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BRIEF COMMUNICATION

Reduction in Oral Ethanol Self-Administration in the Rat by the 5-HT Uptake Blocker Fluoxetine[1]

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HARAGUCHI, M., H. H. SAMSON AND G. A. TOLLIVER. *Reduction in oral ethanol self-administration in the rat by the 5-HT uptake blocker fluoxetine*. PHARMACOL BIOCHEM BEHAV **35**(1) 259–262, 1990.—Long-Evans rats (N = 4) maintained on ad lib food and water were initiated to self-administer ethanol using the sucrose-substitution procedure. Following initiation, the rats received IP injections of fluoxetine HCl in sterile water 30 minutes before selected daily self-administration sessions. On other sessions, the rats were injected with sterile water only. Doses of 1, 2, 3, and 5 mg/kg were tested in a random order. Only one drug dose was given each week and each dose was tested at least twice except the 5 mg/kg dose. As dose increased, responding for ethanol decreased with significant reductions at both the 3 and 5 mg/kg dose. The nature of the decrease was such that the duration of continuous responding at the beginning of the session was reduced respective to control and noninjection performance. Overall, the findings of this study support prior work with fluoxetine and other 5-HT blockers which appear to affect satiety mechanisms and possibly reinforcement efficacy.

Ethanol Fluoxetine Reinforcement Ethanol self-administration Rats

IN previous studies, we have demonstrated that a range of drugs can reduce lever press responding maintained by ethanol reinforcement. Both dopamine agonists and antagonists result in response decreases, but by what appears to be different behavioral actions (16). The inverse benzodiazepine agonist Ro15-4513 has also been shown to decrease ethanol-reinforced responding (20). At very high doses of the opiate antagonist naloxone, ethanol-reinforced responding was also decreased (19). It has been reported that the mu-opiate receptor agonist morphine produces increases in ethanol drinking (8), but morphine's effect upon ethanol reinforced behavior have not been examined.

Recently, the selective serotonin (5-HT) uptake blocker fluoxetine has been shown to reduce ethanol intake in genetically selected rats which have a high ethanol preference (13). Also, fluoxetine has been shown to alter patterns of ethanol drinking behavior (10). However, none of these studies examined the effects of fluoxetine on responding reinforced by ethanol presentation. The present study was undertaken to determine if fluoxetine would alter responding maintained by ethanol reinforcement.

METHOD

Animals

Four male Long-Evans rats obtained from the breeding facilities of the Department of Psychology, University of Washington, previously used in an experiment involving the compound Ro15-4513, served as subjects. The animals were housed in individual stainless steel handing rodent cages with a 12-hour light-dark cycle (lights on at 7:30 a.m.). Temperature and humidity were kept within NIH guidelines. Food (Rodent Blox F-6, Wayne Laboratories) and water were available ad lib except where noted. The animals weighed approximately 574 g (SD ± 44.6) at the start of the present experiment.

Apparatus

The operant chamber and their enclosures have been previously described (17). Briefly, each chamber was equipped with one removable rodent lever and one dipper fluid delivery system (Gerbrands Corporation, Model G5600 B-RH), fitted with a 0.1 ml cup. A 1-watt house light was illuminated when the session was

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in progress. Recording of lever presses and schedule control of dipper presentations were with Apple microcomputers.

Drugs

Fluoxetine hydrochloride was dissolved in sterile water and mechanically shaken for 30 seconds immediately prior to injection. Doses of 1, 2, 3, and 5 mg/kg were tested.

Procedure

The animals were initiated to self-administer 10% ethanol using the sucrose-substitution procedure previously described (18). In a prior experiment involving Ro15-4513, the animals were trained to respond on a concurrent schedule with 10% ethanol and 2% sucrose solutions presented as reinforcers. During the prior study, following initiation and training on the concurrent schedule, the animals received a minimum of 12 injections of Ro15-4513 at doses of 1, 3 and 6 mg/kg. Only a single drug test was performed each week. Thus, prior to fluoxetine testing, the animals had an extensive past history with the injection procedure and responding in the operant situation using a concurrent paradigm.

For the present study, the animals were switched to a single-lever paradigm in which 10% ethanol was the only reinforcer presented. When responding on a fixed-ratio 4 reinforcement schedule was stable (approximately 4 weeks of noninjection conditions), drug testing was begun. Control injections of sterile water were given on Wednesdays and fluoxetine was administered on Thursdays, following the same procedure previously employed with Ro15-4513. All injections were given intraperitoneally, 30 minutes before the start of the session. On Mondays, Tuesdays, and Fridays, the animals received no treatment prior to the start of their daily 30-minute sessions. Doses were administered in a random order, with each dose level except the 5 mg/kg dose tested at least twice. The 5 mg/kg dose was only administered one at the start of the experiment to all animals. Data are presented as means of all injections at each dose for all animals unless noted otherwise.

RESULTS

At the end of the baseline period, the animals reached stable responding at levels not different from those observed in the prior experiment with Ro15-4513 in the same single lever condition. During this baseline period, their average intake during the 30-minute session was 0.49 g/kg (sd = 0.05). During the experiment, the intakes on noninjection sessions did not change from baseline, with the intake on days of control injections having a mean of 0.56 g/kg (sd = 0.10) which was not significantly different from noninjection days.

With increasing doses of fluoxetine, the main effect observed was a decrease in responding, as shown in Fig. 1. Sample cumulative records of responding for one rat under noninjection, vehicle and drug conditions are presented in Fig. 2. An analysis of variance showed a significant decrease in responding only at the 3 mg/kg, $F(2,10) = 17.03$, $p<0.01$, and 5 mg/kg dose, $F(2,4) = 25.05$, $p<0.01$, respective to vehicle and/or noninjection conditions (Fig. 1). At all doses tested, there was no significant difference between noninjection and vehicle performance. Average decreases in responding were 25%, 33%, 49% and 71% for the 1, 2, 3 and 5 mg/kg doses, respectively.

The nature of the decrease in responding was such that responding was confined to short, discrete continuous responding during the first four to six minutes of the 30-minute session with the 3 and 5 mg/kg doses (Fig. 2). With the 1 and 2 mg/kg doses, sequences of continuous responding with pauses between them occurred throughout the session, similar to the vehicle and noninjection session response patterns.

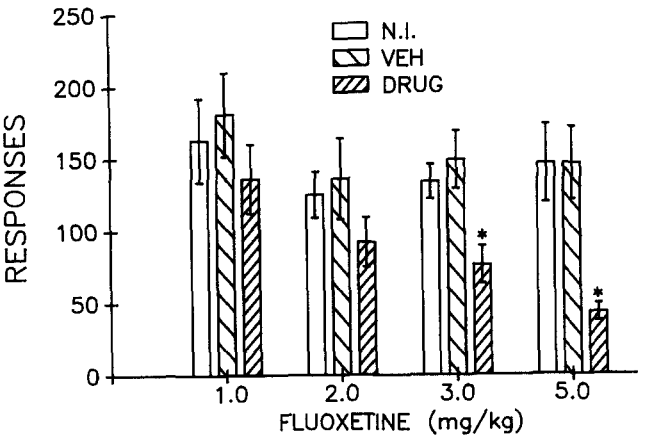

FIG. 1. Effect of fluoxetine upon lever-press responding for 10% ethanol (mean ± SEM). *Significantly different from control and noninjection values at $p<0.01$.

DISCUSSION

The 5-HT uptake blocker fluoxetine produced a dose-dependent decrease in the oral self-administration of ethanol. A decrease in voluntary ethanol intake following the administration of other selective 5-HT uptake blockers such as zimelidine and citalopram have also been reported (1, 4–6, 9, 14, 15) using other paradigms. Fluoxetine and other 5-HT blockers have been found to reduce food intake as well (2–4, 7), raising the argument that 5-HT uptake blockers do not reduce ethanol intake specifically, but suppress consummatory behavior in general. However, in the alcohol-preferring P line of rates, a 10 mg/kg dose of fluoxetine actually increased the intragastric (IG) administration of water and the drinking of a flavored solution associated with the ingestion of ethanol, while reducing the IG administration of 20% ethanol (13). Food intake was not significantly reduced at this dose level, which suggests that not all ingestive behaviors are equally affected by fluoxetine and that there may be some preferential action upon ethanol-drinking behavior.

There are claims that 5-HT plays a role in satiety (2, 3, 10), and it has been shown that peripherally administered 5-HT decreases food intake by affecting meal size and feeding duration (3). Fenfluramine, an indirect 5-HT agonist, and fluoxetine have also been shown to reduce food intake by decreasing meal size and eating rate (2). In the present experiment, the temporal patterns of responding showed that the higher doses of fluoxetine tested reduced size and duration of continuous responding, which could support a satiety explanation.

The specificity of flouxetine's actions upon ethanol self-administration is still not clear, however. In the study involving the P line of rats mentioned previously, the additive reductions in ethanol and food intake produced a significant decrease in body weight (13). Since ethanol can function both as a nutrient and a pharmacological agent, it is possible that fluoxetine enhances the onset of ingestive satiety and also reduces the reinforcing efficacy of ethanol. Since the magnitude of food intake reduction was not as great under fluoxetine treatment in the P rats, the authors speculated that fluoxetine exerts a greater effect upon ethanol drinking than other ingestive behaviors (13). The results of the present study support this since nonfood- or fluid-deprived animals were used and at no time was a decrease in body weight seen.

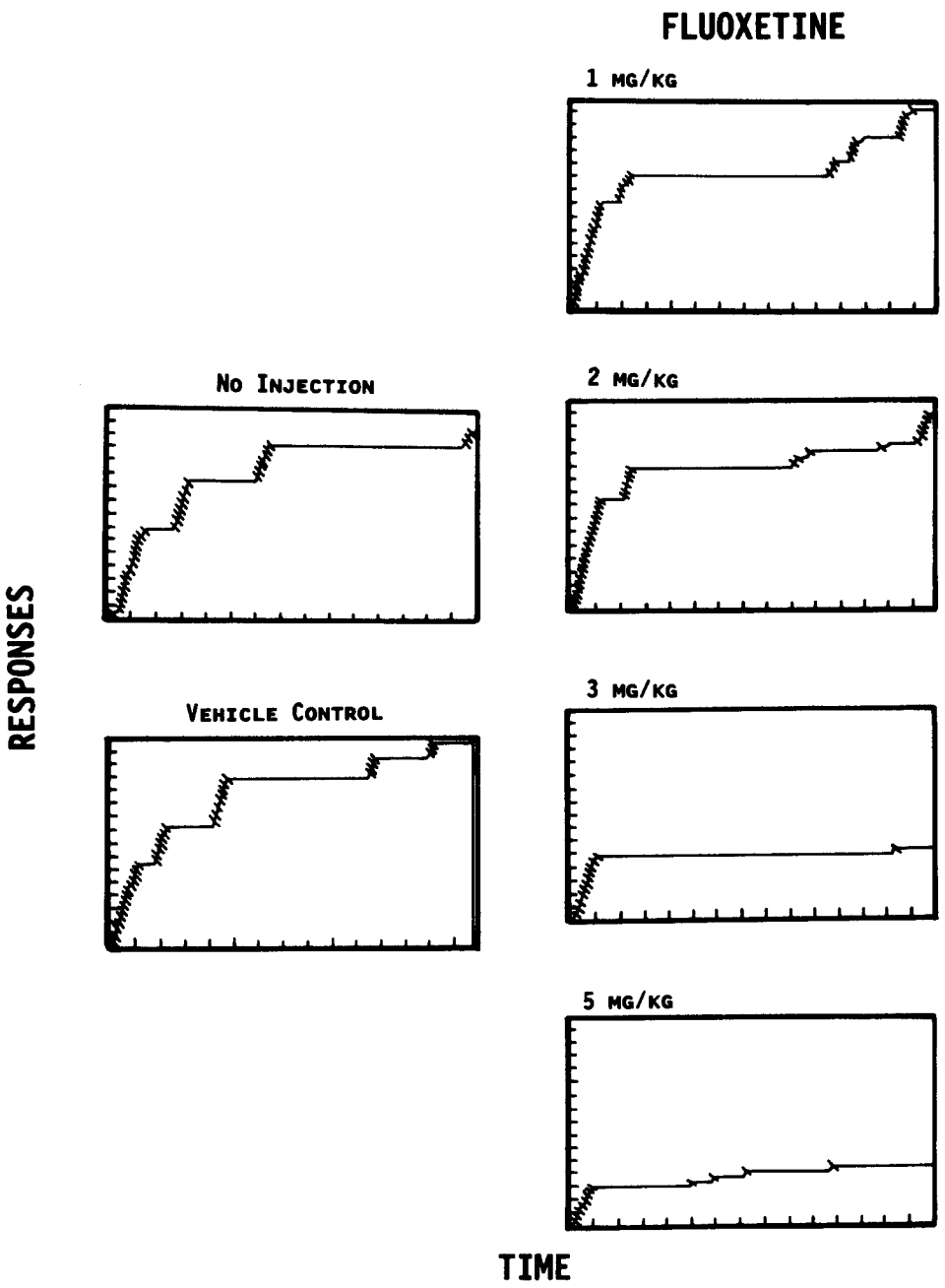

FIG. 2. Sample cumulative records for one rat under noninjection, control injection, and fluoxetine administration. Cumulative responses are indicated on the y axis (one division = 10 responses), with time on the x axis (one division = 2 minutes). Slashes represent reinforcement presentation.

Other work suggests that fluoxetine and other 5-HT uptake blockers affect the consumption of palatable substances in general (5, 11, 12). A dose-dependent reduction in saccharin consumption with fluoxetine administration has been found (11), and it has been shown that zimelidine has a greater effect upon consumption of a 0.1% saccharin solution as compared to a 0.025% concentration or water (5). Peripherally administered 5-HT also decreased the intake of sucrose, saccharin and sweet milk solutions, while increasing the intake of quinine, saline and citric acid solutions (12). Therefore, it appears that 5-HT blockers have a greater effect upon substances which have a greater reinforcing efficacy.

Prior work in our laboratory has demonstrated that other drugs also reduce responding for ethanol, specifically the dopamine agonist apomorphine and the dopamine antagonist haloperidol (16), and the partial inverse benzodiazepine agonist Ro15-4513 (20). Examination and comparison of the cumulative response patterns of responding show that the effects under fluoxetine resembles those under haloperidol, with responding starting out at a normal high rate with no pausing, but terminating earlier respective to control sessions. Thus, the reduction in ethanol intake caused by fluoxetine could be due to a reduction in the efficacy of ethanol's reinforcing properties.

If fluoxetine does attenuate reinforcing efficacy, patterns of responding should appear similar to those seen with the administration of other agents claimed to reduce reinforcement efficacy. The dopamine theory of reinforcement claims that activation of dopamine pathways plays a major role in reinforcement efficacy (21–23). According to this hypothesis, a dopamine antagonist such as haloperidol would diminish the reinforcing effects of various stimuli. The similarity of the response patterns seen after haloperidol and fluoxetine administration suggests that the reinforcing capability of ethanol may be affected by both drugs, resulting in an earlier cessation of self-administration behavior.

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