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Fluoxetine Reduces Saccharin-Induced Elevation of Fluid Intake in Alcohol-Preferring Fawn-Hooded Rats

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KAMPOV-POLEVOY, A. B. AND A. H. REZVANI. *Fluoxetine reduces saccharin-induced elevation of fluid intake in alcohol-preferring Fawn-Hooded rats.* PHARMACOL BIOCHEM BEHAV **58**(1) 51–54, 1997.—Previous work has established that saccharin and alcohol intakes are highly correlated in a variety of rat strains. In addition, it has been shown that alcohol-preferring rats consume saccharin beyond the limit of their normal daily fluid intake (DFI). It has been hypothesized that alcohol-preferring rats have impaired control over consumption of reinforcing substances, which may be related to a deficiency of brain serotonin. In the present study, we examined the effect of the serotonin reuptake inhibitor fluoxetine (2.5, 5.0, 10.0 mg/kg, IP, twice a day) on saccharin intake in alcohol-preferring Fawn-Hooded (FH) rats. It was confirmed that alcohol preferring FH rats almost triple their DFI when saccharin/water choice was introduced. Treatment with fluoxetine resulted in a dose-dependent decrease in saccharin intake to, but not below, the normal level of their DFI. No significant effects of fluoxetine on water intake were observed. Despite a significant (up to 69%) decrease in saccharin intake, only a minimal reduction (<4%) in saccharin preference occurred. We conclude that fluoxetine reduces the exessive elevation of fluid intake observed at the presence of the palatable saccharin solution in Fawn-Hooded rats. These findings may provide more evidence for the involvement of the serotonergic system in the brain in exessive drinking of rewarding substances. © 1997 Elsevier Science Inc.

Saccharin intake Fluoxetine Fawn-Hooded rats Loss of control Serotonin

PREVIOUS work has established that saccharin and alcohol intakes are highly correlated in a variety of rat strains (6,10, 11,17,23). Although all studied rat strains/lines demonstrated high preference for 0.1% (w/v) saccharin solution, only alcohol-preferring animals consumed it beyond the limits of their normal daily fluid intake (DFI). It has been shown that rats with genetically influenced alcohol preference (P, Fawn Hooded [FH]) more than double their DFI when saccharin is available. This increase is significantly higher than that reported for randomly bred rats. It has been demonstrated that alcohol-preferring strains that are known to have a dysfunction of the brain serotonin system, such as P (14) and FH (20,21), had a higher DFI increase in the presence of saccharin compared with alcohol-preferring AA rats with relatively normal serotonergic function (22). These findings have led to the hypothesis that some alcohol preferring rats, such as P and FH rats, have an impaired ability to control consumption of reinforcing substances as a result of dysfunction of the brain serotonergic system that normally regulates satiety (3). To explore this hypothesis, we studied the effects of serotonin reuptake inhibitor fluoxetine on saccharin consumption in alcohol-preferring FH rats, a strain with genetic serotonin dysfunction that exhibits high preference for rewarding substances such as alcohol and saccharin (18,20).

METHOD

Animals

Nineteen male FH rats from a viral-free breeding colony maintained at Skipper Bowles Center for Alcohol Studies,

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TABLE 1

EFFECT OF FLUOXETINE OR SALINE (I.P., TWICE A DAY) ON SACCHARIN AND WATER INTAKE AS WELL AS SACCHARIN PREFERENCE

Dose (mg/kg)	Water intake (ml/kg/day)			Saccharin intake (ml/kg/day)		Saccharin preference (%)	
	W/W	Sacch/W	Sacch/W-Tx	Sacch/W	Sacch/W-Tx	Sacch/W	Sacch/W-Tx
Saline	121.8 ± 8.0[a]	1.3 ± 0.5[a]	8.8 ± 4.9[a]	453.3 ± 38.3[a]	99.7 ± 0.1[a]	99.7 ± 0.1[a]	98.4 ± 0.8[a]
5.0	89.3 ± 8.0[a]	4.6 ± 2.1[a]	4.9 ± 0.8[a]	308.8 ± 31.5[a]	216.6 ± 25.3[b]*	98.5 ± 0.6[a]	97.8 ± 0.3[a]
10.0	92.1 ± 5.2[a]	2.0 ± 1.1[a]	5.2 ± 0.6[a]	327.8 ± 21.9[a]	147.2 ± 15.5[b]*	99.4 ± 0.4[a]	96.5 ± 0.5[a]*
15.0	112.4 ± 15.2[a]	2.2 ± 1.3[a]	4.1 ± 1.1[a]	388.8 ± 62.0[a]	122.3 ± 12.3[b]*	99.5 ± 0.3[a]	96.6 ± 1.0[a]*
F	2.305	1.018	0.835	2.287	19.947	1.431	1.706
p	0.1184	0.4123	0.4953	0.1203	<0.0001	0.2730	0.2084

W/W, water intake when it was available as a sole source of fluids; Sacch/W, choice between 0.1% (w/v) saccharin solution and water; Sacch/W-Tx, choice between 0.1% (w/v) saccharin solution and water during fluoxetine treatment.

Numbers in a column with the same superscript are not significantly different from each other ($p > 0.05$) according to analysis of variance with Fisher LSD post hoc comparisons.

*, Difference between treatment and pre-treatment levels is significant ($p < 0.05$) according to paired *t*-test.

University of North Carolina at Chapel Hill were used in this experiment. The average body weight was 463 ± 7g at the beginning of the experiment. The rats were maintained under constant temperature (22°C) and reversed 12:12 light:dark cycle (lights on from 22:00 to 10:00).

Procedure

Rats were randomly assigned to one of four groups (three groups of five rats and one group of four rats). During the experiment, all animals were kept in individual cages with free access to food. Two 100-ml Richter tubes were attached to the front of each cage. During the first four days, both tubes contained water to establish a baseline DFI. After this, for 24 h, one tube was filled with 0.1% (w/v) saccharin solution and the other contained water to estimate saccharin intake and preference. Then both tubes were filled with water again for 7 days to reestablish baseline DFI. Thereafter, all rats were exposed to a saccharin/water choice for 24 h for the second time. This time, during saccharin/water choice, rats were injected IP with fluoxetine (group 1, 5.0 mg/kg; group 2, 10.0 mg/kg; group 3, 15 mg kg; group 4, saline) twice a day. The first injection was performed at 09:30, 30 min before the exposure of animals to saccharin/water choice, and the second injection was performed at 17:00. Consumption of drinking fluids was recorded daily and body weight was recorded twice per week. Saccharin intake was expressed as ml/kg/day; saccharin preference was calculated as saccharin intake/DFI × 100. Saccharin-induced elevation of DFI was calculated as (DFI during saccharin/water choice − DFI when water only is available)/DFI when water only is available × 100.

Drug Prepartion

A solution of 0.1% (w/v) Na saccharin (Sigma, St. Louis, MO) was prepared daily by dissolving saccharin in distilled water. Fluoxetine HCl (Lilly Research Laboratory) was prepared fresh with saline at different concentrations and always injected 1 ml/kg B.W. Control saline was also injected IP in a volume of 1 ml/kg B.W.

Statistical Analysis

Analysis of variance with Fisher LSD post hoc comparisons was used to estimate differences between treatments. Paired *t*-test was used to compare the DFI data within the groups before and after treatments.

RESULTS

The data showed that when FH rats are given free access to food and water, they drink an average of 98 ± 6 ml/kg/day of water. When rats were exposed to saccharin/water choice for the first time, they almost tripled their DFI (mean DFI increase was 276 ± 39%) with a 99 ± 0.3% preference for saccharin. After reestablishing the baseline for water consumption, rats were injected with different doses of fluoxetine and exposed to saccharin/water choice for a second time. Treatment with fluoxetine, but not saline, caused a dose-dependent reduction in saccharin intake, with no significant effect on wa-

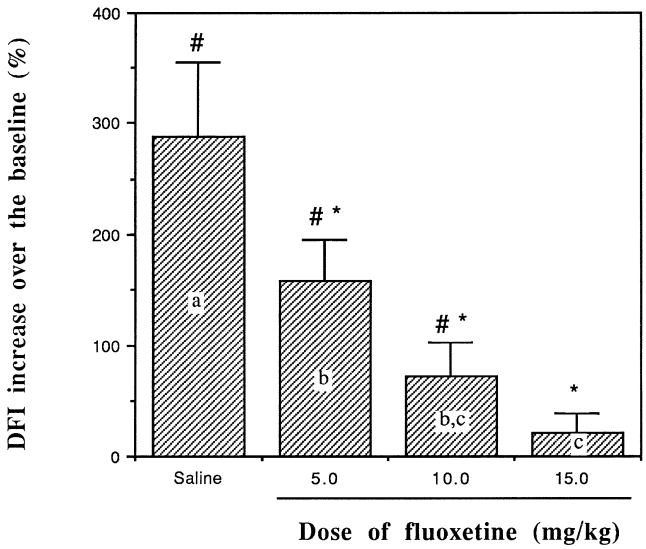

FIG. 1. Effects of fluoxetine (IP; twice a day) on saccharin-induced elevation of DFI in alcohol-preferring Fawn-Hooded rats. Values represent means ± SEM. *, different from the water level ($p < 0.05$); #, different from the sacch/water level ($p < 0.05$). Groups with the same letter are not different from each other ($p > 0.05$) according to Fishers's PLSD post hoc analysis.

ter consumption (Table 1). This resulted in suppression of saccharin-induced elevation of DFI (Fig. 1). Fluoxetine treatment had a minimal (<4%) effect on saccharin preference (Table 1).

DISCUSSION

The present study confirms our previous reports (11,17) regarding propensity of alcohol-preferring FH rats to consume saccharin solution far beyond the limit of their normal DFI. Treatment with fluoxetine, but not control vehicle, resulted in a significant dose-dependent reduction in saccharin intake, with no effect on water consumption. Despite of a dramatic decrease in saccharin intake (up to 69%), saccharin preference remained virtually the same. This was the result of the suppressant effects of fluoxetine on saccharine intake only to a certain extent; i.e., reducing the saccharin intake within the normal DFI, a phenomenon we call it "normalization of DFI." The fact that the fluoxetine treatment, even at the highest dose, had a minimal effect on saccharin preference suggests that fluoxetine did not induce taste aversion to saccharin in this paradigm. However, a more extensive study is needed to directly investigate this possibility.

It has been hypothesized (11,16,20,21) that a deficiency of the brain serotonin (3) may be responsible for excessive consumption of rewarding substances, including sweets and alcohol. Manipulations leading to decreased serotonin function, such as destruction of serotonin neurons with neurotoxins, have been reported to enhance ethanol consumption (7,16). Reduced activity of the brain serotonin system also changes feeding patterns. In humans, reduced activity of brain serotonin system results in carbohydrate obesity and binges with carbohydrates (13,25). In animals, suppression of serotonergic tone, using the general serotonin antagonist methysergide, stimulates food intake in well-sated rats (4). On the other hand, drugs that enhance central serotonergic transmission diminish elective carbohydrate consumption by rats (26).

The existence of a common mechanism, such as dysfunction of brain serotonin system for loss of control, may explain the high level of comorbidity (up to 60%) that exists between eating disorders and substance abuse in humans (8) and strong association (r up to 0.8) between consumption of sweets and alcohol in a variety of mouse (2,5,19) and rat (9–11,17,23) strains/lines.

Alcohol-preferring FH rats that are known for having a dysfunction of the brain serotonergic system (20,21) consumed saccharin solution far beyond their normal DFI (17). Treatment with serotonin reuptake inhibitor fluoxetine reduced saccharin intake to the limits of their normal DFI. These results are consistent with an earlier report by Leander (12), who showed that fluoxetine at doses of 1.25–10.0 mg/kg selectively decreased excessive drinking of saccharin solutions in a dose-dependent manner, with no effect on consumption of water in a limited scheduled access paradigm. The anorectic effect of fluoxetine is believed to be attributed mainly to an increase of postprandial satiety [for discussion see (15,24)], however, there is a report suggesting that the high (10 mg/kg) dose of this drug may also reduce palatability of sugar (1).

The results of the present study are consistent with a large body of evidence suggesting that dysfunction of the brain serotonergic system is one of the underlying causes of excessive consumption of palatable substances and that normalization of the brain serotonergic system by using the serotonin re-uptake inhibitor fluoxetine may reverse this process. Based on these results, we suggest that fluoxetine suppresses the saccharine-induced elevation of DFI in FH rats indicating the involvement of serotonergic system in exessive drinking of paltable solutions.

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