology of as well as a means for searching for potential treatments for alcoholism (Meisch and Henningfield, 1977; Samson, 1986). Methods of studying ethanol self-administration have been refined since the earliest reports (*see* Samson et al., 2000). Among these refinements is the incorporation of the concept of a therapeutic index. For example, a potential pharmacotherapy for alcoholism should reduce behavior maintained by ethanol, but not (or at least to a lesser extent) reduce behavior maintained by

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other events. Further, more attention has been focused on controlling parameters known to be determinants of the behavioral effects of drugs such as baseline response rate or drug history. While these refinements in current methods of studying ethanol-maintained behavior have aided in their application to studies of the neurobiology of alcoholism, the utility of these models in identifying specific neural substrates for ethanol-reinforcement or for predicting potential therapeutic agents remains largely unrealized.

Alcoholism is a behavioral disorder in which seeking and consumption of ethanol occupies an increasing proportion of time and resources of the afflicted. Such problematic behaviors occur in the presence (and often to the exclusion) of other important things such as food, family, or career. Thus, it is important to explore the impact of other concurrently available reinforcing events on behaviors maintained by ethanol, and how the presence of these other concurrently available events might influence the selectivity of pharmacological treatments.

Indeed, responding for ethanol may be more resistant to drug-induced decreases when an alternative is concurrently available. Samson and Grant (1985) used a concurrent fixed-ratio schedule (FR) in rats to explore the effects of chlordiazepoxide on ethanol self-administration. In a counterbalanced design, subjects responded on one lever for ethanol (FR8), and on the other for either water or sucrose (FR8). When rats were responding concurrently for sucrose, responding for ethanol was decreased relatively less following chlordiazepoxide administration than when rats were responding concurrently for water (Samson and Grant, 1985). Because the rats in this study were not water-deprived, it is unclear that water was reinforcing lever-pressing (as evidenced by low rates of responding on the water-associated lever). The increased resistance to disruption of responding for ethanol by chlordiazepoxide when sucrose was concurrently available did not appear to be due to changes in the baseline rate of responding for ethanol as baseline rates did not differ between conditions (Samson and Grant, 1985).

Early studies suggested that selective serotonin reuptake inhibitors (SSRI), including fluvoxamine, could reduce ethanol intake in laboratory animals (Murphy et al., 1985; Maurel et al., 1999). Further research indicated that fluvoxamine could selectively reduce operant responding maintained by ethanol when compared with responding maintained by food (Lamb and Järbe, 2001). A subsequent within-subjects study replicated this finding in subjects responding for ethanol and food under a multiple fixed-ratio schedule designed to match baseline response rates and experimental histories of subjects (Ginsburg et al., 2005). Thus, fluvoxamine appears to preferentially reduce responding for ethanol relative to food, and this effect is not easily explained by differences in subjects' baseline response rates, age, or experimental history.

Based on these studies, fluvoxamine would appear to target brain systems preferentially involved in ethanol reinforcement, and could be considered a candidate pharmacotherapy for alcohol abuse or addiction. However, in humans, fluvoxamine is only effective in a subset of alcoholics (Naranjo and Knocke, 2001; Pettinati, 2001). Further, such beneficial effects tend to dissipate after 7-9 days of chronic treatment; an effect that has also been observed in mice and rats treated with fluvoxamine or other SSRIs (Pettinati, 2001; Gulley et al., 1985; Ginsburg and Lamb, *in press*). Thus, selective effects of fluvoxamine in preclinical studies do not necessarily predict broadly effective therapeutic effects in alcoholics. Such results, while discouraging, should inspire researchers to improve the models currently used.

The present study was designed to study the impact of providing concurrent access to ethanol and food on the rate-decreasing effects of fluvoxamine. Previous research from our laboratory demonstrated that fluvoxamine preferentially decreases responding for ethanol relative to food when each is available in isolation or sequentially under a multiple schedule

(Lamb and Järbe, 2001; Ginsburg et al., 2005). In the present study, rats were trained to respond on a concurrent fixed-ratio schedule of ethanol and food reinforcement. Fixed-ratios for food were adjusted for each subject so that the baseline number of ethanol and food presentations earned each day was similar, and dose-effects curves for fluvoxamine were determined.

Methods

Subjects

Eight adult male Lewis rats (Harlan, Indianapolis, IN) served as subjects. Upon arrival at our institution, rats were singly-housed, handled daily, and allowed *ad libitum* food and water for one week. The room was maintained on a 14/10-hour light/dark cycle and maintained at 20° C. Experiments were conducted during the light cycle. Following a week of acclimation, the daily chow allotment was reduced to approximately 12g of rat chow (Purina, St. Louis, MO) each day following experimental sessions to maintain body weights of 300-350g. Subjects had access to water *ad libitum* while in their home cages.

Apparatus and lever assignment

Eight 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 an IBM-PC compatible 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 (1986). 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 with a 30-sec post-reinforcer timeout 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. 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, Research Diets, Inc., 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, illuminated the overhead house light, and released two food pellets into the hopper. Training proceeded until rats were performing stably on a FR5 schedule with a 30-sec post-reinforcer timeout 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 reinforcers 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 ensure 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 ($p > 0.35$ for each test).

Testing

Doses of fluvoxamine (3-17.8 mg/kg) or saline vehicle were administered on Tuesdays and Fridays. Each dose of fluvoxamine 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, and the results of the double determinations for each dose or vehicle were averaged for each subject. Saline vehicle was also administered 30-min before sessions on Thursday.

Analysis

Response rate was calculated by dividing number of responses on each lever by the total time available during the session (excluding post-reinforcement timeout periods). A repeated-measures analysis of variance (ANOVA) was performed on raw data for reinforcer deliveries or response rate. Reinforcing event (food or ethanol) and fluvoxamine dose were considered as factors. Tukey-Kramer posttests were performed to determine effects that significantly differed from the control condition. Paired t-tests were performed on effects on number of presentations earned at individual doses to determine doses of fluvoxamine that had differential effects on responding for ethanol and food.

Within-session drug effects were calculated by recording responses in each tenth of the experimental session (180-seconds) following each dose of drug or vehicle. Double determinations for each dose were averaged for each subject. To allow comparison between behaviors maintained by food or ethanol, responses following each dose of fluvoxamine were expressed as a percentage of the number of responses in the time-matched bin following saline for each subject. A three-way repeated-measures ANOVA was performed on the normalized results with Time, Dose, and maintaining event (Food or Ethanol) as measures.

ED50s

Group ED50s for fluvoxamine effects on responding for food or ethanol were calculated with the method described by Tallarida and Murray (1987). Effects of fluvoxamine on response rates and number of food and ethanol deliveries were expressed as a percentage each subject's Tuesday/Friday vehicle control values. A linear regression was performed on group data, with dose converted to LOG(dose). Unless necessary to define the linear portion of the curve at 50%, doses that produced less than 20% or greater than 80% of the maximal response were excluded from the regression. The dose required to produce half of the maximal (control) response (ED50) was thus derived for each condition.

Linear regressions

ED50s for fluvoxamine effects on responding for food and ethanol were also calculated for individual subjects using the average of each subjects' double determination. Again, unless necessary to define the linear portion of the curve at 50%, doses that produced less than 20% or greater than 80% of the maximal response were excluded from the regression. Linear regressions were performed on these results to assess potential correlations for ED50 versus response rate for food- and ethanol-maintained responding, and ED50 versus fixed-ratio size for food-maintained responding.

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 session. 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.

Software

ANOVA and Tukey-Kramer posttests were performed with NCSS version 2004, Kaysville, Utah USA, www.ncss.com. Paired t-tests and linear regressions were performed using GraphPad Prism version 4.00 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com. Graphs were prepared with GraphPad Prism version 4.00 for Windows and R for OSX, Version 2.2-1 2005-12-20, R Foundation for Statistical Computing, Vienna, Austria, <http://www.R-project.org>.

Results

Baseline patterns of behavior

As shown in Table 1 and Fig. 1A, The mean numbers of food and ethanol presentations were not different following saline administration. Although the number of food and ethanol presentations did not differ significantly (Food: 20 ± 2 versus Ethanol: 21 ± 1 deliveries – $t(7) = 0.53$), rates of responding for food were higher than for ethanol (Food: 0.80 ± 0.1 versus Ethanol: 0.21 ± 0.03 ; $t(7) = 7.6$, $p > 0.05$). This is not surprising given the larger fixed-ratios assigned to food than to ethanol in each subject (Table 1). Thus, over the experimental session, the number of food and ethanol deliveries were matched, although the response rates for food were greater than for ethanol. Under baseline conditions, the patterns of responding for food and ethanol were similar and steady across the experimental session (see SAL curves in Fig. 2).

Fluvoxamine effects were selective for food-maintained behavior

Behavior maintained by food was more sensitive to reduction by fluvoxamine. This finding was borne out by three lines of evidence: (a) the minimally effective dose of fluvoxamine was lower for number of food presentations and response rate compared with ethanol-maintained behavior; (b) the effects of 10 mg/kg fluvoxamine were greater on number of food presentations and response rate relative to effects on ethanol-maintained behavior; (c) the ED50 for fluvoxamine effects on number of food presentations and response rate was significantly lower than the ED50 for comparable ethanol-maintained behavior. These effects were seen at both the group and individual subject level. These effects did not appear to be due to an interaction between fluvoxamine timecourse and the within-session pattern of responding for food and ethanol. Nor were these effects easily explained by other known determinates of drug effects on behavior such as baseline response rate or fixed-ratio size.

Lower doses of fluvoxamine reduced food-maintained behavior relative to control

On average, fluvoxamine was more potent at reducing responding for food than responding for ethanol, as shown in Fig. 1. Two-factor within-subject ANOVA revealed a significant interaction between fluvoxamine dose and the maintaining event on measures of number of presentations earned and response rate ($F[4,28] = 3.29$ and 16.05 , $p < 0.05$), indicative of differential fluvoxamine dose effects depending on the maintaining event. Fluvoxamine dose had a significant effect on the number of food presentations ($F[4,28] = 30.34$, $p < 0.05$) and response rate ($F[4,28] = 19.25$, $p < 0.05$). Similarly, fluvoxamine dose had a significant effect on number of ethanol presentations ($F[4,28] = 17.90$, $p < 0.05$) and response rate ($F[4,28] = 12.04$, $p < 0.05$). Fluvoxamine dose-dependently decreased responding for both food and ethanol. Tukey-Kramer tests revealed that 5.6, 10, and 17.8 mg/kg fluvoxamine treatments significantly reduced both the number of food pellets earned and response rate for food compared with control ($p < 0.05$). However, only doses of 10 and 17.8 mg/kg fluvoxamine altered the number of ethanol dippers earned and ethanol response rate compared with the control condition ($p < 0.05$).

Fluvoxamine reduced food-maintained behavior to a greater extent than ethanol-maintained behavior at moderate doses

When behaviors maintained by ethanol and food were compared across fluvoxamine doses, food-maintained responding was still more sensitive to the effects of fluvoxamine than ethanol-maintained responding. A two-tailed paired t-test revealed that 10 mg/kg fluvoxamine had a greater effect on number of food deliveries compared with number of ethanol deliveries earned ($t(7) = 2.26$, $p < 0.05$). As shown in Fig. 2, a dose of 10 mg/kg fluvoxamine decreased response rate (expressed as percent control) for food more than for ethanol ($t(79) = 3.74$, $p < 0.005$).

Fluvoxamine ED50 was lower for food-maintained behavior than for ethanol-maintained behavior

Fluvoxamine more potently decreased the number of food presentations earned than the number of ethanol presentations earned, as shown in Fig. 1A. The ED50 for fluvoxamine effects on the number of food presentations for the group was 6.8 mg/kg [95% C.L.: 6.2 – 7.3], while the ED50 for number of ethanol presentations for the group was 10.6 mg/kg [95% C.L.: 8.3 – 13.6]. The ED50 for food-maintained responding was significantly lower than ED50 for ethanol-maintained responding ($p < 0.05$). Six of the eight rats had a lower ED50 for number of food presentations compared with ethanol presentations (Table 1).

Similarly, as seen in Fig. 1B, the potency of fluvoxamine to reduce response rate was significantly greater for food than for ethanol. When fluvoxamine effects on group response-rate were considered, the ED50 for reducing food responding was 5.6 mg/kg [95% C.L.: 4.6 – 6.8], while the ED50 for reducing responding for ethanol was 7.3 mg/kg [95% C.L.: 6.0 – 8.9]. Seven of eight rats had a lower ED50 for food response-rate compared with response-rate for ethanol. (Table 1).

Thus, analyzed in several ways, food-maintained behavior is decreased by fluvoxamine more or at lower doses than ethanol-maintained behavior under the present experimental conditions. However, these effects could be influenced by an interaction between the timecourse of fluvoxamine effects and the within-session pattern of responding for food or ethanol. Additionally, the selective effects of fluvoxamine on responding for food could be influenced by such known determinants of behavioral effects of drugs such as differences in response rate or differences in fixed-ratio size.

Fluvoxamine effects on responding for ethanol and food were consistent within-session

Fluvoxamine effects on responding were consistent across the entire session as shown in Fig. 2. A three-way repeated-measures ANOVA revealed no interaction among Dose, Time, and maintaining event. Nor were interactions present between Time and Dose or Time and maintaining event. Time was also not significant as a main effect. Thus, there was no effect of time. A significant interaction was present between Dose and maintaining event ($F[4, 28] = 3.82, p < 0.05$); an effect expected based on whole session analyses. Main effects of Dose, and maintaining event were significant ($F[4, 28] = 18.92$; $F[1, 7] = 16.17$, respectively $p < 0.05$). A two-tailed paired t-test revealed that the effect of 10 mg/kg fluvoxamine was greater on responses for food relative to ethanol when expressed as a percentage of control ($p < 0.05$). Thus effects of fluvoxamine were consistent across time, and as described in the previous section, the effect of fluvoxamine was greater on food-maintained behavior compared with ethanol-maintained behavior.

Rate-dependency does not appear to account for selective effects of fluvoxamine on responding for food

While the higher rate behavior (maintained by food) was more affected by fluvoxamine than the relatively lower rate behavior maintained by ethanol, no relationship was present (slope did not differ from zero) between response rate and ED50 across both conditions (food and ethanol reinforcement, shown by the dashed line in Fig. 3). Further, when only ethanol-maintained responding is considered (filled squares in Fig. 3), lower response rates were more sensitive to fluvoxamine than higher rates, opposite of results expected for rate-dependent drug effects. A similar relationship was also present for food-maintained responding (filled triangles in Fig. 3), although the regression had more variance. These results are inconsistent with fluvoxamine exerting typical rate-dependent effects, which would explain the differential effects of fluvoxamine on behaviors maintained by food and ethanol. Thus, the difference in the ED50s for ethanol and food-maintained responding does not appear to depend on differences in the baseline rate of responding.

Ratio size does not appear to account for selective effects of fluvoxamine on responding for food

Fixed-ratio size does not appear to explain these results, although the behavior maintained under the larger FR (food) was more sensitive to fluvoxamine effects than the behavior maintained under the smaller FR. A linear regression between FR size and either fluvoxamine ED50 for food presentations or fluvoxamine ED50 for response rate across the subjects yielded slopes that did not differ from zero. When the ED50 for number of reinforcers presented was considered, the regression was [$Y = -0.21X - 13.24, r^2 = 0.31$]; when the ED50 for response rate were considered, the regression was [$Y = -0.06X - 7.17, r^2 = 0.30$].

Discussion

The major finding of the present study is that under a concurrent schedule of ethanol and food availability, fluvoxamine decreased responding for food more or at lower doses than responding for ethanol. In contrast, in previous studies in which ethanol and food were available under either a multiple schedule or in separate groups, fluvoxamine had the opposite effect, decreasing responding for ethanol to a greater extent or at lower doses than responding for food (Lamb and Järbe, 2001; Ginsburg et al., 2005). The increased resistance to acute fluvoxamine effects on responding for ethanol relative to responding for food suggests that the context in which responding occurs may be an important determinant of the direction and extent of selective treatments effects.

Several lines of evidence demonstrate that food-maintained behavior was more sensitive to fluvoxamine compared with ethanol-maintained behavior in the present study. The ED50 for fluvoxamine effects on number of presentations earned and response rate was significantly lower when the maintaining event was food compared with ethanol. Food-maintained behavior (measured in number of presentations earned and average response-rate) was reduced compared with control at lower doses than ethanol-maintained responding. Food-maintained behavior was also reduced to a greater extent than ethanol-maintained behavior following a 10 mg/kg fluvoxamine dose. These effects do not appear to be due to an interaction between the timecourse of fluvoxamine and the within-session pattern of responding. Following vehicle administration, food and ethanol were similarly distributed throughout the experimental session. There were no interactions between Dose and Time or maintaining event and Time, nor was there a significant main effect of Time. Effects of fluvoxamine are not likely due to rate dependency as the relationship between baseline response rate and fluvoxamine ED50 for each maintaining event were opposite to those expected due to rate-dependency. Fixed ratio size is unlikely to be the cause of the observed effects as no relationship was present between ratio size and ED50. Thus, fluvoxamine effects appear to be reinforcer specific rather than due to an interaction between drug time course and differential response patterns for food and ethanol or other known determinates of behavioral effects of drugs.

Drug addiction occurs in the presence of other competing events. When the seeking and consumption of drug predominates over other activities, addiction can ensue. Current methods of assessing ethanol reinforcement have provided a framework to begin to understand processes involved in the maintenance of ethanol-reinforced behaviors and the subsequent development of addiction. However, most of these methods provide ethanol availability in isolation. Studies have demonstrated that pretreatment with some pharmacologic agents can reduce ethanol intake to a greater extent than food (or sucrose) intake (Czchowski, 2005; Lamb and Järbe, 2001; Freedland et al., 2001). Such results have led some to conclude that the targets of these pharmacologic agents are preferentially involved in the mechanisms of ethanol-reinforcement and could be viable candidates as pharmacotherapeutic agents for alcoholism. However, some evidence exists that providing a concurrently available alternative to ethanol can alter the effects of drugs when compared with responding for ethanol in isolation.

Samson and Grant (1985) examined the effects of chlordiazepoxide on responding for ethanol when either water or a weak sucrose solution was concurrently available. Rats were not water-deprived, and when water was the available alternative, response-rates were low on the water-associated lever, and water was not clearly reinforcing lever-pressing (Samson and Grant, 1985). However when sucrose was available, response rates on the sucrose-associated lever were similar to response-rates for ethanol and responding for ethanol was relatively more resistant to decrements following acute chlordiazepoxide treatments (Samson and Grant, 1985).

Similarly, responding for ethanol was more sensitive to naltrexone than responding for food under independent progressive ratios (Rodefer et al., 1999). However, the effects of a related drug (naloxone) were far less robust under a concurrent variable-interval variable-interval (VI VI) schedule for both ethanol and food (Petry, 1995). Thus, in this study ethanol self-administration was relatively less sensitive to naltrexone-like effects when an alternative reinforcer was concurrently available.

Similar results demonstrating reduced sensitivity to pharmacologic disruption in the presence of an alternative have also been described for other drug-maintained behaviors such as responding for deliveries of cocaine. Buprenorphine, a mu-opioid agonist,

selectively reduced cocaine self-administration compared with food in monkeys performing under a multiple second-order schedule (Lukas et al., 1995). However, subsequent studies in monkeys performing under a concurrent VI VI schedule of cocaine and food reinforcement with well-matched baseline rates revealed no such selective effect during chronic treatment with another mu-opioid agonist, methadone (Negus and Mello, 2004).

Taken together with our results, the studies described above suggest that the sensitivity to pharmacologic disruption of behavior maintained by drugs can be reduced in the presence of an alternative. There are several possible explanations for this observation. Results of studies utilizing food-reinforcement suggest that behavioral momentum may influence pharmacologic disruption of drug-maintained behavior. Samson and Grant (1985) suggested that stimulus control could be altered when an alternative is concurrently available, which could impact the effects of pharmacologic agents on drug-maintained behavior. They also suggest that the presence of a concurrently available alternative could alter the demand curve for self-administered drug. Additionally, rate-dependency and fixed-ratio size could alter the effects of pharmacologic agents on drug self-administration.

Operant responding is more resistant to disruption (by prefeeding or extinction) following additional sources of reinforcement. Nevin (1974) has described his Behavioral Momentum theory in a seminal work. Nevin proposes that behavioral momentum imparts behavior with a resistance to change. A behavior with high behavioral momentum would be expected to be more resistant to changes due to prefeeding or extinction. The degree of behavioral momentum and thus resistance to change appears to be determined by the overall rate of reinforcement, and is largely independent of baseline response rate. The addition of another source of reinforcement increases behavioral momentum by increasing the overall rate of reinforcement. Although much of Nevin's work was performed with food reinforcement, Shahan and Burke (2004) recently demonstrated similar results for ethanol-maintained responding when non-contingent food is provided simultaneously.

The behavioral momentum theory of Nevin was derived from disruption of food-maintained behaviors due to prefeeding or extinction conditions (Nevin et al 1990; Cohen, 1986). While the impact of behavioral momentum on the effects of pharmacologic agents may depend on the drug studied, the effects of fluoxetine (which is of the same pharmacological class as fluvoxamine) appear to be influenced by behavioral momentum (Harper, 1990; Cohen, 1986).

In the present study, behavioral momentum for ethanol-maintained behavior and for food-maintained behavior was equal. Under this condition of equal behavioral momentum, food-maintained behavior was more sensitive to the effects of fluvoxamine than ethanol-maintained behavior. However, when food- and ethanol-maintained behaviors were studied under the multiple schedule (Ginsburg et al., 2005), behavioral momentum for each behavior was relatively lower, and was likely decreased more for ethanol-maintained behavior than for food-maintained behavior. This seems reasonable as the added value of the food deliveries to the ethanol-lever stimulus complex should be greater than the added value of the ethanol deliveries to the food-lever stimulus complex as a larger fixed-ratio for food was needed to equate the number of presentations earned. Further studies in which the rates of food and ethanol reinforcement are varied and responding is subjected to a fluvoxamine challenge are necessary to clarify these points.

Stimulus control of ethanol-reinforced operant responding may be altered in the concurrent condition, when compared with independent or multiple component paradigms. Samson and Grant (1985) discussed the results of their experiment in terms of stimulus-control. In their study, ethanol-maintained responding was more resistant to chlordiazepoxide disruption

when presented concurrently with sucrose rather than water. The authors concluded that if the addition of concurrently available sucrose increased stimulus-control, their results would be consistent with other studies on the effect of external stimulus control. However, others have suggested that the addition of a concurrently available reinforcer results in weakened stimulus control (Nevin et al. 1990). Weakened stimulus control might be expected to result in greater sensitivity to pharmacologic agents. Relatively lower stimulus control can reduce the effects of amphetamine and cocaine. However, stimulus control has a lesser impact on effects of pentobarbital, chlorpromazine, and promazine (Laties, 1972; Katz, 1983). No data is available on whether stimulus control modulates the effects of fluvoxamine or related drugs; therefore additional studies are necessary to interpret the present results in terms of altered stimulus control.

Another possible explanation suggested by Samson and Grant (1985) that could relate to our results is that the addition of concurrent food availability alters the demand curve for ethanol (Hursh, 1993). Concurrent access to food could increase the elasticity of demand for ethanol. Other studies in which ethanol and sucrose were concurrently available and FR requirements were varied support such ethanol/sucrose substitution (Samson et al., 1982). However, how might explain our results or those of Samson and Grant are not clear. Reducing the demand for ethanol should make ethanol *more* sensitive to disruption by fluvoxamine, however in both the present report and that of Samson and Grant (1985), ethanol-maintained behavior was relatively *less* sensitive to drug-induced disruption in the presence of a concurrent reinforcer.

It is unlikely that the effects of fluvoxamine are rate-dependent. The behavioral effects of some drugs depend on the control response rate (Dews and Wenger, 1977). Specifically, high rate behaviors are typically more sensitive to rate-decreasing effects of some drugs than low rate behaviors. In previous studies, fluvoxamine or other SSRIs did not exert rate-dependent effects in rats and pigeons (Rastogi and McMillan, 1985; Lamb and McMillan, 1986). In the present study, behaviors maintained at higher response rates tended to be less sensitive to disruption by fluvoxamine which is opposite of the relationship expected due to rate-dependent effects. It is important to note that our analysis of potential rate-dependent effects of fluvoxamine was performed between-subjects, though most analyses of this behavioral mechanism are performed within-subjects using interval schedules. However, at least one study has shown that the behavioral effects of amphetamine, a drug with prototypical rate-dependent effects, is present both between- and within-subjects (Beecher and Jackson, 1976).

Previous research has demonstrated that fixed-ratio size can influence the effect of certain drugs on operant behaviors. Larger FR size has been shown to result in greater sensitivity to decreases in responding following cocaine and reduced development of tolerance to these effects (e.g. Hoffman et al. 1987). While this possible explanation could be extended to our studies, differences in FR size do not appear to fully explain our results. When the FR for ethanol and food are the same, ethanol-maintained FR responding is more sensitive to fluvoxamine disruption than responding for food (Lamb and Järbe, 2001; Ginsburg et al., 2005). However, in the present report, the food FR was relatively larger than the ethanol FR (see Table 1), and food-maintained responding was more sensitive to fluvoxamine effects, consistent with an effect due to differences in FR size. It is important to note that these comparisons are confounded by the concurrent presence of food availability in the present study, and additional studies will be necessary to fully evaluate this potential behavioral mechanism. Still, this hypothesis does not appear to explain the effects of fluvoxamine on responding for food, as the regressions between food FR size and ED50 of disruption of number of food presentation or response rate for food had slopes that did not differ from

zero. Therefore, it is possible, yet unlikely, that FR size was a determinant of the inverted effect reported presently compared with previous reports.

In conclusion, the major finding of the present study was that responding for food was more sensitive to disruption by fluvoxamine than responding for ethanol when both were concurrently available. This is in contrast to conditions in which food and ethanol are available independently, where ethanol-maintained behavior appears to be more sensitive to decreases following fluvoxamine administration (Lamb and Järbe, 2001; Ginsburg et al. 2005). Several hypotheses have been proposed that could account for the inversion of the selective effect of fluvoxamine, including: increased resistance to change due to increased reinforcer frequency, strengthened stimulus control over ethanol-maintained responding, altered demand for food and ethanol, and the impact of fixed-ratio size. While further studies are required to clarify the role of each of these potential explanations, the body of data is perhaps most consistent with an increased resistance to change due to increased reinforcer frequency. Others have described the relationship between the availability of an alternative reinforcer and drug choice under similar conditions (Beardsley et al., 1978; Vuchinich and Tucker, 1988; Nader and Woolverton, 1992). While these studies have examined the consequences of the presence and relative cost of an alternative reinforcer, few studies have explored the impact of such manipulations on the effects of drug administration. Because drug abuse and addiction involves the choice between alternatives (see Vuchinich and Tucker, 1988), currently used methods of assessing drug-reinforced behaviors in which drug is independently available of other explicit sources of reinforcement may not account for the increased resistance of such behavior to disruption by pharmacologic treatments in the presence of these other sources of reinforcement. The present study provides evidence that the context under which behavior occurs is an important determinant of the selectivity of fluvoxamine effects. Context may also influence similar treatments, and should be considered when interpreting the effects of pharmacologic treatments on ethanol self-administration.

Acknowledgments

The authors wish to thank Gerardo Martinez for technical assistance during these studies. This work was supported by PHS grant AA012337. Studies described herein comply with APA standards in the treatment of animal subjects.

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Fig. 1.

Effects of fluvoxamine on concurrently available ethanol and food. Fixed-ratios for food were adjusted for each subject to provide similar numbers of presentations of food and ethanol during each daily 30-min session. Each subject responded under a fixed-ratio 5 for ethanol. Effects of each dose of fluvoxamine in each subject is the average of two separate determinations. Points represent group mean $\pm$ S.E.M. A.) Effects of fluvoxamine on number of food or ethanol presentations/session. As shown above SAL, the number of presentations did not significantly differ following saline administration. B.) Effects of fluvoxamine on response rate for ethanol and food. As shown above SAL, response rate for food was significantly higher than response rate for ethanol ($p < 0.05$).

* significantly different than number of ethanol presentations (comparison made in panel A only), $p < 0.05$.

significantly different than respective control, $p < 0.05$.

Fig. 2.

Within-session effects of fluvoxamine. Cumulative responses in each tenth of a session were recorded and normalized to each subject's maximum responses for food or ethanol following saline. Data following saline administration (SAL) are reproduced in each panel for comparison. Points represent mean $\pm$ S.E.M. for all eight subjects. Points for which no error bars are visible have an SEM that is within the region of the point. Note that patterns of responding for food and ethanol are similar, and effects of fluvoxamine are consistent across the entire session. Similar to results in Fig. 1, the minimally effective dose of fluvoxamine was lower for food-maintained behavior compared with ethanol-maintained behavior. Further, responding for food was significantly lower than responding for ethanol following a dose of 10 mg/kg fluvoxamine as determined with a paired t-test ($p < 0.05$).

Fig. 3.

Linear regression between response-rate and fluvoxamine ED50 for reducing response rate in individual subjects. The average ED50 for the relatively higher rate behavior (food(Δ)-maintained) was lower than the ED50 for ethanol($\square$)-maintained behavior, which could be consistent with a rate-dependent effect. However, no correlation was observed when response rate versus ED50 was considered across both conditions as indicated by the dashed line.. Further, positive correlations (parallel solid lines) were observed for response rate (LOG(response rate)) versus ED50 for food($\blacktriangle$)- and ethanol($\blacksquare$)-maintained responding, which is the opposite of the typical rate-dependent relationship.

Table 1

Individual subject data

SUBJECT	Reinforcer	Ratios (food/ ethanol)	Reinforcers Delivered (control)	Response Rate (control)	ED50s (reinforcer deliveries)	ED50s (response rate)
1064	Food	30	21	0.58	4.8	3.9
	Ethanol	5	15	0.10	3.9	3.3
1065	Food	30	15.5	0.69	7.0	5.5
	Ethanol	5	22	0.16	9.4	6.2
1066	Food	25	18	0.79	7.5	4.6
	Ethanol	5	23	0.20	15.0	12.5
1067	Food	32	18	0.78	5.3	4.8
	Ethanol	5	17.5	0.12	10.2	8.9
1069	Food	25	14	0.46	7.1	6.8
	Ethanol	5	20.5	0.13	7.4	7.0
1090	Food	15	23.5	0.81	6.7	6.4
	Ethanol	5	22	0.25	13.5	9.4
1091	Food	8	30.5	0.90	15.2	6.7
	Ethanol	5	20.5	0.38	13.0	8.1
1092	Food	35	17.5	1.41	10.7	6.0
	Ethanol	5	28	0.32	15.1	10.5
Averages	Food	25 ± 3.2	20 ± 2	0.80 ± 0.10	8.0 ± 1.2	5.6 ± 0.4
(mean ± S.E.M.)	Ethanol	5*	21 ± 1	0.21 ± 0.03*	11.0 ± 1.4*	8.2 ± 1.0*

* indicates significant difference compared with food-maintained behavior