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Effects of Ro 15-4513, Fluoxetine and Desipramine on the Intake of Ethanol, Water and Food by the Alcohol-Preferring (P) and -Nonpreferring (NP) Lines of Rats

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McBRIDE, W. J., J. M. MURPHY, L. LUMENG AND T.-K. LI. *Effects of Ro 15-4513, fluoxetine and desipramine on the intake of ethanol, water and food by the alcohol-preferring (P) and -nonpreferring (NP) lines of rats.* PHARMACOL BIOCHEM BEHAV **30**(4) 1045–1050, 1988.—The effects of the IP administration of RO 15-4513 (1, 2 and 4 mg/kg), fluoxetine (5 and 10 mg/kg) and desipramine (5 and 10 mg/kg) on the intake of 10% ethanol, H_2O and food were determined in the selectively bred alcohol-preferring (P) and -nonpreferring (NP) lines of rats with daily access to fluids being limited to single 2-hour sessions. The imidazobenzodiazepine Ro 15-4513 (a partial inverse benzodiazepine agonist) significantly reduced the intake of 10 % ethanol by the P rats to 50–60% of control levels in the first 30 minutes without altering food or H_2O intake. The attenuating actions of 2 mg/kg Ro 15-4513 on ethanol intake could be completely blocked by the central benzodiazepine receptor antagonist Ro 15-1788 (10 mg/kg). Ro 15-1788, by itself, produced no effects on alcohol and H_2O consumption. The 5 mg/kg dose of fluoxetine significantly reduced 10% ethanol intake by the P rats to 20% of control values without altering either H_2O or food consumption. The 10 mg/kg dose of fluoxetine further reduced ethanol intake by the P rats, but this dose also reduced daily food intake to approximately 70% of normal. Desipramine at both doses significantly ($p<0.05$) reduced both ethanol and food uptake by the P rats and had a tendency to reduce H_2O consumption as well. In general, the three drugs had effects in the NP rats similar to those observed for the P group, although the effects on 10% ethanol intake were difficult to compare because of the low, variable intake of alcohol by the NP group. The data are consistent with the involvement of serotonin and the GABA-benzodiazepine receptor complex in alcohol drinking behavior.

Alcohol preferring rats GABA-benzodiazepine receptor Monoamine uptake inhibitors Fluoxetine Desipramine Ro 15-4513

STUDIES with the selectively bred, alcohol-preferring P line of rats indicated that a single IP injection of a monoamine uptake inhibitor, fluoxetine or desipramine, significantly reduced the daily voluntary intake of ethanol [17]. Monoamine uptake inhibitors that exhibit high specificity for serotonin have been consistently reported to decrease volitional intake of ethanol in laboratory rats [1, 7, 22–24]. However, the results with norepinephrine (NE) uptake inhibitors, such as desipramine have been less consistent. Both Murphy *et al.* [17], using P rats, and Daoust *et al.* [7], using Long-Evans rats with high alcohol drinking, reported that desipramine reduced the voluntary intake of ethanol, whereas Rockman *et al.* [24] reported that NE uptake inhibitors did not alter alcohol intake in Wistar rats.

In addition to the possible involvement of the monoamines in some of the CNS effects of alcohol, there has been recent evidence implicating the GABA-benzodiazepine (BDZ)-CL^- receptor ionophore as a site of action of ethanol. Suzdak *et al.* [27] reported that pharmacologically relevant concentrations of ethanol stimulated the GABA receptor-mediated influx of $^{36}Cl^-$ into isolated brain vesicles. Furthermore, these authors reported that the imidazobenzodiazepine Ro 15-4513 antagonized the augmenting effects of ethanol on GABA-stimulated Cl^- influx and blocked the intoxicating effects of high-dose ethanol. Both the in vitro and in vivo antagonizing effects of Ro 15-4513 on the actions of ethanol could be prevented by the central benzodiazepine receptor antagonist Ro 15-1788 [27], suggesting a novel in-

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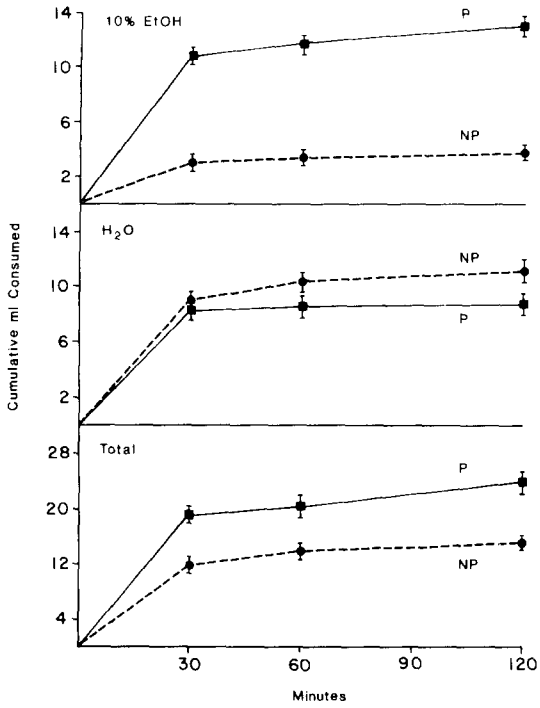

FIG. 1. Cumulative ml of 10% ethanol (EtOH) and H_2O consumed during the 2-hour period of fluid availability by the alcohol-preferring (P) and -nonpreferring (NP) lines of rats. Data are the means±S.E.M. of all the control data for the four experiments. The number of determinations for each point is 24.

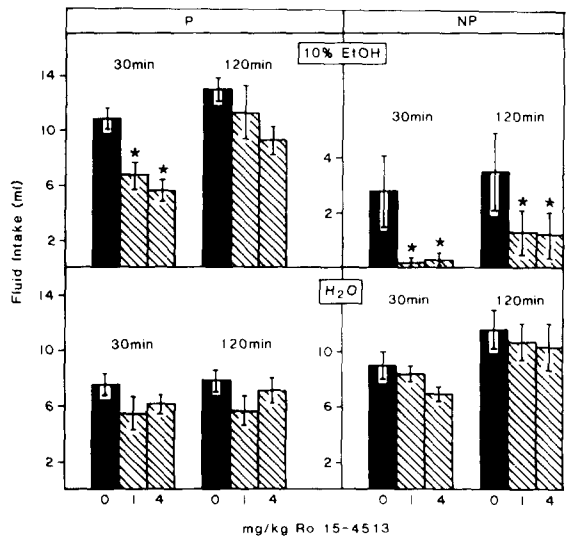

FIG. 2. Effects of the IP administration of 1 and 4 mg/kg Ro 15-4513 on the intake of 10% ethanol (EtOH) and H_2O by P and NP rats after the first 30 and during the 120 minutes of schedule fluid availability. Data are the means±S.E.M. (N=6 rats each). *$p<0.05$ vs. control values by ANOVA and post hoc Duncan's test.

teraction of Ro 15-4513 with the GABA-BDZ-Cl^- receptor complex and the involvement of this receptor complex in the mediation of some of the CNS actions of ethanol. Ro 15-4513 is considered to be a partial inverse benzodiazepine agonist [3,15] and has been reported to suppress, in a dose-dependent manner, operant responding for 10% ethanol by Long-Evans rats, which were initiated to self-administer ethanol orally using the sucrose-fading procedure [26]. Although the findings of Samson *et al.* [26] suggest a possible blocking action of Ro 15-4513 on the CNS reinforcing properties of ethanol, it would be important to determine the effects of this drug on the drinking behavior of the P line of rats, for which there is evidence that ethanol de novo is a positive reinforcer [19,28]. Therefore, the present study was undertaken to determine if the administration of Ro 15-4513 would reduce the volitional oral intake of 10% (v/v) ethanol by the P rat and obtain evidence that this blocking action occurs at a BDZ receptor complex. For these experiments, free-fed animals were restricted to a single two-hour period of fluid availability. Previous studies indicated that the P rat will drink sufficient 10% ethanol under conditions of limited access to raise BACs to intoxicating levels [16]. This experimental approach was used because of the possible short duration of action of the drugs [8] and the ability to measure drug actions on both H_2O and 10% ethanol intake when food is available ad lib. For comparative purposes, experiments were extended to include (a) drug effects of BDZ agents on the selectively-bred, alcohol-nonpreferring NP line of rats, and (b) determining the effects of the monoamine uptake inhibitors, fluoxetine and desipramine, on the drinking behavior of both the P and NP rats. Such studies with monoamine uptake inhibitors have not been previously carried out with the NP rats, nor have studies been undertaken with conditions of restricted access for both drinking fluids. Comparison of the effects of the different agents on the drinking behavior of the P and NP rat lines might yield information on some of the neuronal systems involved in their disparate alcohol drinking behavior.

METHOD

Adult male P and NP rats (n=6 each) of the S-26 generation weighed approximately 350 g at the beginning of the study. The rats were individually housed in a temperature and humidity controlled room with a normal day-night light cycle (lights on at 0600 hr and off at 1800 hr). All animals had been tested for ethanol preference at 45–60 days of age, as previously described [14]; during testing, the P rats consumed 6.5±0.4 g ethanol/kg body wt./day while the NP group drank only 0.4±0.1 g/kg/day.

For the present experiments, animals were given food ad lib but fluid availability was limited to 2 hours each day between 1000 to 1200 hr when the rats were allowed access to two Richter tubes, one containing water and the other 10% ethanol, the positions of which were randomly switched. Water and ethanol intakes were monitored throughout the two-hour period while food intake was determined by weighing the powdered food remaining at the end of the 2 hour period of fluid availability as well as after 24 hours. Drug injections (IP) were given approximately 5 minutes before the availability of fluids and included fluoxetine HCl (Eli Lilly & Co.) desipramine HCl (Sigma), Ro 15-4513 (ethyl-8-azido-5,6-dihydro-5-methyl-6-oxo-4H-imidazo-[1,5α][1,4] benzodiazepine-3-carboxylate; Hoffmann-LaRoche) and Ro 15-1788 (same structure as Ro 15-4513 except fluoro substituted at position 8 for azido; Hoffman-LaRoche). Control data were obtained from rats given IP injections of vehicle only. The volume of injection were approximately 1 ml/kg body wt. Fluoxetine and desipramine were dissolved in

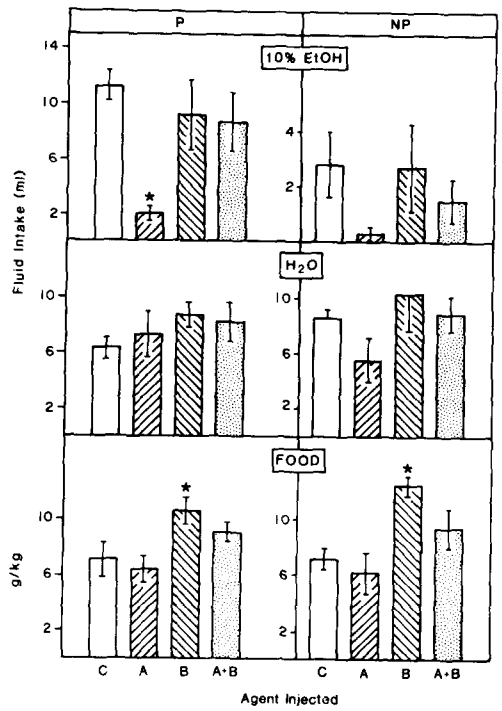

FIG. 3. Effects of the IP administration of vehicle (C), 2 mg/kg Ro 15-4513 (A), 10 mg/kg Ro 15-1788 (B), and Ro 15-1788 followed by Ro 15-4513 (A+B) on the intake of 10% ethanol (EtOH) and H_2O during the first 30 minutes and on food consumption during the 2 hours of scheduled fluid availability. Data are the means±S.E.M. (N=6 rats each). *$p<0.05$ vs. control values using ANOVA and post hoc Duncan's test.

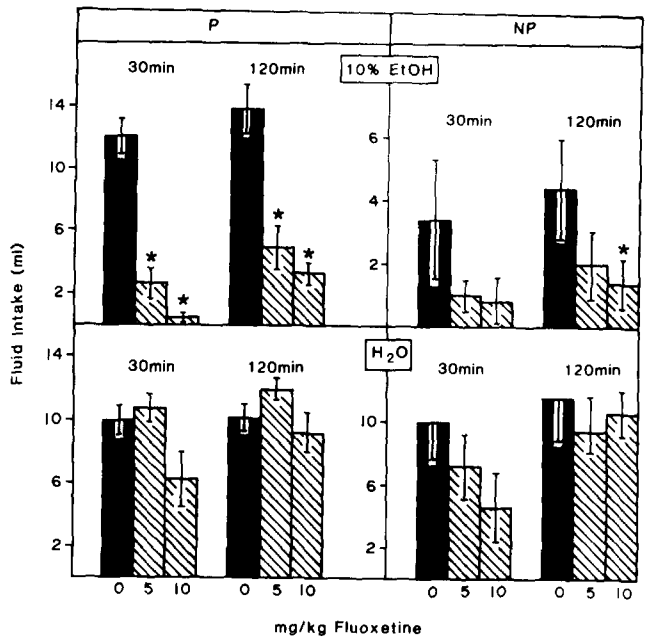

FIG. 4. Effects of IP administration of 5 and 10 mg/ kg fluoxetine on the intake of 10% ethanol (EtOH) and H_2O by P and NP rats after the first 30 and during the 120 minutes of schedule fluid availability. Data are the means±S.E.M. (N=6 rats each). *$p<0.05$ vs. control values using ANOVA and post hoc Duncan's test.

sterile water. Ro 15-1788 was dissolved in water containing 2–3 drops of Tween 80. Ro 15-4513 was dispersed in water containing 2–3 drops of Tween 80 and this suspension was pulse sonicated for approximately 30 seconds to help dissolve the drug. Rats given drug injections were not given another injection until subsequent days indicated fluid and food intakes had stabilized and returned to control levels. Rats were usually given only one trial at each drug dose. Statistical differences were determined with a repeated measures analysis of variance and post hoc Duncan's tests.

RESULTS

On the 2-hour schedule of fluid availability, the P rats consumed approximately 11 to 13 ml of 10% ethanol (2.0±0.2 g/kg) and 8 to 9 ml of H_2O (Fig. 1). However, the NP rats drank only 3 to 4 ml of 10% ethanol (0.6±0.2 g/kg) and 9 to 11 ml of H_2O during the 2-hour period (Fig. 1). With both rat lines, most of the fluids were consumed during the first 30 minutes with only 1 to 2 ml of either H_2O or 10% ethanol consumed during the remaining 90 minutes (Fig. 1). The total fluid volume consumed for the P rats was approximately 7 ml higher than that for the NP rats. This was clearly due to the higher volume of 10% ethanol taken in by the P animals (Fig. 1).

Administration of 1 and 4 mg/kg Ro 15-4513 significantly reduced the intake of 10% ethanol by the P rats in the first 30 minutes to 60 and 50% of control values, respectively (Fig. 2). After 120 minutes, intake of the P rats given Ro 15-4513 had recovered to nearly normal levels. The consumption of H_2O by the P line was not altered by these doses of Ro 15-4513 at either the 30 or 120 minute time points (Fig. 2). For the NP rats, both doses of Ro 15-4513 had similar effects and reduced the intake of 10% ethanol to approximately 10 and 35% of control levels at 30 and 120 minutes, respectively (Fig. 2). The intake of H_2O by the NP group was not altered by Ro15-4513 (Fig. 2).

The IP administration of the BDZ antagonist, Ro 15-1788 (10 mg/kg), had little effect on either 10% ethanol or H_2O consumption by the P and NP rats (Fig. 3). However, this dose of Ro 15-1788 blocked the attenuating actions of Ro 15-4513 on ethanol intake by P rats (Fig. 3). A similar effect was observed for the NP rats but their small, highly variable intake of 10% ethanol precluded finding statistical differences.

Ethanol intake of the P rats at 30 minutes was reduced to 20 and 4% of control values by 5 and 10 mg/kg fluoxetine, respectively (Fig. 4). This effect of fluoxetine was still evident after 120 minutes. On the other hand, fluoxetine did not significantly alter the H_2O intake of the P rats (Fig. 4). As was the case for the P rats, fluoxetine reduced the ethanol intake of the NP animals (Fig. 4), but statistical significance was observed only at the 10 mg/kg dose after 120 minutes (Fig. 4). The 10 mg/kg dose of fluoxetine also had a tendency to lower H_2O intake of the NP rats after 30 minutes, although the difference was not statistically significant. However, by 120 minutes, the values for H_2O intake of the drug- and vehicle-injected animals were similar (Fig. 4).

The intake of 10% ethanol after 30 minutes by the P rats was reduced to 70 and 20% of control values by 5 and 10 mg/kg desipramine, respectively, although only the higher dose caused a statistically significant decrease (Fig. 5). This

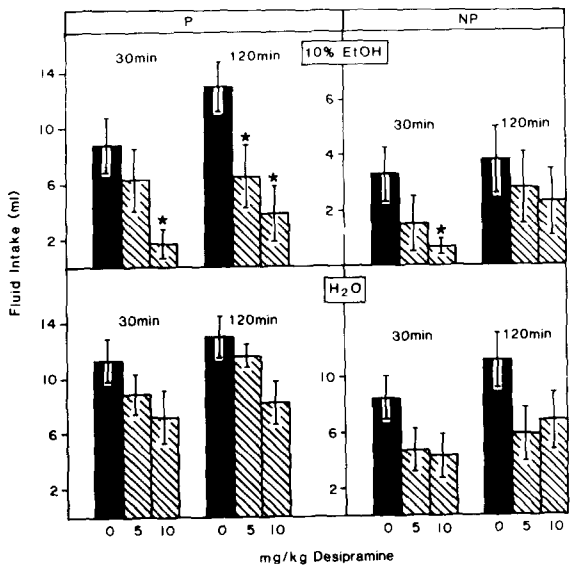

FIG. 5. Effects of the IP administration of 5 and 10 mg/kg desipramine on the intake of 10% ethanol (EtOH) and H_2O by P and NP rats after the first 30 and during the 120 minutes of scheduled fluid availability. Data are the means±S.E.M. (N=6 rats each). *$p<0.05$ vs. control values using ANOVA and post hoc Duncan's test.

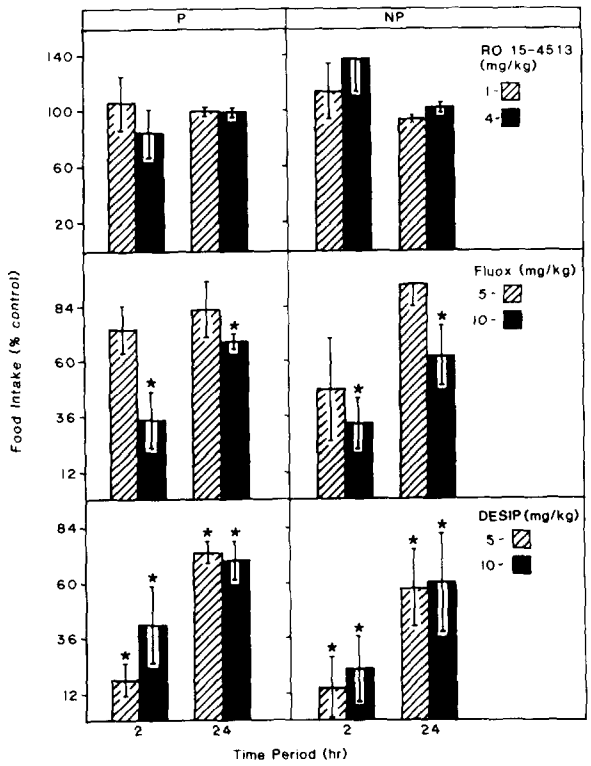

FIG. 6. Effects of Ro 15-4513, fluoxetine and desipramine on food consumption (given as percent of values for food intake by control animals) during the 2 hours of fluid availability and over a 24-hour period. Data are the means±S.E.M. (N=6 rats each). *$p<0.05$ vs. control values using ANOVA and post hoc Duncan's test.

attenuating action by both doses of desipramine on ethanol consumption of the P rats was clearly evident after 120 minutes. The amount of 10% ethanol consumed by the NP animals was reduced to 20 and 45% of control intake by desipramine within the first 30 minutes (Fig. 5), but ethanol intake almost completely recovered to the normally low levels after 120 minutes. Desipramine had a tendency to reduce the amount of H_2O consumed by both the P and the NP rats, although the differences were not statistically significant (Fig. 5). The effects of desipramine on H_2O intake by NP rats was quite variable (for example, the range of H_2O values after 30 minutes for the 10 mg/kg dose was 0 to 10 ml) and, therefore, in spite of apparent differences between the control and drug treated animals, the results were not statistically significant.

Fluoxetine, 10 mg/kg, and desipramine, 5 and 10 mg/kg, significantly reduced food intake by the P and NP rats at both 2 and 24 hours (Fig. 6). However, Ro 15-4513 (Figs. 3 and 6) and the 5 mg/kg dose of fluoxetine (Fig. 6) did not alter food intake. On the other hand, 10 mg/kg Ro 15-1788 significantly increased the food intake approximately 60% during the 2-hour period of fluid availability for both the P and NP rats (Fig. 3). This effect was not observed during this 2-hour period if Ro 15-1788 and Ro 15-4513 (2 mg/kg) were given together (Fig. 3). No differences in 24-hour food consumption values between control and Ro 15-1788-injected animals were observed for both the P and NP lines.

DISCUSSION

With restricted availability of fluids to single 2-hour sessions daily, it was possible to examine the effects of different pharmacological agents on the intake of both ethanol and H_2O by the selectively bred alcohol-preferring (P line) and -nonpreferring (NP line) rats. Under these conditions, the total fluid intake was approximately 22 and 15 ml for the P and NP rats, respectively (Fig. 1). This is well below the daily intake of 45±3 and 40±1 ml obtained for these P and NP rats, respectively, under conditions of 24-hour free-choice availability of H_2O and 10% ethanol. Under the 24-hour free-choice conditions, the ratio of ml of 10% to ml of H_2O consumed was 17±3 and 0.09±0.02 for the P and NP rats, respectively. However, under the present restricted access conditions, the ratio values were reduced to 1.5 for the P animals and increased to 0.3 for the NP rats. The higher ratio for the NP rats with restricted fluid access is likely due to the NP animals initially choosing to drink from the randomly switched 10% ethanol bottle in an effort to satisfy their thirst. The lower ratio for the P rats could result from a combination of two factors: (a) the need to satisfy their thirst and (b) the drive to drink ethanol, the amount of which is regulated so the BACs do not exceed 50–100 mg% [16,29]. The intake of 10% under the present conditions is similar to the amount consumed by P rats when access only to 10% ethanol was restricted while H_2O was freely available [16]. With unrestricted access to both ethanol and H_2O, P rats drink 10% ethanol in bursts of 6–8/day and appear to satisfy their thirst and alcohol requirements mainly through the consumption of ethanol solutions [16].

Fluoxetine, a 5-HT uptake inhibitor [9,30], desipramine, a NE uptake inhibitor [21], and RO 15-4513, a BDZ receptor partial inverse agonist [3,15], all reduced the intake of 10% ethanol without significantly altering the consumption of H_2O by the P rats (Figs. 2, 4, and 5). These findings are in agreement with published reports indicating that 5-HT up-

take inhibitors [1, 7, 17, 22–24], NE uptake inhibitors [7,17] and Ro 15-4513 [26] could all reduce the volitional intake of ethanol by rats. The present findings suggest at least three neuronal systems (5-HT, NE and GABA) may be involved in maintaining alcohol drinking behavior of the P rat. Desipramine (5 and 10 mg/kg doses) also significantly reduced food intake of the P rat (Fig. 6), suggesting that its actions may be more widespread and may generally affect ingestive behaviors. Reduced food intake by rats has been reported following administration of 10 mg/kg desipramine [18]. On the other hand, the 5 mg/kg dose of fluoxetine markedly attenuated 10% ethanol intake by the P rat without altering food or H_2O consumption, suggesting that the 5-HT systems involved in alcohol drinking behavior may be more sensitive to the effects of fluoxetine than are the 5-HT systems regulating other ingestive behaviors.

The finding that Ro 15-4513 selectively reduced 10% ethanol intake without altering H_2O and food consumption (Figs. 2 and 3), and that this attenuating effect on ethanol intake was blocked by Ro 15-1788 (Fig. 3), a BDZ receptor antagonist [12,13], is consistent with published results that Ro15-4513 can selectively block the actions of ethanol at the GABA-BDZ-Cl^- receptor [3, 20, 27]. These results with Ro 15-4513 and Ro 15-1788 support the concept that ethanol is acting at the GABA-BDZ-Cl^- receptor ionophore and, moreover, that this receptor complex may be part of or may interact with the brain reward system mediating the reinforcing properties of ethanol in the P rat. However, the finding that the BDZ antagonist Ro 15-1788 alone did not alter ethanol intake by the P rats suggests that the BDZ component of the complex may not be involved in the rewarding properties of alcohol. Beaman *et al.* [2] also observed that Ro 15-1788 did not alter intake of a solution of 6% ethanol–5% sucrose by Sprague-Dawley rats.

The effects of Ro 15-4513, fluoxetine and desipramine on H_2O and food intake of NP rats were similar to the results observed for the P rats (Fig. 2–6), except the response of the NP rats administered desipramine were more variable (Figs. 5 and 6). It is difficult to compare the effects of fluoxetine, desipramine and Ro 15-4513 on the 10% ethanol intake of the NP rats with data for the P rats since ethanol intake of the NP group was relatively low ($^1/_3$ level of P group) and variable (Figs. 2–5). However, there was a tendency for fluoxetine and desipramine to reduce 10% ethanol intake in the NP rat in a manner similar to that observed with these monoamine uptake inhibitors for the P group (Figs. 4 and 5). on the other hand, Ro 15-4513 more effectively reduced the intake of 10% ethanol in the NP group than in the P group since statistically significant reductions in the drug treated group were observed for the NP rats at 30 and 120 minutes but only at 30 minutes for the P group (Fig. 2). The reasons for this differential effect by Ro 15-4513 are unknown but it might be that, compared to the P line, the NP rats are more sensitive to and/or have a lower rate of elimination of this drug.

The BDZ receptor antagonist Ro 15-1788 stimulated food intake by the P and NP rats during the 2-hour period of fluid availability (Fig. 3), an effect which did not last over the 24-hour period. These results are counter to data of others who reported that BDZ agonists stimulated food consumption by rats while BDZ antagonists like Ro 15-1788 block this augmentation [6]. Consequently, this food intake response to Ro 15-1788 may be due to the present experimental paradigm and/or unique to these lines of rats. Furthermore, the enhanced food intake caused by Ro 15-1788 seems to involve an action at the BDZ-receptor since the increase can be blocked by Ro 15-4513 (Fig. 3).

There is ample evidence that serotonin is involved in food intake [4] and that 5-HT uptake inhibitors such a zimeldine and fluoxetine can reduce food intake by rats [10, 11, 25]. The present data on the reduced food intake by the P and NP rats administered the higher (10 mg/kg) dose of fluoxetine are in agreement with these findings. Previously, we have reported that fluoxetine had a tendency to have a mild anorectic effect in some P rats [17]. Under the present experimental conditions of limited fluid availability, a consistent anorectic effect with the 10 mg/kg dose of fluoxetine was observed (Fig. 6).

Gill and Amit [10] reported that the 5-HT uptake inhibitor zimeldine had a potent anorectic action, and that its action on ethanol intake was secondary to its primary action on reducing food intake. However, this does not seem to be the case for fluoxetine. With the present experimental condition, the 5 mg/kg dose of fluoxetine only reduced 10% ethanol consumption by the P rats (Fig. 4) and had no effect on food consumption during this 2-hour period of fluid availability (Fig. 6). On the other hand, the effects of desipramine on ethanol intake by the P rat (Fig. 5) may be secondary to its effects on food consumption (Fig. 6).

In conclusion, the present study (a) provides additional data supporting the involvement of 5-HT in the alcohol drinking behavior of the P rat, and (b) indicates the GABA-BDZ-CL^- receptor complex as a possible site of action of ethanol in the CNS of the P line of rats that is involved in regulation of voluntary ethanol intake.

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