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Attenuation of Alcohol Consumption by MDMA (Ecstasy) in Two Strains of Alcohol-Preferring Rats

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REZVANI, A. H., P. L. GARGES, D. B. MILLER AND C. J. GORDON. *Attenuation of alcohol consumption by MDMA (ecstasy) in two strains of alcohol-preferring rats.* PHARMACOL BIOCHEM BEHAV 43(1) 103–110, 1992.— Alcohol preference and manifestation of alcoholism are thought by many to be associated with serotonin (5-HT) dysfunction in the brain. Thus, experiments were performed to determine the effect of acute and subchronic administration of (±) 3,4-methylenedioxymethamphetamine (MDMA), an amphetamine analog that stimulates 5-HT release, on alcohol preference in two strains of alcohol-preferring rats, the Fawn-Hooded (FH) and alcohol-preferring (P) rats. Rats were individually housed and provided free access to a solution of 10% ethanol, food, and water. Ethanol, food, and water intakes were measured daily. After establishing a stable baseline for ethanol and water intake, each rat was injected SC with a dose of 5.0 mg/kg MDMA or an equal volume of saline for 1 or 3 consecutive days. Body temperature was recorded immediately before and 120, 240, and 360 min after MDMA treatment. Ethanol, food, and water intake were measured for the preceding 24 h. Further, to determine the effect of MDMA on alcohol metabolism rats were injected with 5.0 mg/kg MDMA or saline and 15 min later with 2.5 g/kg alcohol. Then, blood alcohol levels were determined at 1, 3, and 5 h after alcohol administration. Our results show that a single administration of 5.0 mg/kg MDMA significantly decreased ethanol intake in both FH and P rats and increased water intake. Subchronic administration of 5.0 mg/kg MDMA for 3 consecutive days significantly attenuated alcohol intake in both strains but only increased water intake in P rats. Administration of MDMA induced hyper- and hypothermia in FH and P rats, respectively. This drug failed to exert any significant effect on the pharmacokinetics of alcohol, indicating a central effect. These findings suggest that MDMA exerts an inhibitory action on alcohol preference, possibly by enhancing serotonergic and/or dopaminergic systems in the CNS.

Fawn-Hooded rats Alcohol-preferring rats Drinking behavior Serotonin Alcohol
Alcohol preference Body temperature

5-HYDROXYTRYPTAMINE (5-HT) has been proposed by several investigators to be involved in the etiology of alcoholism (27,32,37,40). Both human and experimental animal data support the contention that central 5-HT plays a significant role in alcohol preference. Pharmacological manipulation of 5-HT content in the brain markedly influences alcohol drinking in both experimental animals (27,37,40) and humans (32). Several groups of investigators have found that alcohol preference in selectively bred alcohol-preferring (P) rats (28) and humans (32) can be influenced by serotonergic drugs. Recently, it has been shown that the Fawn-Hooded (FH) rat, a strain that possesses a genetic serotonin impairment, (1,7) also exhibits a high preference for alcohol (35,37,40). In addition, it has been shown that P rats have lower levels of 5-HT and its metabolite [5-hydroxyindoleacetic acid (5-HIAA)] (30) and a greater number of 5-HT binding sites in frontal cortex and hippocampus than their control, alcohol nonpreferring (NP) rats (50). Furthermore, in another alcohol-drinking strain of rats, the Sardinian strain, it has been demonstrated that 5-HT_1 receptor agonists attenuate alcohol intake (23,46). Thus, it appears that reduced activity of CNS serotonergic pathways is a key factor in the manifestation of alcohol preference.

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To further investigate the role of the 5-HT system in alcohol drinking, we examined the effect of (±)3,4-methylenedioxymethamphetamine (MDMA) on alcohol preference in two strains of alcohol-drinking rats. MDMA, popularly known as "ecstasy" or "Adam," is structurally related to amphetamine and is commonly abused for recreational purposes (13,29). It is also used as an adjunct to psychotherapy by some therapists because of its proposed anxiolytic effect (29). MDMA has recently been shown to produce a positive conditioned place preference and reduction in fluid intake, including alcohol solution, in fluid-deprived rats (4). The drug has been proposed to interact with both serotonergic and dopaminergic systems in the CNS (11,12,42,45,51). MDMA has been found to be a potent releaser of both 5-HT and dopamine (DA) (14,41). It has been shown that single or multiple administrations of MDMA caused a significant reduction in tryptophan hydroxylase activity. Furthermore, the concentrations of 5-HT and its major metabolite, 5-HIAA, in several serotonergic nerve terminals were decreased significantly by MDMA indicating a massive release of 5-HT from presynaptic vesicles (42,45). A significant elevation in concentrations of DA in the neostriatum (43), nucleus accumbens, and caudate of rats (51) has been reported. MDMA has also been shown to increase body temperature, a response believed to be mediated by stimulation of the central serotonergic pathways (15, 31,33).

Since MDMA modulates the serotonergic-dopaminergic systems, which presumably are involved in the manifestation of alcohol preference, we found it interesting to examine the effect of this drug on two strains of rats, P and FH, that exhibit 5-HT impairment and show preference for alcohol.

METHOD

Animals

Rats used came from two colonies of alcohol-drinking FH and P rats established at the University of North Carolina and the Indiana University, respectively. The history of the FH strain is a bit obscure. It may be derived from cross breeding of German brown rats with Wistar and white Lashley rats (47). It has been shown that these rats possess an altered serotonergic function in the central and peripheral nervous systems (1,7,49). Recently, it has been discovered that these rats exhibit a high preference for alcohol that can be attenuated by administration of serotonergic compounds (39,40). P rats, which have been selectively bred for alcohol preference and are derived from Wistar rats (25), have been used extensively as an animal model of human alcoholism (27,40).

Adult, male FH rats weighing 0.48 ± 0.04 kg and P rats weighing 0.61 ± 0.04 kg were housed individually in wire mesh cages (26 × 34 × 20 cm) under a constant temperature of 21 ± 1°C and a 12 D : 12 L reversed cycle (10 a.m.-10

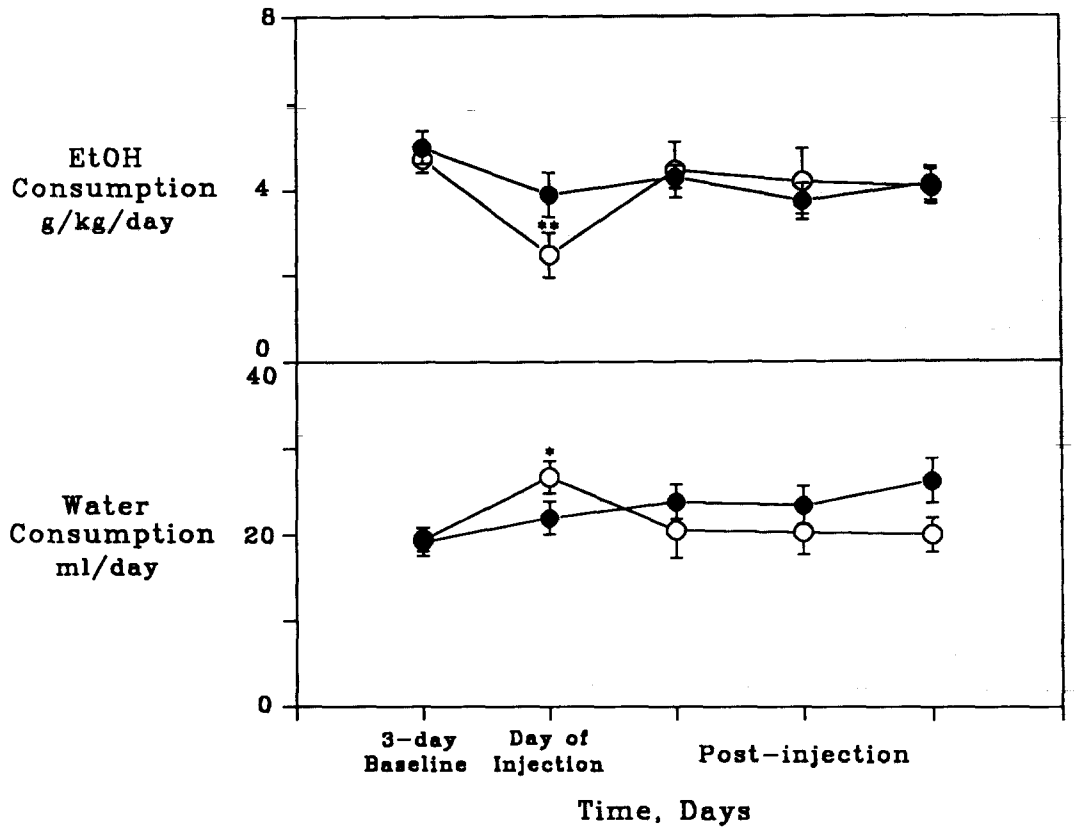

FIG. 1. Effects of SC acute administration of saline (●—●) and 5.0 mg/kg MDMA (○—○) on alcohol (top) and water (bottom) intake in Fawn-Hooded rats. Data are the means ± SEM. *$p < 0.01$,**$p < 0.001$, comparing MDMA with the 3-day baseline.

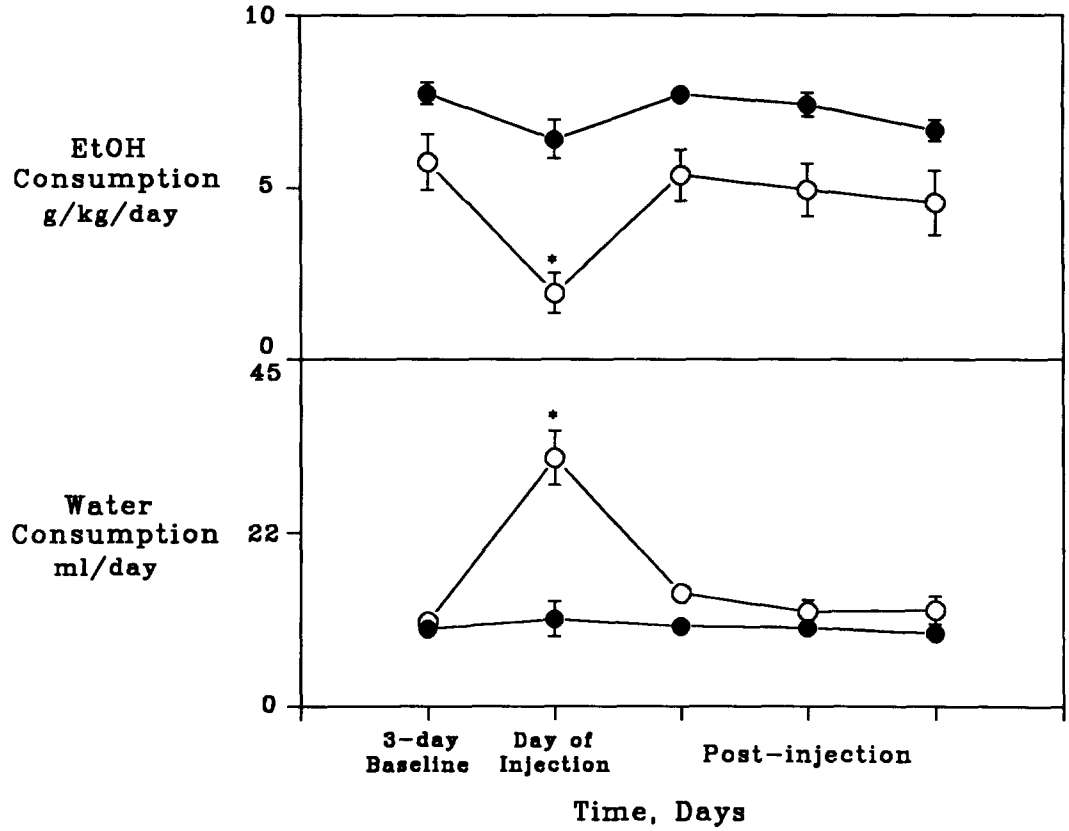

FIG. 2. Effects of SC acute administration of saline (●—●) and 5.0 mg/kg MDMA (○—○) on alcohol (top) and water (bottom) intake in alcohol-preferring rats. Data are the means ± SEM. *$p < 0.01$, comparing MDMA with the 3-day baseline.

p.m. dark). Animals were fed Agway Prolab Rat/Mouse/Hamster 3000 formula (Agway, Syracuse, NY) and water ad lib. Using the standard method of Waller et al. (48), all rats were screened and tested for alcohol preference as follows. They were given free access to water in a graduated Richter (Frenchtown, NJ) tube and food for 2 days. Next, they were given free access to food and a solution of 10% (v/v) alcohol as a sole source of fluid for 3 days. During that period, rats became accustomed to drinking from Richter tubes and to the taste of alcohol (37). Thereafter, they were given free access to both water and a 10% solution of alcohol for at least 2 weeks. The positions of the tubes were randomly changed to prevent position preference. Food was available ad lib throughout. Food, water, alcohol intake, and body weight were recorded every day at 9:00 a.m.

Preparation of Drugs

Solutions of MDMA were prepared in pyrogen-free glassware in sterilized isotonic saline and passed through a 0.22-μM millipore filter (Millipore Corp., Bedford, MA) into a pyrogen-free glass bottle and stoppered. One dose of MDMA (5.0 mg/kg body weight) was used. The volume of vehicle saline or drug injected was 1 ml/kg body weight. A 10% (v/v) solution of alcohol was prepared daily from 95% reagent grade alcohol and distilled water.

Experimental Protocol

Following the standard method used in our laboratory (36,37,40), a stable baseline for alcohol and water intake was established during testing for alcohol preference. Each rat (n = 15 for FH and n = 9 for P rats) was then injected SC at approximately 9:30 a.m. with either saline or a dose of 5.0 mg/kg MDMA. The interval between injections was at least 5 days. In another series of experiments to determine the effect of subchronic administration of MDMA, the same P rats (n = 9) and seven of the same FH rats were injected SC with a dose of 5.0 mg/kg MDMA or an equal volume of saline for 3 consecutive days, following a crossover design with 1-week interval. Throughout the study, water, food, and alcohol intake were measured every day at 9:00 a.m. for the preceding 24 h. In addition, to determine the effect of MDMA on body temperature a thermistor probe lubricated with Dibucaine (Parke-Davis, Morrow, GA) was inserted about 5.0 cm into the rectum of the animal and colonic body temperature was recorded immediately before and 120, 240, and 360 min after MDMA administration.

To determine the effect of MDMA administration on alcohol metabolism, the following experiments were carried out. Six male FH rats and six male P rats naive to MDMA were injected SC with 5.0 mg/kg MDMA or an equal volume of saline and 15 min later with 2.5 g/kg alcohol (16% v/v)

following crossover design with 1-week interval. Twenty-microliter blood samples were obtained from the tip of the tail of each rat at 1, 3, and 5 h after alcohol administration. Blood samples were transferred immediately to a microcentrifuge tube containing 180 μl tertbutanol (0.3 mg/ml) as an internal standard. After shaking, the tubes were stored at −20°C until gas chromatography (GC) analysis. Then, each vial was centrifuged and 5.0 μl of the supernatant was injected into a gas chromatograph (Varian Aerograph Model 2400, Sugarland, TX) equipped with a flame ionization detector and a 60/80 Carbopack B/5% Carbowax 20M, 6 × 2 mm ID glass column (Supelco, Bellefonte, PA). The chromatographic conditions were as follows: carrier gas (N_2) flow rate 20 ml/min; 60–110°C at 10°C/min temperature program; injector temperature 120°C; detector temperature 140°C. Blood alcohol concentrations are expressed as mg/dl (36).

Statistical Analysis of Data

The results are expressed as means ± SEM and statistical differences between drug- and saline-treated groups were determined using analysis of variance (ANOVA) and Newman-Keuls tests.

RESULTS

Acute Administration

When given free access to food, alcohol, and water, FH and P rats consumed an average of 4.85 ± 0.24 and 5.75 ± 0.82 g/kg body weight alcohol, respectively, and 19.3 ± 1.03 and 2.13 ± 0.74 ml/day water, respectively. A single injection of 5.0 mg/kg MDMA resulted in a significant reduction in alcohol intake in FH, $F(1, 7) = 34.64$, $p = 0.0006$, and P, $F(1, 4) = 71.42$, $p = 0.001$, rats and a commensurate increase in water intake in both FH, $F(1, 7) = 12.96$, $p = 0.009$, and P, $F(1, 4) = 43.93$, $p = 0.003$, rats.

The proportion of alcohol intake to total fluid intake (alcohol plus water) in conjunction with total alcohol intake has been used as a reliable index of alcohol preference (25,36,37,48). The proportion of alcohol intake in FH rats significantly, $F(1, 14) = 7.15$, $p = 0.02$, decreased with injections of MDMA from a value of 0.51 ± 0.04 with saline to a value of 0.34 ± 0.05 after injection of 5.0 mg/kg MDMA. For P rats, this value decreased significantly, $F(1, 7) = 22.3$, $p = 0.002$, from 0.96 ± 0.04 with saline to 0.35 ± 0.11 following MDMA administration.

Administration of 5.0 mg/kg MDMA compared to the 3-day baseline significantly, $F(1, 7) = 14.40$, $p = 0.007$, lowered food intake in FH but not P rats, $F(1, 4) = 5.63$, $p = 0.08$. To compare the effect of MDMA on alcohol intake in FH vs. P rats, the magnitude of the change in alcohol intake from the baseline was measured. This value in P rats when administered with 5.0 mg/kg MDMA was significantly, $F(1, 11) = 5.13$, $p = 0.045$, greater than that for FH rats under the same treatment. While the mean decrease in alcohol intake for P rats was 3.88 ± 0.45 g/kg, this value for FH rats was 2.4 ± 0.41 g/kg (Figs. 1 and 2).

Compared to control saline, administration of 5.0 mg/kg

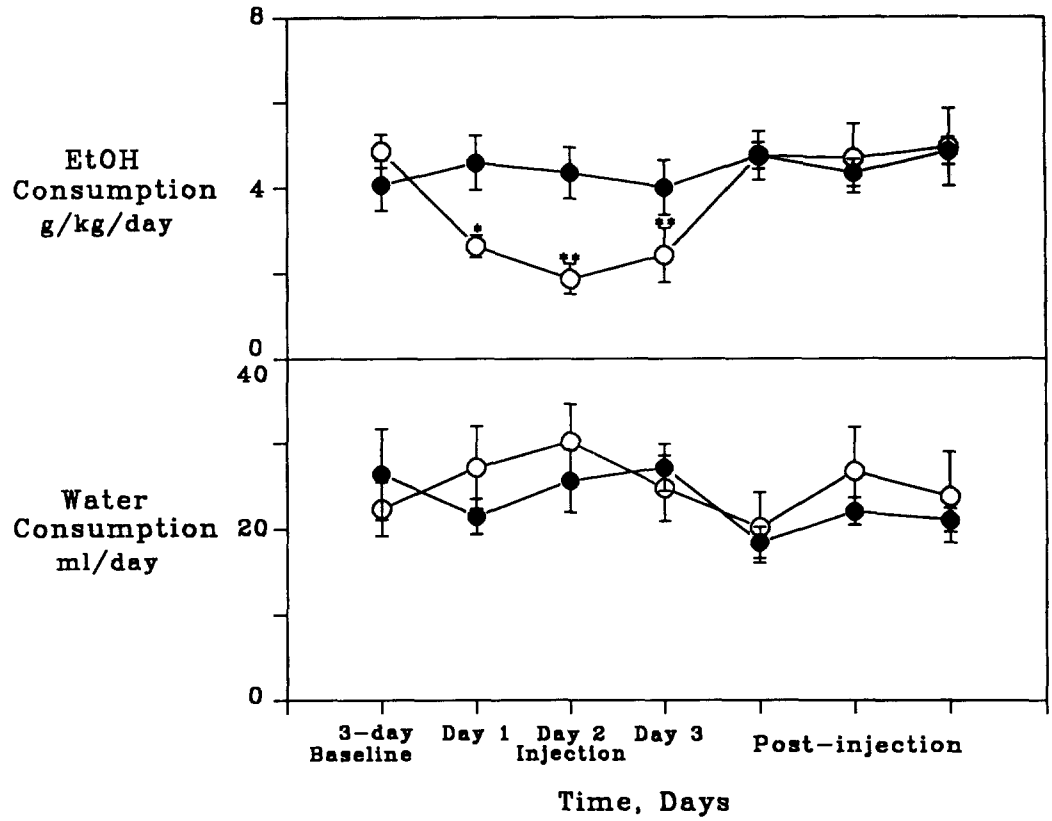

FIG. 3. Effect of SC subchronic administration of saline (●—●) and 5.0 mg/kg MDMA (○—○) on alcohol (top) and water (bottom) intake in Fawn-Hooded rats. Data are the means ± SEM. *$p < 0.05$, **$p < 0.01$, comparing MDMA with corresponding saline effect.

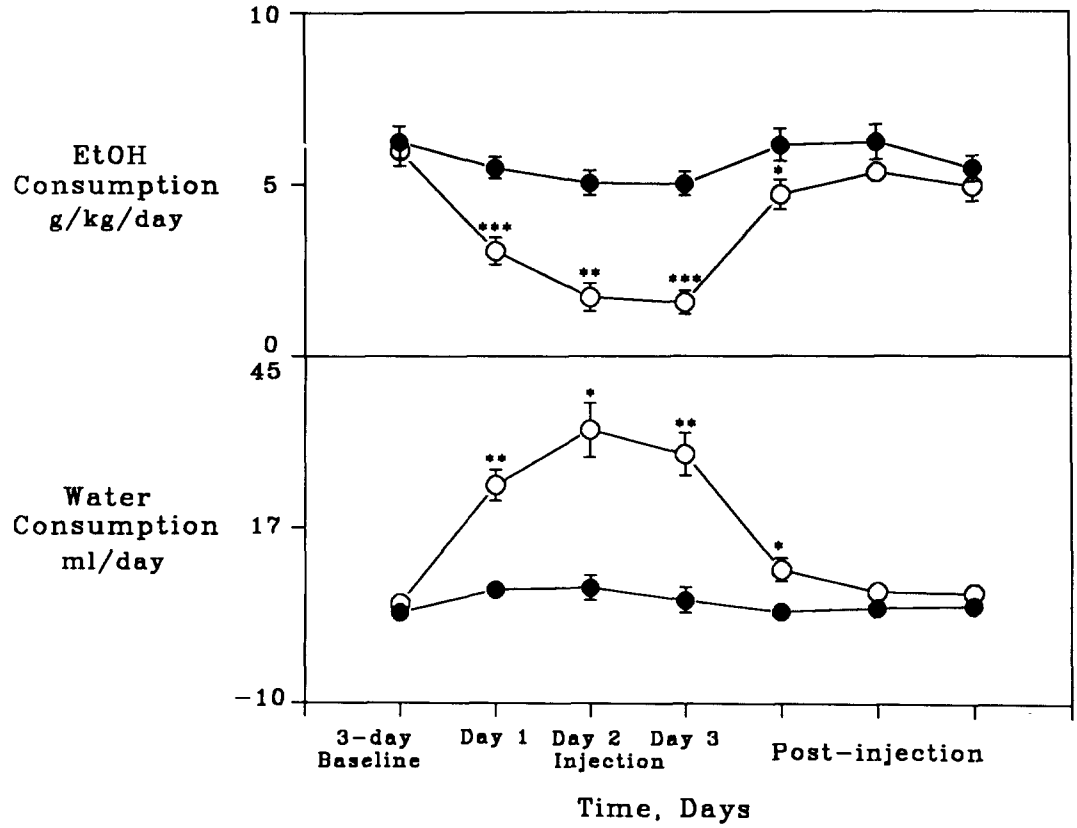

FIG. 4. Effect of SC subchronic administration of saline (●—●) and 5.0 mg/kg MDMA (○—○) on alcohol (top) and water (bottom) intake in alcohol-preferring rats. Data are the means ± SEM. *$p < 0.01$, **$p < 0.001$, ***$p < 0.0001$, comparing MDMA with corresponding saline effect.

MDMA did not significantly {$F(1, 11) = 2.19$, $p = 0.169$, for FH rats and $F(1, 9) = 4.15$, $p = 0.76$, for P rats} affect the pharmacokinetics of alcohol in either strain of rats. The peak values of blood ethanol concentrations for saline- and MDMA-treated FH rats were 273.7 ± 15.65 and 311 ± 23.3 mg/dl, respectively. The corresponding values for P rats were 355.24 ± 17.88 and 371.88 ± 11.5 mg/dl.

Subchronic Administration

Three-day administration of 5.0 mg/kg MDMA in FH rats significantly reduced the amount of alcohol intake for all 3 days, $F(3, 6) = 11.80$, $p = 0.002$. However, neither water (Fig. 3) nor food intake changed significantly. The same subchronic treatment significantly decreased ethanol intake in P rats, $F(3, 8) = 44.29$, $p = 0.0001$, and commensurately increased water intake significantly for all 3 days, $F(3, 8) = 22.3$, $p = 0.0001$ (Fig. 4). Food intake decreased significantly for the first 2 days only [for day 1, $F(1, 8) = 32.5$, $p = 0.0005$, for day 2, $F(1, 8) = 13.68$, $p = 0.006$]. Similar to the acute experiment, P rats were more sensitive than FH rats to the inhibitory effect of MDMA on alcohol intake. The magnitude of the change in alcohol intake with MDMA compared with control saline in P rats in days 1 and 2 was not significantly different from that of FH rats. However, on the third day FH rats showed development of tolerance, thus causing the magnitude of the change in alcohol intake to be significantly, $F(1, 14) = 13.80$, $p = 0.0023$, greater in P rats.

Temperature

Both acute and subchronic administration of MDMA in FH and P rats induced a significant change in body temperature; however, the effect was opposite in these two strains (Fig. 5). In FH rats, acute administration of 5 mg/kg MDMA caused a significant ($p < 0.01$) hyperthermia that lasted more than 4 h. The same dose of the drug when administered in P rats caused a significant ($p < 0.01$) hypothermia, lasting more than 2 h, followed by a slight rebound hyperthermia.

DISCUSSION

The present study demonstrates that administration of MDMA, in acute or subchronic form, can significantly attenuate alcohol preference in two strains of alcohol-preferring rats. Interestingly, attenuation of alcohol intake in both strains by acute administration was accompanied by a significant elevation in water intake, thus leading to a reduction in alcohol preference. Moreover, while MDMA had a similar effect on alcohol preference in both P and FH strains it caused nearly opposite thermoregulatory responses. Administration of MDMA did not cause any behavioral changes. Thus, the decrease in alcohol consumption produced by MDMA does not seem to be the result of behavioral changes.

The effect of MDMA on alcohol preference may involve several neuronal mechanisms, but most likely it is the activation of the CNS serotonergic-dopaminergic systems. Recently, it was shown that MDMA decreases the intake of both

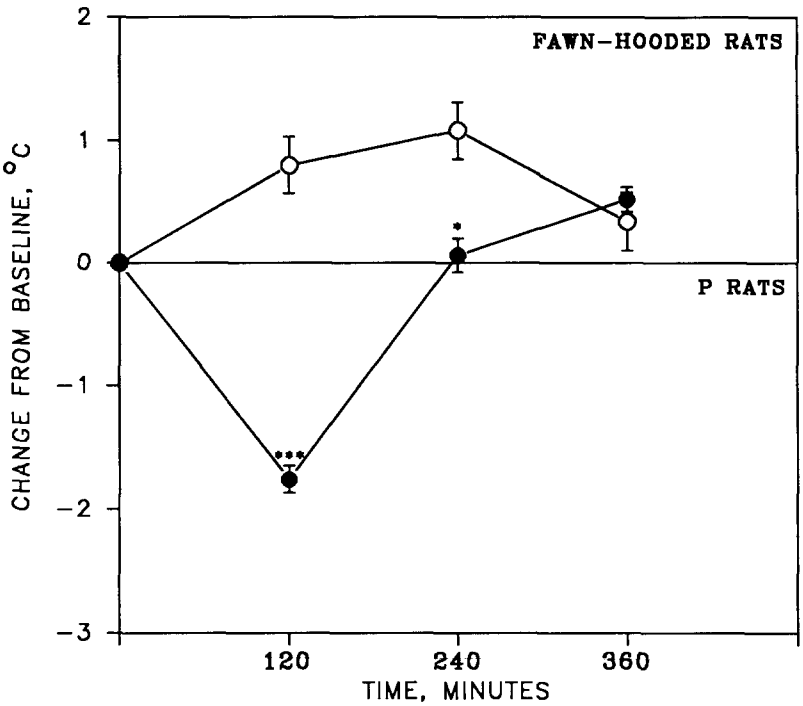

FIG. 5. Effect of SC acute administration of 5.0 mg/kg MDMA on colonic temperature in Fawn-Hooded (○—○) and alcohol-preferring (●—●) rats. Data are the mean ± SEM. $*p < 0.01$, $***p < 0.0001$, comparing FH with P rats.

a sweetened alcohol solution and water in fluid-deprived rats, an effect possibly attributed to its serotonergic action (4). The reinforcing property of alcohol is proposed to be related to its facilitating influence on both 5-HT and DA systems (6,8,28). It has been shown that alcohol preference in alcohol-preferring strains of rats (10,27,38,40), monkeys (5), and humans (32) can be suppressed by drugs that enhance serotonergic pathways. It has been demonstrated that FH rats with dysfunctional central serotonergic systems exhibit a high preference for alcohol, and pharmacological enhancement of 5-HT activity reduces alcohol intake in this strain as well (38,40). Further, P rats have been shown to have lower levels of 5-HT and 5-HIAA in cerebral cortex and hippocampus than their control, alcohol nonpreferring rats (30). Similarly the administration of 5-HT reuptake inhibitors, fluoxetine and fluvoxamine, attenuate alcohol intake in this strain (27). Thus, it is postulated that hypoactivity of the 5-HT system in the brain is one of the causes of excessive drinking and it is possible that MDMA exerts its inhibitory action on alcohol intake by releasing 5-HT into the synaptic cleft (22), therefore enhancing the 5-HT system, as has been shown with other 5-HT releasers such as fenfluramine (38).

In addition, it has been shown that MDMA inhibits the reuptake of 5-HT in vitro (19), a property similar to fluoxetine, which also attenuates alcohol intake in rats (27) and humans (32). The fact that FH rats were less affected by MDMA than P rats indicates subsensitivity of FH rats to serotonergic compounds. FH rats have also been shown to be less sensitive to the food intake suppressant effects of serotonergic compounds such as 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) (a 5-HT_{1a} agonist), *m*-chlorophenylpiperazine (mCPP) (a 5-HT_{1B} agonist), and fenfluramine (49), suggesting subsensitivity of 5-HT_1 receptors in the FH strain compared to Wistar and Sprague-Dawley strains (16,49). MDMA, in addition to its indirect 5-HT-releasing property (22), has also been shown to have equal affinity for 5-HT_1 and 5-HT_2 sites (26). Further, it has been demonstrated that the B_{max} values for [^{3}H]8-OH-DPAT binding in the striatum of FH rats were significantly lower than those for Sprague-Dawley and Wistar rats (21).

Involvement of central dopaminergic systems in alcohol preference has also been suggested. Overall, it has been proposed that the lower content of DA in the nucleus accumbens might be associated with high alcohol intake in P rats (28). Thus, pharmacological enhancement of the dopaminergic system can alter alcohol drinking. For example, administration of DA releaser amphetamine or D_2 agonist bromocryptine attenuates alcohol intake in P rats (28). Further, it has been shown that a single dose of MDMA significantly elevates the DA content in the brain (19,45,51) and rats rotate in the same direction after MDMA injections as they do after amphetamine, suggesting a dopaminergic component of MDMA's action (24). MDMA may be acting as an indirect DA agonist (13) and its ability to elicit positive affect is modulated by dopaminergic pathways (3).

The opposite effects of MDMA on thermoregulation of these two strains of rats indicate a fundamental difference between their serotonergic systems. Serotonergic systems in the brain play a paramount role in the regulation of body temperature. Microinjection of 5-HT into the anterior hypothalamus/preoptic area generally results in elevation of body temperature (31). Thus, the MDMA-induced hyperthermia in FH rats may be the result of the MDMA-induced 5-HT release. However, the same drug caused hypothermia in P rats.

One explanation for this difference is the contribution of different 5-HT receptor subtypes in hypo and hyperthermia. Indeed, there is evidence for opposing roles of 5-HT_{1A} and 5-HT_2 receptors in the regulation of body temperature (17,18). It has been shown that 5-HT agonist-induced hyperthermia in rats is mediated by 5-HT_2 receptors (17,18,34) whereas 5-HT agonist-induced hypothermia involves the activation of 5-HT_{1A} receptors (2,17,18,20). Further, it has been speculated that some receptors of the 5-HT_2 type, which are involved in hyperthermia, are more responsive in FH rats than those in Sprague-Dawley rats (17, 18). Recently, it was demonstrated that the B_{max} values for 8-OH-DPAT (5-HT_{1A} agonist) binding in the striatum of FH rats were significantly lower than those of the Sprague-Dawley and Wistar rats, but the B_{max} values for ketanserin (5-HT_2 agonist) were significantly higher in FH compared to Sprague-Dawley rats (21). In addition, it has been demonstrated that P rats have a higher density of 5-HT_{1A} binding sites in some limbic regions (50). Thus, the opposite thermoregulatory responses observed in FH and P rats may be associated with the differences in density and/or sensitivity of 5HT_{1A} and 5-HT_2 receptors, which mediate hypo- and hyperthermia, respectively. However, other neurotransmitters are involved in mammalian thermoregulation so the role of other systems cannot be ruled out and remains to be investigated. To further understand the mechanism of action of MDMA on alcohol preference and body temperature, more experiments with DA and 5-HT compounds are needed.

Overall, MDMA, given acutely or subchronically, caused a rapid and significant attenuation in alcohol consumption, but not total fluid intake, that was fully reversible in two strains of alcohol-preferring rats. It is possible that MDMA exerts its inhibitory action on alcohol preference by stimulating central serotonergic and/or dopaminergic systems. However, alcohol drinking is a complex behavior and is likely to involve other neurotransmitter systems as well. It is interesting to note that alcohol preference recovered soon after cessation of MDMA treatment. However, some studies have shown that prolonged MDMA treatment destroys serotonergic neurons in the CNS (9). Considering the intricate role of 5-HT pathways in alcohol preference, it will be of interest to understand if permanent changes in alcohol preference occur with even more prolonged MDMA treatment.

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