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Spiroxatrine Augments Fluoxetine-Induced Reduction of Ethanol Intake by the P Line of Rats

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McBRIDE, W. J., J. M. MURPHY, L. LUMENG AND T.-K. LI. *Spiroxatrine augments fluoxetine-induced reduction of ethanol intake by the P line of rats.* PHARMACOL BIOCHEM BEHAV **34**(2) 381–386, 1989.—The present study was undertaken to determine if spiroxatrine, a reported 5-HT_{1A} antagonist, could block the attenuating effects of fluoxetine (a 5-HT uptake inhibitor) on voluntary ethanol intake by the selectively bred alcohol-preferring P line of rats. Fluoxetine (10 mg/kg, IP) significantly reduced the intake of 10% ethanol by P rats approximately 50% during the 4-hour period of alcohol availability. Spiroxatrine (4 mg/kg, IP) was without effect on ethanol intake when given alone. However, when given 5 minutes before fluoxetine (10 mg/kg, IP), this dose of spiroxatrine augmented the reduction of ethanol intake to approximately 15% of control values after 4 hours. Similar experiments conducted with 1 mg/kg (IP) 8-hydroxy-2(di-N-propylamino) tetralin (DPAT) demonstrated that this 5-HT_{1A} agonist also enhanced the attenuating effects of fluoxetine on ethanol intake. Likewise, spiroxatrine augmented the DPAT reduction of alcohol intake. Spiroxatrine enhanced the effect of DPAT and fluoxetine on food intake as it did on ethanol intake. The results suggest that spiroxatrine behaved as a partial agonist and/or modulator and not as an antagonist at 5-HT_{1A} receptors under the present experimental conditions.

Alcohol drinking Alcohol-preferring rats Spiroxatrine Fluoxetine 8-Hydroxy-2-(di-N-propylamino) tetralin

CONSISTENT findings have been reported concerning the effects of specific serotonin (5-HT) uptake inhibitors on alcohol intake in laboratory rats. It has been demonstrated that (a) zimelidine reduced the volitional intake of ethanol by stock Wistar rats (17–19); (b) daily injections for two weeks of the 5-HT uptake inhibitor doxepine or clomipramine significantly attenuated the intake of 12% (v/v) ethanol by male Long-Evans rats (3); and (c) other 5-HT uptake blockers, such as viqualine, citalopram and fluvoxamine, reduced ethanol consumption in a population of alcohol-drinking Wistar rats (11). In addition, the voluntary oral ethanol intake of the selectively bred alcohol-preferring P line of rats was reduced following IP administration of fluoxetine or fluvoxamine (13,14). More recently, it was reported that intragastric administration of fluoxetine markedly attenuated the intragastric self-administration of ethanol by P rats (15).

The reduction of ethanol intake by the uptake inhibitors presumably occurs through their immediate and sustained inhibition of 5-HT reuptake, thereby increasing the extracellular concentrations of 5-HT at the synaptic site (7). Relatively little is known about the subtypes of 5-HT receptors that may be involved in regulating alcohol intake, although attempts have been made to block the effects of the 5-HT uptake inhibitors with receptor antagonists. Neither metergoline, LY 53857 nor methysergide alone was found to alter ethanol intake, and furthermore, none of these antagonists blocked the attenuating effects of 5-HT uptake inhibitors on alcohol consumption (14,17). These latter results would suggest that 5-HT_2 and 5-HT_{1C} receptors were not involved in mediating alcohol drinking since metergoline, LY 53857 and methysergide have high affinities for both 5-HT sites (9). Recent studies indicated that B_{max} values for the 5-HT_1 receptor were higher in the frontal and posterior cerebral cortex and hippocampus of the alcohol-preferring (P) than in the alcohol-nonpreferring (NP) line of rats (23). These data provide support for an involvement of 5-HT_1 receptors in regulating ethanol intake of P rats.

Specific antagonists for subtypes of 5-HT_1 receptors have not been identified until recently, when it was reported that spirox-

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atrine (a) acted as an antagonist at 5-HT_{1A} receptors in canine cerebral vessels and (b) demonstrated highly selective binding to 5-HT_{1A} recognition sites compared with 5-HT_{1B} and 5-HT_2 binding sites (16). Therefore, the present study was undertaken to determine if the attenuating effects of fluoxetine on alcohol intake by the P line of rats could be blocked by spiroxatrine. In addition, experiments were conducted to determine if spiroxatrine could inhibit the actions of 8-hydroxy-2-(di-N-propylamine) tetralin (DPAT), a 5-HT_{1A} agonist (9, 10, 21, 22).

METHOD

Adult female alcohol-preferring P rats (N = 12) of the S-26 generation (approximately 250–320 g) were housed individually. The same animals were used for all alcohol drinking experiments. The colony room was maintained at 22 ± 1°C and 50% relative humidity with a shifted light-dark cycle such that lights went off at noon and on at midnight. All animals had been tested for ethanol preference at 45–60 days of age, as previously described (12). They consumed greater than 5 g ethanol/kg body wt./day and exhibited preference ratios of 10% (v/v) ethanol to water greater than 2:1. Ethanol and water intakes were measured with the aid of Richter tubes. Food consumption was monitored by weighing the amount of food in a container before and after each experiment.

Four-Hour Scheduled Access to Ethanol

For these experiments, animals were given food and water ad lib but access to the 10% ethanol solution was limited to a single 4-hour period beginning at noon, the start of the dark cycle. Ethanol intake was monitored hourly during this period, while food and water were measured over the 24-hour period. Stable baseline intakes of 10% ethanol, water and food were established prior to the IP injection of saline. Rats were injected with saline on 3–4 occasions to habituate them to handling. Usually, there was a 2–3 day interval between the saline injections. Drug treatments began after intakes of 10% (v/v) ethanol following saline injections were indistinguishable from baseline values on days that animals did not receive any injection.

All drugs were administered intraperitoneally (IP) in sterile saline to which was added 2–3 drops of Tween 80 per 10 ml (Sigma Chemical Co.). The injection volume employed was one ml/kg body weight. The drugs used were fluoxetine (Lilly), spiroxatrine (Research Biochemicals) and (±)-8-hydroxy-2-(di-N-propylamino) tetralin hydrobromide (DPAT, Research Biochemicals). Vehicle or drug injections were given 10–15 minutes before ethanol was made available. In the case where two drugs were injected, they were given approximately 5 minutes apart with spiroxatrine or DPAT preceding fluoxetine.

Two-Hour Limited Access Period for 10% Ethanol and Water

For these experiments, animals were given food ad lib but all fluid availability was limited to 2 hours each day beginning at noon, the start of the dark cycle. During this two-hour period, rats were allowed access to two randomly positioned Richter tubes, one containing water and the other 10% (v/v) ethanol. Water and ethanol intakes were monitored at 30, 60 and 120 minutes. Food intakes over 24 hours were determined by weighing the powdered food at the beginning of the daily two-hour period.

Vehicle or drugs (DPAT and spiroxatrine) were administered IP 10–15 minutes before availability of the two fluids. Rats given drug injections were not given another injection until subsequent days performance indicated that fluid and food intakes had stabilized at control levels. In the case where both DPAT and spiroxatrine were injected, spiroxatrine was administered 5 minutes before DPAT.

Behavioral Activity and 5-HT Syndrome Measurements

A separate group of P female rats (N = 6, 250–300 g) were used for these behavioral experiments. The ability of spiroxatrine (8 mg/kg) to block the effects of DPAT (1 mg/kg) on behavioral activity was measured in a 43.2 cm square photocell activity monitor (Columbus Instruments, Opto-Varimex) for one hour after injections. The effects of spiroxatrine alone (4 and 8 mg/kg) were also assessed in the activity monitor. In addition to the photocell ambulation score, the animals were observed every 5 min and evaluated for the presence of the following signs of the 5-HT behavioral syndrome (21,22): (a) flat body posture, (b) forepaw treading, (c) resting tremor, (d) head weaving, and (e) Straub tail. Each behavior was rated according to a four point scale: 0 = absent, 1 = equivocal, 2 = present, and 3 = intense.

Statistics

Statistical differences for ethanol, water and food intakes as well as for behavioral activity were determined with a repeated measure analysis of variance and post hoc Duncan's test.

RESULTS

Because some drugs have a relatively short duration of action, their effects on alcohol intake were studied in a time frame when ethanol consumption was regular and predictable, namely, by scheduling and limiting the availability of ethanol (14).

The first experiment was designed to determine if spiroxatrine could antagonize the attenuating actions of fluoxetine on ethanol intake. The 10 mg/kg dose of fluoxetine markedly reduced the intake of 10% ethanol over the 4-hour period, although the inhibition of intake at 4 hours was approximately half that seen after one hour (Fig. 1). A 4 mg/kg dose of spiroxatrine had no apparent effect on the intake of ethanol by the P rats (Fig. 1). However, this dose of spiroxatrine, when given 5 minutes before 10 mg/kg fluoxetine, significantly augmented the actions of this 5-HT uptake inhibitor on alcohol intake (Fig. 1).

The enhanced reduction in ethanol intake by spiroxatrine plus fluoxetine over that observed with fluoxetine alone was not expected. Therefore, the effect of the 5-HT_{1A} agonist DPAT (9) on ethanol intake of the P rats was also determined. The administration of 1 mg/kg DPAT reduced the intake of ethanol approximately 60% during the first hour (Fig. 1). However, within 2–4 hours, the intake of ethanol had nearly returned to control levels. As with spiroxatrine, DPAT augmented the reduction of alcohol intake by 10 mg/kg fluoxetine (Fig. 1).

The second experiment was designed to determine if spiroxatrine could antagonize the actions of DPAT on ethanol intake. The duration of action of DPAT on ethanol intake was approximately one hour (Fig. 1). During this time, DPAT was also observed to produce a flattened body posture (21,22) which might interfere with the ability of the rat to drink any solution offered. Therefore, the experimental design was altered so that both 10% ethanol and H_2O intake could be monitored over a shorter time frame. If the actions of DPAT were specific for ethanol, a reduction in H_2O intake should not be observed. The 1 mg/kg dose of DPAT significantly reduced the intakes of both 10% ethanol (Fig. 2) and H_2O (Fig. 3) during the first hour. However, both intakes recovered to control levels by 2 hours. A 16 mg/kg dose of spiroxatrine had no significant effect on the intake of either 10% ethanol (Fig. 2) or H_2O (Fig. 3). However, this dose of spiroxatrine markedly augmented the attenuating effects of DPAT on the intake of both fluids (Figs. 2 and 3).

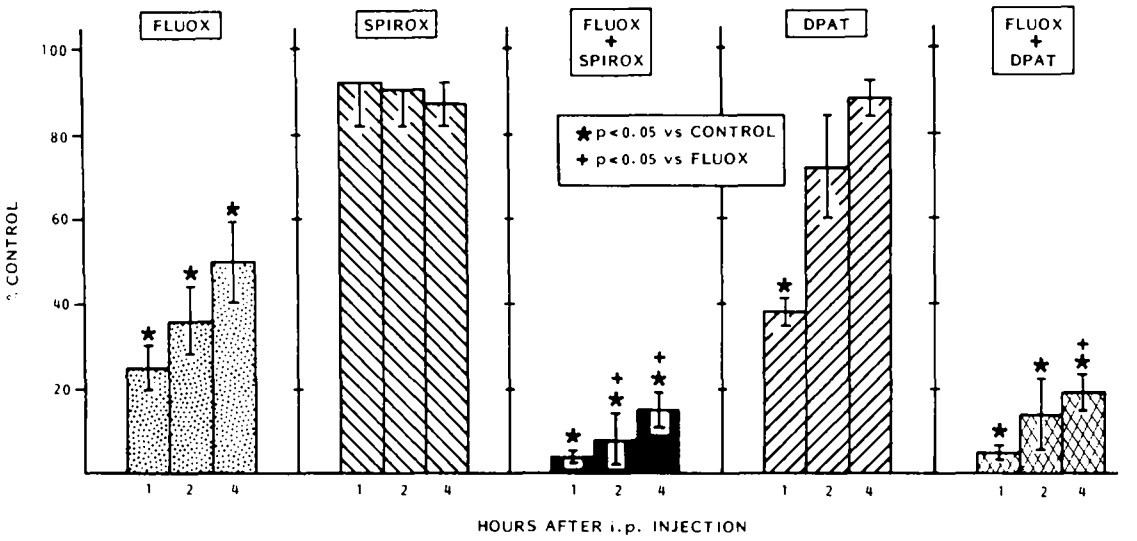

FIG. 1. Effects of 10 mg/kg fluoxetine (Fluox), 4 mg/kg spiroxatrine (Spirox), 10 mg/kg Fluox plus 4 mg/kg Spirox (Fluox + Spirox), 1 mg/kg 8-hydroxydipropylaminotetralin (DPAT) and 10 mg/kg Fluox plus 1 mg/kg DPAT (Fluox + DPAT) on the intake of 10% ethanol by female P rats (N = 12) during the 4-hour period of ethanol availability. Vehicle control values for the various experiments ranged from (a) 0.9 ± 0.1 to 1.1 ± 0.2 g/kg during the first hour; (b) 1.2 ± 0.1 to 1.5 ± 0.1 g/kg during the first two hours; and (c) 2.3 ± 0.2 to 2.5 ± 0.2 g/kg over the 4-hour period. In terms of volumes of 10% ethanol, this amounted to approximately 4, 6 and 10 ml consumed during the one-, two- and four-hour periods, respectively.

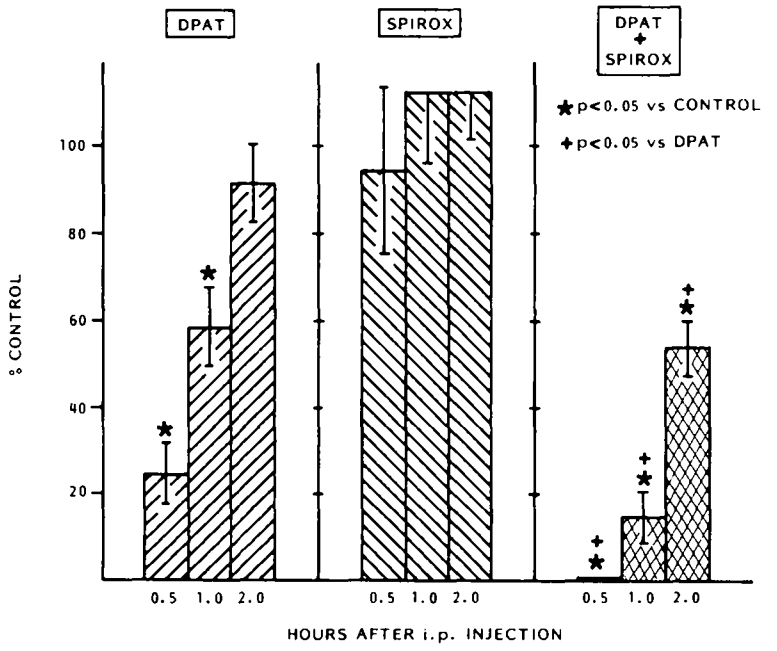

FIG. 2. Effects of 1 mg/kg DPAT, 16 mg/kg Spirox and 1 mg/kg DPAT plus 16 mg/kg Spirox (DPAT + Spirox) on the intake of 10% ethanol by female P rats (N = 12 for DPAT; N = 6 for Spirox and DPAT + Spirox experiments) during the two-hour period of fluid availability. Vehicle control values for the various experiments ranged from (a) 1.4 ± 0.2 to 1.9 ± 0.2 g/kg after 30 minutes; (b) 1.6 ± 0.2 to 2.2 ± 0.2 g/kg after 60 minutes; and (c) 1.6 ± 0.2 to 2.3 ± 0.3 g/kg after 120 minutes. In terms of volumes, this amounted to approximately 6, 7 and 8 ml of 10% ethanol consumed after 30, 60 and 120 minutes, respectively.

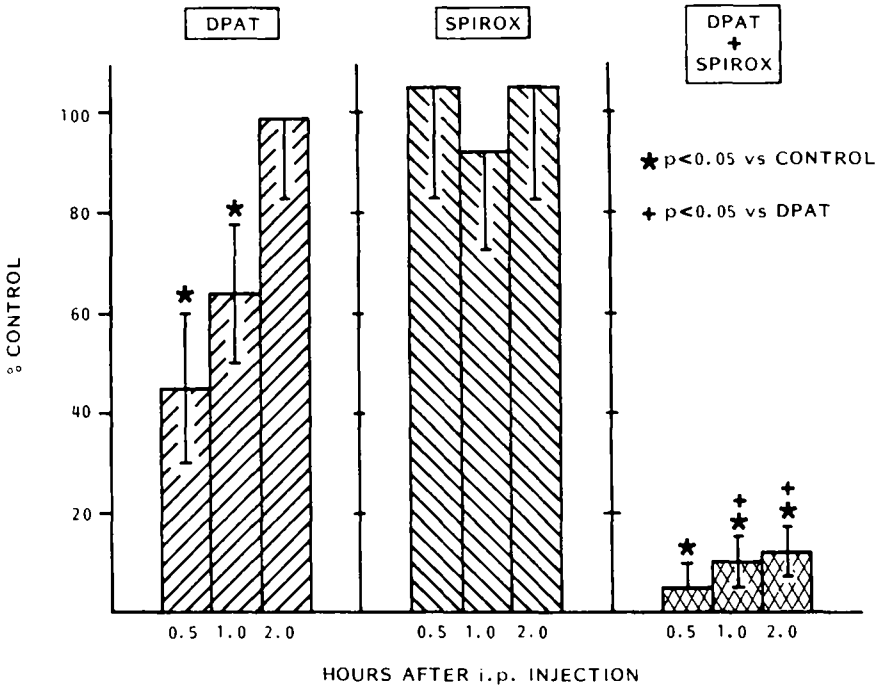

FIG. 3. Same for Fig. 2 except values are for H_2O intake by female P rats (N = 12 for DPAT; N = 6 for Spirox and DPAT + Spirox experiments). Quantities of H_2O consumed by vehicle-injected rats were 6 ± 1, 7 ± 1 and 9 ± 1 ml after 30, 60 and 120 minutes, respectively.

When given alone, neither 4 or 16 mg/kg spiroxatrine nor 1 mg/kg DPAT altered food intake significantly (Fig. 4). However, spiroxatrine and DPAT each enhanced the attenuating actions of fluoxetine on 24-hour food intake. Furthermore, when spiroxatrine and DPAT were given together there was a 35% reduction in food intake by the P rats (Fig. 4).

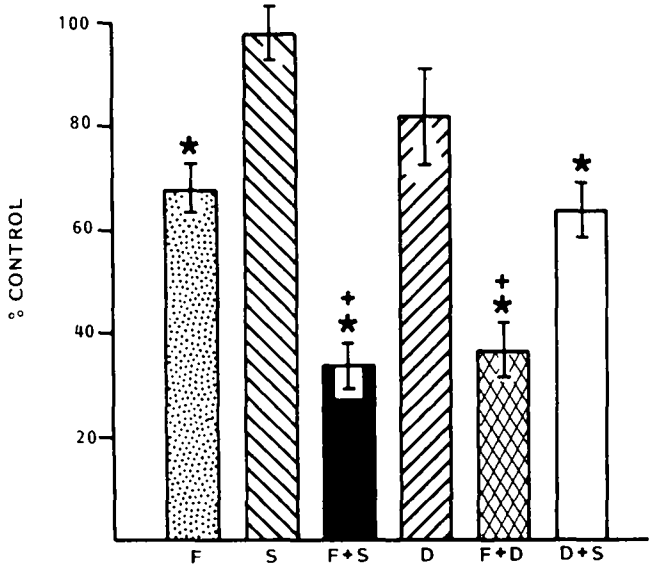

FIG. 4. Effect of 10 mg/kg fluoxetine (F), 16 mg/kg spiroxatrine (S), 10 mg/kg fluoxetine plus 4 mg/kg spiroxatrine (F+S), 1 mg/kg DPAT (D), 10 mg/kg fluoxetine plus 1 mg/kg DPAT (F+D) and 1 mg/kg DPAT plus 16 mg/kg spiroxatrine (D+S) on 24-hour food intake of P rats (N = 12 for F, F+S, D and F+D experiments; N = 6 for S and D+S experiments). Food intake for the vehicle-injected rats was 52 ± 2 g/kg/day. *$p<0.05$ vs. control; †$p<0.05$ vs. fluoxetine.

In a separate experiment to assess the degree of drug-induced motor impairment, the effects of DPAT (1 mg/kg, IP) on open-field ambulatory activity and signs of the 5-HT behavioral syndrome (21,22) were determined for female P rats (N = 6). Compared to saline control values, DPAT significantly ($p<0.05$) increased the ambulatory movements 2-fold during the 60-minute observation period (1,170 ± 130 vs. 2,370 ± 340 photobeam interruptions). Except for the flattened body posture which was observed only during the first 30 minutes, no other signs of the 5-HT behavioral syndrome (21,22) were clearly noticeable after DPAT administration. Spiroxatrine (8 mg/kg, IP) had no observable effect on the behavioral actions of DPAT in these experiments except for a 25% reduction in ambulatory movements (1,800 ± 250 photobeam interruptions). The effects of spiroxatrine alone were indistinguishable from saline in both ambulatory movements and signs of the 5-HT behavioral syndrome.

DISCUSSION

The data are consistent with the concept of spiroxatrine acting more like an agonist than an antagonist under the present experimental conditions, since this agent augmented the actions of fluoxetine, a 5-HT uptake inhibitor, and DPAT, a 5-HT_{1A} agonist (Figs. 1–4). These results are not in agreement with the reported antagonist action of spiroxatrine at 5-HT_{1A}-like receptors in canine cerebral vessels (16) and may indicate a dual or unique action of spiroxatrine at different 5-HT_{1A} receptor sites. However, it has been reported that (^{3}H) spiroxatrine has "agonist-like" binding properties in its interaction with 5-HT_{1A} receptor sites in homogenates of rat hippocampal membranes (8). Therefore, it is possible that spiroxatrine may be exerting weak or partial agonist actions at certain 5-HT_{1A} sites involved in mediating ingestive behaviors.

The data are also consistent with the possibility that spiroxatrine may be acting as a modulator at 5-HT_{1A} receptor sites to enhance the actions of 5-HT and 5-HT agonists. In addition, the effects of spiroxatrine may be a result of an action at a nonserotonergic receptor.

Spiroxatrine itself did not alter the intake of 10% ethanol by the P rats (Figs. 1 and 2), but it did augment the actions of fluoxetine and produce a further reduction in alcohol consumption (Fig. 1). The effects of spiroxatrine on the attenuating action of fluoxetine on ethanol intake was similar to that observed when DPAT and fluoxetine were administered together (Fig. 1). Since binding studies are consistent with a highly selective effect of spiroxatrine at 5-HT_{1A} recognition sites (8, 9, 16), the data suggest that the 5-HT_{1A} receptor is involved in regulating alcohol intake and that the attenuating effects of 5-HT uptake inhibitors on ethanol intake may be mediated at least in part through this receptor. Previous findings for fluoxetine, using the schedule of limiting access to both 10% ethanol and H_2O to a single two-hour period each day, indicated that this 5-HT uptake inhibitor significantly reduced 10% ethanol intake of P rats, but did not alter H_2O consumption (13).

The fluid deprivation schedule of limiting access to both 10% ethanol and H_2O to a single two-hour period each day permitted a more differential assessment of the effects of DPAT than did the 4-hour access period. Motor abnormalities have been reported following injection of DPAT (21,22), which may impair the ability of the animal to drink at all. The time course of the recoveries of 10% ethanol and H_2O intakes following IP injection of DPAT were very similar and indicate that the actions of DPAT were not specific to alcohol intake but were more widespread and might possibly be due to the impaired motor function (flattened body posture) observed over the first 30 minutes. However, in the case of spiroxatrine, factors other than abnormal motor functions need to be considered since this drug further reduced and prolonged the actions of DPAT on fluid intake without noticeably affecting the 5-HT behavioral syndrome.

There is ample evidence that serotonin is involved in mediating food intake (2), and that 5-HT uptake inhibitors can reduce food intake by rats (5, 6, 20). The present finding of reduced 24-hour food intake by female P rats following the IP administration of 10 mg/kg fluoxetine is similar to the findings observed for male P rats on the 2-hour schedule of fluid availability (13). The finding that the anorectic effect of fluoxetine was enhanced by spiroxatrine and DPAT (Fig. 4) would suggest that 5-HT_{1A} receptors may also be involved, at least in part, in mediating eating behavior of the P rat.

There is evidence from other studies suggesting the involvement of the 5-HT_{1A} receptor in mediating food intake. Compared to control values, food intake was markedly reduced in food-deprived rats within the first hour after SC administration of 1 mg/kg DPAT when food was made available (1), while in food nondeprived rats a 0.5 mg/kg SC dose of DPAT increased food intake within the first two hours following drug treatment (10). Contrary to these results, in the present study, a 1 mg/kg IP dose of DPAT did not alter food intake over a 24-hour period (Fig. 4) or during the two-hour period of fluid availability (15.7 ± 1.5 for control vs. 14.5 ± 2.0 g/kg for DPAT; $N = 12$). This lack of effect of DPAT on food intake observed in the present study may be because subcutaneous administration of DPAT is far more potent than is intraperitoneal injection (4).

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