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Suppression of Alcohol Consumption by Fenfluramine in Fawn-Hooded Rats With Serotonin Dysfunction

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REZVANI, A. H. AND D. R. GRADY. *Suppression of alcohol consumption by fenfluramine in Fawn-Hooded rats with serotonin dysfunction.* PHARMACOL BIOCHEM BEHAV 48(1) 105–110, 1994.—The high preference for alcohol intake observed in Fawn-Hooded rats has been attributed to the central serotonin (5-HT) dysfunction in this strain. To further characterize the involvement of 5-HT in alcohol-seeking behavior in Fawn-Hooded rats, the effect of both acute and subchronic administration of fenfluramine, a 5-HT releaser, on alcohol intake and preference was determined. Rats were individually housed and provided free access to a solution of 10% alcohol, food, and water. After establishing a stable baseline, rats were injected twice daily for 1 day or for 5 consecutive days either with saline or 0.1, 0.25, 0.5, and 1.0 mg/kg of fenfluramine at 0930 h and 1600 h, and their consumption of alcohol, food, and water was measured for 24 h. Another group of rats scheduled with a limited access (1 h/day) to alcohol and free access to food and water were injected with either saline or 0.25, 0.5, 0.75, and 1.0 mg/kg fenfluramine 20 min before exposure to alcohol, and their alcohol consumption was measured at the end of 1 h exposure. Further, to determine the effect of fenfluramine on alcohol metabolism, rats were injected with 1.0 mg/kg fenfluramine or saline and 15 min later with 2.5 g/kg alcohol (16%, v/v). Blood alcohol levels were then measured at 1, 3, and 5 h after alcohol administration. Our results demonstrate that both acute and subchronic administration of fenfluramine dose-dependently attenuate alcohol intake and increased water intake without a significant effect on food intake. Fenfluramine did not affect the pharmacokinetics of alcohol, indicating a central effect. These findings provide more support for the involvement of the serotonergic system in excessive alcohol consumption and indicate that fenfluramine exerts an attenuating effect on alcohol intake by enhancing the activation of serotonergic systems in the brain.

Fawn-Hooded rats Drinking behavior Serotonin Alcohol Alcohol preference Fenfluramine Blood alcohol

THE neurotransmitter serotonin [5-hydroxytryptamine (5-HT)] has been shown to be involved in of a wide variety of neurobiological functions and behaviors, including depression, mood disorders, anxiety, feeding disorders, and alcoholism. Pharmacological manipulations of the serotonergic systems in the brain markedly influence alcohol consumption in rats (15,17,18,30), monkeys (4), and human alcoholics (8,20–23). Further, it has been shown that selectively bred alcohol-preferring (P) rats have lower levels (12–26%) of 5-HT and its metabolite (5-HIAA) in frontal cortex, nucleus accumbens, and anterior striatum, thalamus, hypothalamus, and pons-medulla (19), and a greater number of 5-HT binding sites in frontal cortex and hippocampus than alcohol-nonpreferring (NP) rats (39). Similar associations, i.e., serotonin deficiency and alcohol intake, have been reported in C57BL inbred mice (40) and Fawn-Hooded rats (30). However, in one strain of alcohol-preferring rats, an opposite relationship has been demonstrated. The alcohol-preferring AA rats have been shown to have higher concentration of 5-HT than the alcohol-avoiding ANA rats. Further, no significant differences exist between these rat lines in the ligand binding sites of the $5\text{-HT}_{1\text{-}3}$ receptors (12).

Several serotonergic agonists and antagonists have been shown to reduce alcohol intake in experimental animals. These include 5-HT_1 agonists such as buspirone (4), 8-OH-DPAT (13,14,19), 5-HT_2 receptor blockers such as ritanserin (24,25),

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5-HT_3 antagonists such as MDL 72222 (6), ondansetron, ICS 205930 (35), and zacopride (11), and serotonin releaser such as fenfluramine (7,17,18,35). D,L-5-HTP, a 5-HT precursor, also has been shown to reduce alcohol consumption in alcohol-preferring rats (17,18). In addition, several serotonin uptake inhibitors such as fluoxetine (8,20,21), fluvoxamine (36), citalopram (23), and zimelidine (22) have been shown to reduce alcohol consumption in human alcoholics and heavy drinkers. Several mechanisms have been proposed for the attenuating effects of these compounds on alcohol intake. Increasing the levels or the availability of brain serotonin has been suggested as one possible mechanism. However, other mechanisms have been proposed for some of these compounds. For example, it has been speculated that MDL 72222 suppresses ethanol intake by preventing ethanol-induced stimulation of the firing of mesolimbic dopamine neurons believed to be involved in the brain reward system (6). All together, these data indicate that the serotonergic systems in the brain are involved in alcohol drinking behavior, and it appears that reduced activity of the CNS serotonergic system is a major factor in the manifestation of alcohol preference (3,30).

To further investigate the role of the 5-HT system in alcohol drinking, we examined the effect of fenfluramine on alcohol preference in Fawn-Hooded rats. Fenfluramine (*N*-ethyl-methyl-m-(trifluoro-methyl) phenethylamine) is a 5-HT releaser which, upon injection, increases the level of 5-HT in the synaptic cleft. Thus, it can activate the serotonergic pathways in the brain (32). Recently, it has been shown that the Fawn-Hooded (FH) rat, a Wistar-derived strain that possesses a genetic 5-HT impairment (1,5,9,10), also exhibits a high preference for alcohol (26,30,31). Fawn-Hooded rats exhibit a general subsensitivity to serotonergic compounds in terms of food intake, hypothermia, and motor activity (2,9,38). When compared with Wistar and Sprague-Dawley rats, Fawn-Hooded rats demonstrate a lower density of 5-HT_{1A} receptor in striatum and brain stem, and a greater number of 5-HT_2 receptors in the striatum and frontal cortex (10). It also has been demonstrated that the B_{max} values for [^{3}H]paroxetine (a selective serotonin reuptake inhibitor) binding in the hypothalamus were significantly less in Fawn-Hooded rats compared with those of Wistar and Sprague-Dawley rats. This strain of alcohol preferring rats drinks enough alcohol to develop tolerance to its hypothermic action. In a limited scheduled access paradigm, they also drink enough alcohol in 1 h to elevate their blood alcohol levels to about 80 mg/dl (29). Thus, it seems that Fawn-Hooded rats drink alcohol for its pharmacologic/reinforcing effects. Because a reciprocal relationship exists between brain serotonin function and uncontrolled alcohol drinking, we hypothesize that fenfluramine, by activating the serotonergic systems in the brain, would attenuate alcohol consumption in Fawn-Hooded rats.

METHOD

Animals

Adult male Fawn-Hooded rats used in this project weighed 0.418 ± 0.01 (SEM) kg at the beginning of the experiment. Rats were obtained from a viral-free colony of alcohol-preferring Fawn-Hooded rats established at the University of North Carolina School of Medicine. Animals were housed individually in suspended stainless steel wire mesh cages (26 × 34 × 20 cm) under a constant temperature of 21 ± 1°C and a 12 D : 12 L reversed cycle (0930–2130 h dark). Animals were fed Agway Prolab Rat/Mouse/Hamster 3000 Formula (Agway, Syracuse, NY) and water ad lib.

Screening for Alcohol Preference

Rats were screened for alcohol preference using the standard two-bottle method (28,37). They were first given free access to tap water in a graduated Richter tube for 1 day. The next day they were given free access to a solution of 10% (v/v) ethanol in a graduated Richter tube as a sole source of fluid for 3 consecutive days. This procedure allowed them to become accustomed to drinking from the tube and to the taste of alcohol. Thereafter, rats were given free access to tap water and a solution of 10% ethanol for at least 2 weeks. Food was available ad lib throughout. Food, water, and ethanol intake and body weight were recorded every day between 0900 and 0930 h.

Blood Ethanol

A group of eight adult male Sprague-Dawley rats weighing 0.538 ± 24 (SEM) kg were used for measuring the effect of fenfluramine on blood ethanol. This group of rats had free access to food and water but not ethanol.

Preparation of Drugs

Solutions of fenfluramine (Sigma, St. Louis, MO) were prepared daily in pyrogen free glassware with a sterilized isotonic saline. Five doses of fenfluramine (0.1, 0.25, 5.0, 0.75, and 1.0 mg/kg b.wt.) were used. The volume of saline vehicle or drug injected was 1 ml/kg b.wt. A 10% (v/v) solution of ethanol was prepared daily from 95% reagent grade alcohol and distilled water (28).

Experimental Protocol

Acute effects of fenfluramine on ethanol, water, and food intake. Following the standard method of Waller et al. (37), and after establishing a stable baseline for ethanol and water intake in Fawn-Hooded rats, at approximately 0930 h and 1600 h a single SC injection of saline or one of the doses of fenfluramine (0.1, 0.25, 0.5, and 1.0 mg/kg b.wt.) was given to each rat (n = 8). All animals in this group received all of the treatments, i.e., saline and four doses of fenfluramine. The interval between injections was at least 1 week. Throughout the study, water, food, ethanol intake, and body weight were measured every morning between 0900 and 0930 for the proceeding 24 h. Food intake was measured by weighing the food container each day at 0930 h.

In another study, the acute effect of fenfluramine on ethanol and water intake was determined in another group of adult male Fawn-Hooded rats (n = 11) that had limited access to ethanol. This group of rats had free access to food and water but limited access (1 h/day) to a solution of 10% ethanol from 0900–1000 h. After being on the scheduled limited access for several weeks and establishing a stable baseline for alcohol intake, all rats were injected in a crossover design with either one of the doses of fenfluramine (0.25, 0.5, 0.75, and 1.0 mg/kg; subcutaneously) or saline 20–30 min before exposure to alcohol. The intervals between injections were at least 3 days. Both alcohol and water intake were measured at the end of 1 h alcohol exposure.

Subchronic effects of fenfluramine on ethanol, water, and food intake. In another group of adult male Fawn-Hooded rats (n = 11), after establishing a stable baseline for ethanol and water intake, animals were injected (SC) in a crossover design with either 1.0 mg/kg of fenfluramine or saline twice a day at approximately 0930 h and 1600 h for 5 consecutive days. In the crossover design, the interval between saline in-

jections (1st treatment) and fenfluramine injections (2nd treatment) was 4 days. The interval between fenfluramine administration (1st treatment) and saline administration (2nd treatment) was 2 weeks. Throughout the study, water, food, and ethanol intake were measured every day between 0900 and 0930 h.

Effects of fenfluramine on blood ethanol. Adult male Sprague-Dawley rats (n = 8) were injected subcutaneously with either 1.0 mg/kg of fenfluramine or an equal volume of saline and 15 min later with an IP dose of 2.5 g/kg of ethanol (16% v/v) following a crossover design with 1 week interval. Blood samples (20 μl) were obtained from the tip of the tail of each rat at 1, 3, and 5 h after ethanol administration. Blood samples were transferred immediately to a microcentrifuge tube containing 180 μl of *tert*-butanol (0.3 mg/ml), as an internal standard. After shaking, the tubes were stored at −20°C until gas chromatography (GC) analysis. Each vial was centrifuged and 5 μl of this supernatant was injected into a GC (Varian Aerograph Model 2400) equipped with a flame ionization detector and a 60/80 carbopack B/5% Carbowax 20M, 6 × 2 mm IV glass column (Supelco, St. Louis, MO). The chromatographic conditions were carrier gas (N_2), flow rate 20 ml/min.; 60–100°C at 10°C/min temperature program; injector temperature 120°C; detector temperature 140°C. Blood ethanol concentrations are expressed as mg/dl of blood (27).

Statistical analysis of data. The results are expressed as means ± standard error of means, and statistical differences between drug-treated and saline-treated groups were determined by using ANOVA with repeated measures and Tukey's protected t-test for multiple comparison.

RESULTS

Acute Effects of Fenfluramine

When given free access to food, ethanol, and water, Fawn-Hooded rats consumed an average of 5.23 ± 0.38 g/kg b.wt. ethanol and 45 g/kg b.wt. water per day. Compared with saline, a single injection of 0.1, 0.25, 0.5, or 1.0 mg/kg of fenfluramine significantly reduced the amount of ethanol intake ($p < 0.05$ for the dose of 0.1 mg/kg and $p < 0.01$ for other doses of fenfluramine) and concomitantly increased water intake (Fig. 1). The proportion of ethanol intake to total fluid intake (ethanol + water), which has been used as a reliable index of alcohol preference in similar studies (18,30), was significantly reduced following the administration of 0.25, 0.5, and 1.0 mg/kg of fenfluramine ($p < 0.01$) (Fig. 2). Fenfluramine had no significant effect on food intake.

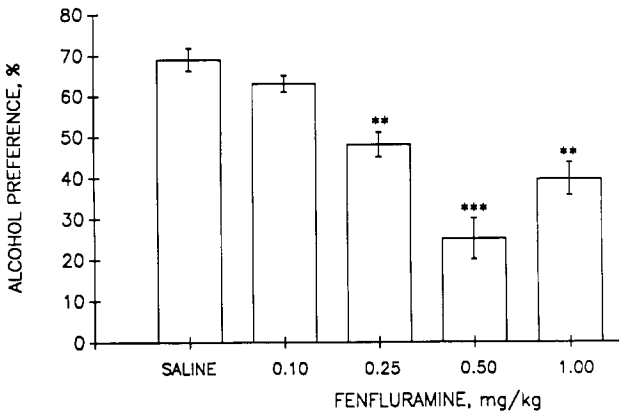

FIG. 2. Effects of acute administration of saline and different doses of fenfluramine on alcohol preference in Fawn-Hooded rats. Data are the mean ± standard error of mean (n = 8). **$p < 0.001$ as compared with corresponding saline values.

Fawn-Hooded rats, when given a scheduled limited (1 h/day) access to ethanol, drank an average of 0.81 ± 0.07 g/kg b.wt. ethanol in 1 h. Compared with saline, administration of different doses of fenfluramine (0.25, 0.5, 0.75, and 1 mg/kg) 20–30 min before ethanol exposure significantly ($p < 0.02$) reduced alcohol intake (Fig. 3) without affecting water intake.

Subchronic Effects of Fenfluramine

Compared with saline, administration of 1.0 mg/kg fenfluramine twice a day for 5 consecutive days significantly reduced both alcohol intake ($p < 0.01$) (Fig. 4) and alcohol preference ($p < 0.01$) (Fig. 5).

Subchronic administration of fenfluramine, but not saline, significantly ($p < 0.01$) and continuously increased water in-

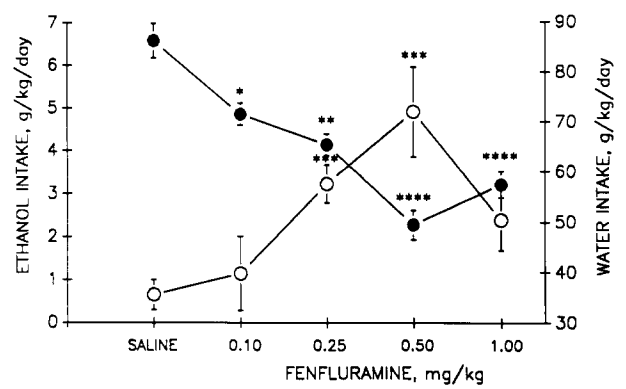

FIG. 1. Effects of acute administration of saline and different doses of fenfluramine on the daily intake of 10% ethanol (●) and water (○) by Fawn-Hooded rats. Data are the means ± standard error of mean (n = 8), *$p < 0.05$; **$p < 0.01$ as compared with corresponding saline values.

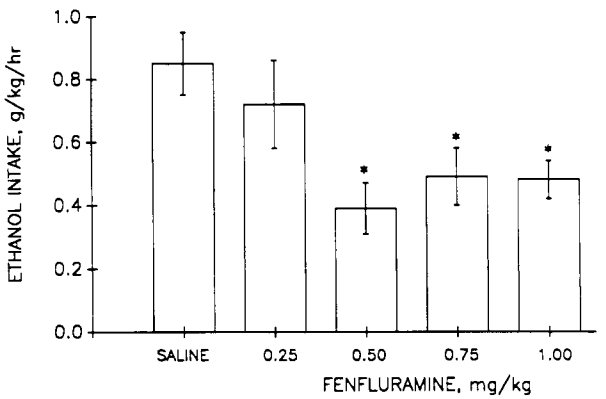

FIG. 3. Effects of acute administration of saline and different doses of fenfluramine on ethanol intake in Fawn-Hooded rats with limited access (1 h/day) to ethanol. Data are the mean ± standard error of mean (n = 11), *$p < 0.02$.

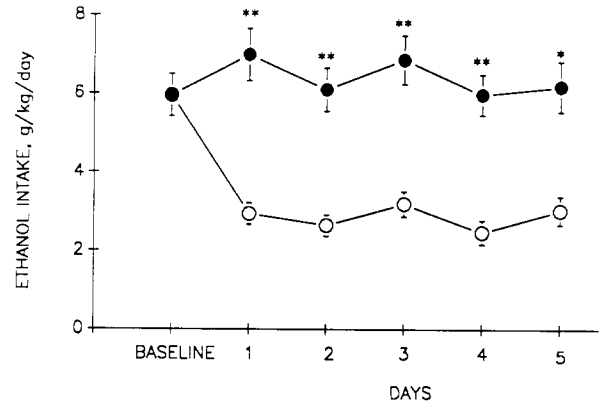

FIG. 4. Effects of subchronic administration of saline (●) and fenfluramine (1.0 mg/kg twice a day) (○) on intake of ethanol by Fawn-Hooded rats. Data are the means ± standard error of mean (n = 11), $^{**}p < 0.01$.

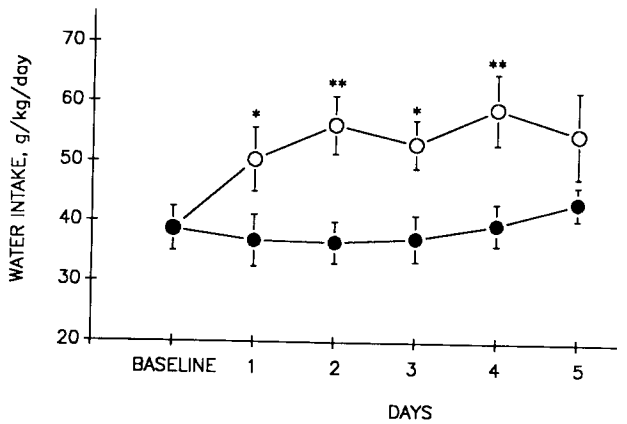

FIG. 6. Effects of subchronic administration of saline (●) and fenfluramine (1.0 mg/kg twice a day) (○) on water intake in Fawn-Hooded rats. Data are the means ± standard error of mean (n = 11), $^{*}p < 0.05$, $^{**}p < 0.01$) compared with corresponding saline values.

take (Fig. 6). Subchronic effects of fenfluramine on alcohol and water intake sustained during the course of the experiment. Subchronic administration of 1.0 mg/kg of the drug did not exert a significant effect on the food intake except on the first day ($p < 0.05$) of the drug administration (Fig. 7).

Effects of Fenfluramine on Blood Ethanol

Compared with saline, a single SC injection of 1.0 mg/kg fenfluramine 15 min before ethanol (2.5 g/kg, 16% v/v) administration (IP) did not significantly affect the pharmacokinetics of ethanol in rats.

DISCUSSION

The central serotonergic system has been implicated in the regulation of a wide variety of neurobiological functions and behaviors including regulation of appetite, circadian rhythms, sleep, depression, mood and anxiety, and impulse control (34). Further, previous studies consistently have suggested a reciprocal relationship between central serotonin function and alcoholism (15,30,33,35). The present study supports the existence of a reciprocal relationship between the central serotonin deficiency and alcohol consumption, which has been documented in both experimental animals (15,18,30,35) and humans (20–23). Our results demonstrate that administration of fenfluramine, a serotonin releaser, can significantly attenuate alcohol preference in a dose-dependent manner in Fawn-Hooded rats without affecting food intake. It has been shown that Fawn-Hooded rats exhibit a high preference for alcohol because of a genetic impairment in their serotonergic systems (30,31). Recently, a genetic analysis of 5-HT_{1A} and 5-HT_2 receptors in several regions of the brain confirmed that Fawn-Hooded rats, which have been derived from Wistar rats, relative to Sprague-Dawley and Wistar rats, have an altered serotonergic function (10).

Fenfluramine, by releasing 5-HT in the synaptic cleft, enhances the 5-HT neuronal activity. Therefore, similar to 5-HT uptake inhibitors such as fluoxetine, it attenuates alcohol preference in alcohol-drinking animals. Interestingly, the doses used in the present study selectively blocked alcohol intake

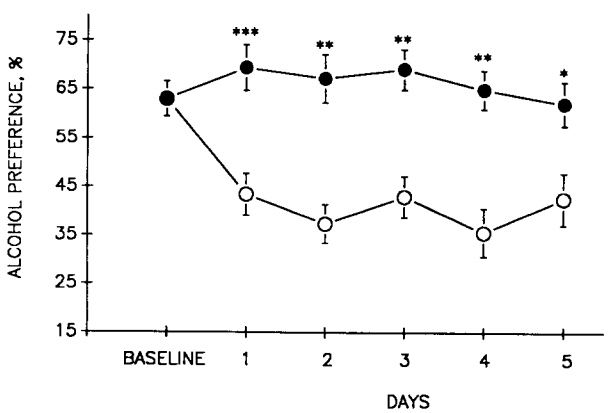

FIG. 5. Effects of subchronic administration of saline (●) and fenfluramine (1.0 mg/kg twice a day) (○) on alcohol preference in Fawn-Hooded rats. Data are the means ± standard error of mean (n = 11), $^{**}p < 0.01$ compared with corresponding saline values.

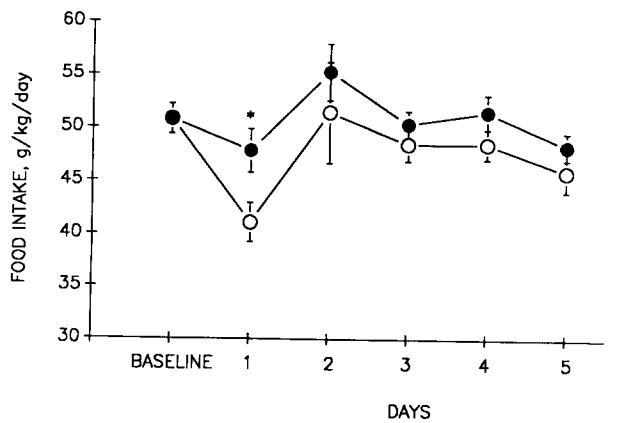

FIG. 7. Effects of subchronic administration of saline (●) and fenfluramine (1.0 mg/kg twice a day) (○) on food intake in Fawn-Hooded rats. Data are the means ± standard error of mean (n = 11), $^{*}p < 0.05$ compared with corresponding saline values.

but not other consummatory behaviors such as food intake. Although the water intake was increased dose-dependently, the total fluid intake did not change significantly, indicating a specific effect of fenfluramine only on alcohol consumption.

Our findings also support other investigators' reports on the effect of dexfenfluramine on alcohol intake. Rowland and Morian (33) reported that both acute and subchronic (7 days) administration of dexfenfluramine reduced alcohol intake in alcohol-preferring (P) rats. It also has been demonstrated that fenfluramine suppresses ethanol intake in chickens, an effect that can be amplified by a dietary tryptophan supplement (7,16).

Although the anorectic effects of fenfluramine are very well established in different species [for review see (32)], this drug failed to significantly affect the food intake in Fawn-Hooded rats even after 5 days of treatment. One possible explanation for the lack of significant effect of fenfluramine on food intake is that the Fawn-Hooded rats are subsensitive to serotonergic compounds. Indeed, there is a growing body of evidence to support the serotonergic subsensitivity and alteration of the serotonergic system in the Fawn-Hooded rats (2,9,10,30,38). Our results support earlier reports that Fawn-Hooded rats are subsensitive to the anorectic effects of several 5-HT agonist, including mCPP, 8-OHDPAT, and fenfluramine (38). Aulakh et al. (2) have demonstrated that Fawn-Hooded rats are less sensitive to the hyperphagic effect of 5-HT_{1A} agonists such as buspirone and 8-OHDPAT. This indicates that presynaptic 5-HT_{1A} receptors mediating hyperphagia are subsensitive in the Fawn-Hooded strain. Thus, the fact that the food intake did not change significantly in these experiments confirms previously reported findings on serotonergic subsensitivity in Fawn-Hooded rats (2,9). Further, because 5-HT_{1B} has been proposed to be involved in feeding behavior, it is conceivable that the failure of various doses of fenfluramine to decrease food intake is because of subsensitivity of 5-HT_{1B} receptors in this strain.

In summary, Fawn-Hooded rats with genetic serotonin impairment exhibit a high preference for alcohol intake under different conditions. Activation of serotonergic systems by acute or subchronic administration of fenfluramine significantly reduce their alcohol intake. It has been suggested that the anorectic property of fenfluramine may account for its ability to reduce alcohol intake. This hypothesis cannot account for the reduced alcohol intake because the food intake was not significantly affected by fenfluramine. Thus, based upon the present findings in the Fawn-Hooded rats with genetic serotonin dysfunction, it would appear that fenfluramine exerts its selective suppressant effect on alcohol intake and preference by releasing serotonin in the synaptic cleft, therefore activating the serotonergic system.

Overall, these findings provide more evidence for the serotonin deficiency hypothesis of alcoholism and usefulness of Fawn-Hooded rats as an animal model of alcoholism with serotonin dysfunction. Experiments are underway with tryptophan diet in combination with other serotonergic compounds to further explore the mechanism of alcohol consumption in Fawn-Hooded rats with respect to the serotonergic system in the brain.

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