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Suppression of Ethanol Intake in Alcohol-Preferring Rats by Prior Voluntary Saccharin Consumption

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KAMPOV-POLEVOY, A. B., D. H. OVERSTREET, A. H. REZVANI AND D. S. JANOWSKY. *Suppression of ethanol intake in alcohol-preferring rats by prior voluntary saccharin consumption.* PHARMACOL BIOCHEM BEHAV **52**(1) 59–64, 1995.—In a situation offering a free choice between 0.1% saccharin solution and tap water, Fawn Hooded (FH) rats consumed 363.0 ± 33.5 ml/kg/day of saccharin solution. Subsequently those animals drank 3.0 ± 0.4 g/kg of ethanol in a free choice between water and 10% ethanol solution. Control FH rats that did not have access to saccharin consumed 5.0 ± 0.5 g/kg/day of ethanol in the same situation (difference between groups was significant: $p = 0.006$). When control rats were exposed to the choice between 10% ethanol solution and 0.1% saccharin solution for 4 days they consumed 383.7 ± 27.5 ml/kg/day of saccharin solution and their ethanol intake dropped to 1.2 ± 0.3 g/kg/day. When these rats were returned back to alcohol/water choice and exposure to saccharin was discontinued, their alcohol intake was still reduced (3.7 ± 0.3 g/kg/day for at least 10 consecutive days). Exposure of alcohol-experienced alcohol-preferring P rats with high (6.8 ± 0.5 g/kg/day) and stable alcohol intake to saccharin/water choice for 4 days also resulted in a significant attenuation of their ethanol intake for at least 6 days following saccharin cessation. Thus, voluntary consumption of saccharin can suppress subsequent alcohol intake in both alcohol-naive and alcohol-experienced rats.

Ethanol intake suppression Saccharin intake Alcohol-preferring P rats Fawn Hooded rats

NUMEROUS studies have demonstrated an association between saccharin and alcohol intake in rats (21,25,34,42) and in mice (2,12,35). In some rat strains, especially in those with genetically determined alcohol preference [such as alcohol-preferring (P) and Fawn Hooded (FH) rats] the propensity to consume saccharin is so strong that they almost triple their daily fluid intake when saccharin is available (34,42). On the other hand, there is an indication that prior exposure of some rat strains to saccharin solution may subsequently attenuate their voluntary alcohol intake (34). Although it is known that palatable substances may decrease intake of many addictive substances such as alcohol (25,29), amphetamine (27), morphine (28), and phencyclidine (7) when given as an alternative, there is no evidence that this effect may last for a considerable amount of time after discontinuation of exposure to sweets. Because our previous work demonstrated that alcohol-preferring P and FH rats drank less ethanol than generally reported following exposure to saccharin (30,34,37), it was hypothesized that high voluntary intake of saccharin may inhibit subsequent alcohol intake in alcohol-preferring FH and P rats.

METHOD

Animals

Experiments were performed on 20 male Fawn Hooded (FH) rats selected from the viral-free breeding colony maintained at the Skipper Bowles Center for Alcohol Studies, University of North Carolina at Chapel Hill and 20 P rats supplied by The University of Indiana Medical School in Indianapolis. The body weights of FH and P rats at the beginning of the experiment were 213 ± 9.5 g and 516.1 ± 10.7 g, respectively. Rats were maintained under conditions of constant temperature (22°C) and humidity and a reversed 12L : 12D cycle (lights on from 2200–1000 h).

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Experiment 1

Effects of the saccharin ingestion on subsequent ethanol intake of FH rats with and without prior experience with alcohol. Twenty FH rats were randomly divided into experimental (Exp) and control (Ctrl) groups, with 10 animals in each group. Animals were housed individually in wire mesh cages with two graduated Richter tubes. Access to standard laboratory chow was provided ad lib during the whole experiment. Positions of the tubes were rotated daily to avoid place preference. The Exp and Ctrl groups were exposed to a series of two-bottle choice tests, as illustrated in Table 1.

Experiment 2

Effects of saccharin ingestion on subsequent ethanol intake of alcohol-experienced P rats. Twenty P rats were housed in individual cages with two graduated Richter tubes, one with tap water and other with 10% (v/v) ethanol solution for at least 30 days. Access to standard laboratory chow was ad lib during the entire experiment. Positions of the tubes were rotated daily to avoid place preference. After establishing a stable baseline of alcohol intake and preference for 4 consecutive days (day 1-4) animals were randomly divided into two equal groups: experimental (Exp) and control (Ctrl). For the next 4 consecutive days (days 5-8) Ctrl rats were switched to water-only regime, whereas Exp rats had a choice between tap water and 0.1% (w/v) saccharin solution. Then all rats were returned to the free choice between tap water and 10% (v/v) ethanol solution for 10 days (days 9-18).

Measurements

In both experiments fluid intake was measured daily at 0900 h, and body weights were recorded twice weekly. For each solution an intake was obtained and corrected for body weight and then averaged for each experimental period. Preference for each solution was calculated by dividing the amount of solution drunk by the volume of total fluid intake and multiplying by 100. In Experiment 1 the food consumption was measured during each phase of the experiment.

Statistical Analysis

Comparisons between the groups have been done using one-way analysis of variance (ANOVA), followed by Fisher's PLSD post hoc analysis. Within-group dynamics of intake of alcohol, food, and total fluid intake under the different experimental conditions were evaluated with paired *t*-tests.

RESULTS

Experiment 1

As can be seen from Table 2, there was no significant differences in baseline total fluid intake (days 1-4) between Exp and Ctrl groups. When the Exp group was exposed to 0.1% (w/v) saccharin solution (days 5-9) animals consumed it in large amounts, which resulted in 111% ($p < 0.0001$) increase of their daily fluid intake over baseline. Water consumption of Ctrl rats during this period remained similar to the baseline.

When rats were subsequently exposed to a free choice between 10% (v/v) alcohol and tap water for the first time (days 10-19), Exp animals consumed significantly less alcohol compared to Ctrl rats during the first (days 10-14; $p = 0.0114$) and the second (days 15-19; $p = 0.0365$) part of this phase (Fig. 1); however, the difference in the alcohol preference was significant ($p = 0.0041$) only during the first part of this phase (Fig. 2). Exposure to saccharin did not cause any changes in the daily fluid intake of rats in the experimental group (Table 2).

Table 2 illustrates that when rats were exposed to a free choice between 10% (v/v) alcohol and 0.1% (w/v) saccharin solutions (days 20-22), Exp and Ctrl rats consumed high amounts of saccharin solution and their daily ethanol intake dramatically decreased. When animals were returned back to alcohol/water choice (days 23-32), Ctrl rats reduced their ethanol intake to the level of the baseline (days 10-19) ethanol intake in Exp group (Fig. 1). Alcohol preference showed a similar pattern; however, it did not reach statistical significance ($t = 1.944$, $p = 0.0837$) (Fig. 2). In the Exp group exposure to saccharin/ethanol choice resulted in further suppression of alcohol intake during the first 5 days of phase 5. During the second part of this phase ethanol intake was returned to the baseline (phase 3). Alcohol preference showed a similar pattern (Fig. 2). Exposure to saccharin/ethanol choice did not cause any changes in the daily fluid intake of rats in either the Exp or Ctrl groups (Table 2).

There was a 7-16% decline in food consumption compared to the baseline in the Exp group after the exposure to the saccharin/water choice, although there was no difference in the food intake between Exp and Ctrl groups. Food consump-

TABLE 1

PROTOCOL OF EXPERIMENT 1

	Purpose	Drinking Fluids
Phase 1 (day 1-4)	Estimation of baseline fluid intake	Both tubes were filled with tap water
Phase 2 (day 5-9)	Estimation of spontaneous saccharin intake (Experimental group)	*In Experimental group:* one tube was filled with 0.1% (w/v) saccharin solution and the other with tap water. *In Control group:* both tubes were filled with tap water
Phase 3 (days 10-19)	Estimation of spontaneous alcohol intake	One tube was filled with 10% (v/v) ethanol solution and the other with tap water
Phase 4 (days 20-22)	Estimation of alcohol intake in the presence of saccharin	One tube was filled with 10% (v/v) ethanol solution and the other with 0.1% (w/v) saccharin solution
Phase 5 (days 23-32)	Estimation of voluntary alcohol intake after exposure to alcohol/saccharin choice	One tube was filled with 10% (v/v) ethanol solution and the other with tap water

TABLE 2

DAILY CONSUMPTION OF WATER, 0.1% SACCHARIN SOLUTION (Sacch), 10% ETHANOL SOLUTION (EtOH), AND FOOD INTAKE IN FAWN HOODED RATS FROM THE CONTROL AND EXPERIMENTAL GROUPS DURING DIFFERENT PHASES OF THE EXPERIMENT 1

	Phase 1	Phase 2	Phase 3		Phase 4	Phase 5	
	Days 1-5	Days 6-9	Days 10-14	Days 15-19	Days 20-22	Days 23-27	Days 28-32
EtOH intake (ml/kg/day)							
Ctrl group	–	–	63 ± 6.5	67 ± 8.0	15 ± 3.6	49 ± 4.4	45 ± 4.7
Exp group	–	–	33 ± 8.5*	44 ± 5.8*	9.4 ± 2.2	32 ± 3.7*	39 ± 6.6
Water intake (ml/kg/day)							
Ctrl group	183 ± 9.1	204 ± 5.8	146 ± 10.7†	149 ± 21.3	–	148 ± 6.0†	145 ± 13.2
Exp group	189 ± 6.6	34 ± 14.5†	179 ± 8.6*	148 ± 10.1†	–	155 ± 5.9†	144 ± 8.4†
Sacch intake (ml/kg/day)							
Ctrl group	–	–	–	–	346 ± 31.6	–	–
Exp group	–	363 ± 5.1	–	–	384 ± 27.5	–	–
Fluid intake (ml/kg/day)							
Ctrl group	183 ± 9.2	205 ± 5.8	209 ± 8.8	215 ± 22.8	385 ± 27.5†	196 ± 9.2	190 ± 9.5
Exp group	189 ± 6.6	397 ± 25*†	212 ± 10.6†	192 ± 9.3	347 ± 31.5†	187 ± 5.5	182 ± 4.8
Food intake (g/kg/day)							
Ctrl group	102 ± 3.9	113 ± 3.9	101 ± 5.3		91 ± 11.8	94 ± 4.8	
Exp group	105 ± 4.5	109 ± 2.1	98 ± 2.9†		91 ± 2.5†	88 ± 4.9†	

Values are means ± SEM. *Difference with control group is significant ($p < 0.05$).
†Difference with Phase 1 is significant ($p < 0.05$).

tion in the Ctrl group was unchanged throughout the whole experiment (Table 2).

Experiment 2

Table 3 illustrates that there were no significant differences in baseline ethanol intake and preference between Exp and Ctrl groups of P rats. When Exp rats were exposed to the saccharin solution (days 5-8) they consumed it in considerable amounts, with a preference ratio of 95.5 ± 1.1%, which resulted in a 171.5 ± 19.3% increase of their daily fluid intake over baseline ($p < 0.0001$). During the same period of time Ctrl animals had access to water only and their daily fluid intake decreased 17 ± 5.8% ($p = 0.0097$). When all animals were switched back to alcohol/water choice (days 9-18), rats in the Exp group substantially reduced their ethanol intake compared to baseline (Table 3); fluid intake compared to baseline was also reduced for 3 consecutive days. In the Ctrl group, both ethanol intake and daily fluid intake returned to baseline levels (Table 3). No significant changes in ethanol preference following saccharin exposure were found.

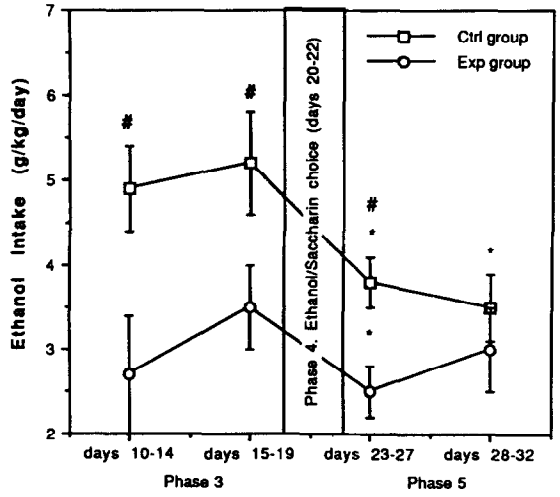

FIG. 1. Ethanol intake in Fawn Hooded rats from control (Ctrl) and Experimental (Exp) groups before (phase 3) and after (phase 5) exposure to saccharin/ethanol choice. Data are means ± SEM. *Significant difference from days 15-19 ($p < 0.05$). #Significant difference from control (Ctrl) group ($p < 0.05$).

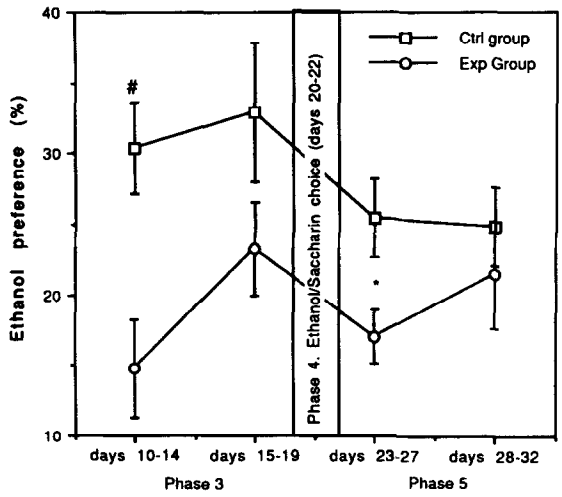

FIG. 2. Ethanol preference in Fawn Hooded rats from control (Ctrl) and Experimental (Exp) groups before (phase 3) and after (phase 5) exposure to saccharin/ethanol choice. Data are means ± SEM. *Significant difference from days 15-19 ($p < 0.05$). #Significant difference from control (Ctrl) group ($p < 0.05$).

TABLE 3

INTAKE OF WATER, 0.1% SACCHARIN SOLUTION (Sacch), 10% ETHANOL SOLUTION (EtOH), AND DAILY FLUID INTAKE IN P RATS DURING DIFFERENT PHASES OF EXPERIMENT 2

	Days 1-4 EtOH/Water	Days 5-8 Sacch/Water or Water only	Days 9-13 EtOH/Water	Days 14-18 EtOH/Water
EtOH intake (ml/kg/day)				
Ctrl group	93 ± 7.1	–	95 ± 3.8	91 ± 2.5
Exp group	87 ± 6.7	–	68 ± 6.3*†	78 ± 7.7
Water Intake (ml/kg/day)				
Ctrl group	10 ± 2.1	84 ± 6.6	11 ± 3.1	11 ± 1.6
Exp group	9 ± 1.9	11 ± 2.8*	9 ± 2.5	9 ± 2.4
Sacch intake (ml/kg/day)				
Ctrl group	–	–	–	–
Exp group	–	241 ± 8.0	–	–
EtOH preference (%)				
Ctrl group	90 ± 2.6	–	90 ± 2.8	91 ± 1.5
Exp group	90 ± 2.3	–	88 ± 3.5	88 ± 4.3
Fluid intake (ml/kg/day)				
Ctrl group	103 ± 8.2	84 ± 6.6†	107 ± 3.3	103 ± 3.5
Exp group	97 ± 5.9	253 ± 6.9*†	78 ± 5.9*†	89 ± 7.0

Values are means ± SEM.
*Difference with control group is significant ($p < 0.05$).
†Difference with baseline (days 1-4) is significant ($p < 0.05$).

DISCUSSION

The present results confirmed our previous reports (34,43) regarding high propensity of FH and P rats for saccharin intake, including the tendency to drink saccharin to the extent that daily fluid intake was more than doubled.

The 4-day exposure of naive FH rats to saccharin solution (Exp group) resulted in a 40% decrease in their subsequent alcohol intake for at least 10 consecutive days, compared to the non-preexposed Ctrl group. The similar effect on the ethanol intake can be seen after exposure of alcohol-experienced Ctrl rats to saccharin/ethanol choice (Table 2). The alcohol preference of alcohol-experienced Ctrl rats also decreased, but not significantly ($t = 1.944$, $p = 0.0837$). The magnitude of the effect of saccharin consumption on subsequent ethanol intake and preference is comparable to one of subchronic (5 day) administration of fenfluramine (1.0 g/kg, SC, twice a day) reported elsewhere (36). The second exposure of Exp rats to saccharin solution (phase 4) resulted in an additional 5 consecutive days of significant reduction in alcohol intake and preference. Therefore, we may conclude that exposure of alcohol-naive FH rats to the palatable saccharin solution results in the suppression of subsequent ethanol intake and preference for up to 10 consecutive days. The degree of this suppression is comparable with the effect of drugs known for their antialcohol effects, such as fenfluramine (36). In alcohol-experienced FH rats the magnitude of such effect was smaller and suppression of alcohol preference did not reach a significant level. It should also be emphasized that the antialcohol effect of saccharin exposure was specific and did not affect the total fluid or food intake of FH rats (Table 2).

Experiment 2 demonstrated that exposure of alcohol-experienced P rats to the saccharin solution resulted in 22 ± 5.1% attenuation of their ethanol intake for a 5-day period. The decrease in ethanol intake was less pronounced compared to that seen for alcohol-naive FH rats and was not accompanied by the decrease in ethanol preference. Such lack of correlation between the effects on the alcohol intake and preference is not unusual for the agents with a mild antialcohol effect. For example, Froehlich et al. (15) reported that naloxone in doses of 0.075-1.0 mg/kg significantly suppresses alcohol intake in alcohol-preferring HAD rats, but alcohol preference remains unchanged until higher doses (3.0-18.0 mg/kg) have been administered. A similar pattern has been observed with Ca^{++} channel blocker verapamil. A dose of 10 mg/kg significantly suppreses alcohol intake in alcohol-preferring P rats without significant effect on ethanol preference. A higher dose was neeed to significantly reduce both alcohol intake and preference (37).

Thus, even a short exposure to saccharin may induce a long-lasting attenuation of ethanol consumption in both alcohol-naive and -experienced FH rats as well as in alcohol-experienced P rats. The magnitude of this effect in alcohol-naive FH rats is highest and comparable with the effect of chronic treatment with fenfluramine (36). In FH rats that were exposed to alcohol for 13 days (phases 3 and 4) this effect was less pronounced. In P rats that had access to alcohol for more than 30 days the saccharin-induced suppression of alcohol intake was even lower, but still statistically significant.

There is a variety of factors that may contribute to the suppression of alcohol intake by the exposure to saccharin solution. One possibility is a negative contrast shift, when after exposure to highly palatable solutions, consumption of less palatable substances may be reduced (20). However, such shifts have occurred when postabsorbtive feedback is limited, which happens, for example, during short exposure to the substance (20). In present experiments ad lib access to the rewarding substance was provided, so the influence of the negative contrast shift is less likely. There is also a large amount of literature suggesting that the postabsorbtive effects of ethanol, rather than its taste, are the reinforcing factors for rats [for discussion see (16)].

It is also possible that the suppressing effects of saccharin ingestion on subsequent alcohol intake may be mediated by endogenous opioids. It has been reported that access to palatable food leads to increased release and breakdown of hypothalamic beta-endorphin in rats (10,11) and in humans (18), and may lead to the development of tolerance to opioids (3,32). Ingestion of palatable substances may also increase opiate receptor binding affinity in both genetically obese mice (ob/ob) and their lean littermates (28). A similar increase in opiate receptor binding has been observed in weanling rats that had access to sucrose for a 3-week period (28). Thus, sweets appear to stimulate the endogenous opioid system both by inducing a release of beta-endorphin and by increasing the binding affinity for opioids at the receptor site. As a result of such stimulation, 20-min access to saccharin may substantially potentiate hypothermic effect of a low dose (2.0 mg/kg, SC) of morphine to the level "that typically occurs in animals given large doses of morphine" (5). Glucose ingestion potentiates and prolongs the analgesic effect of morphine in tail flick test (9) and increases response latencies to a painful stimulus (4). Chronic exposure to saccharin may lead to the development of tolerance to opioids (32). Such tolerance may be detected after 24 h of ingestion of sweet solutions and progressively increases over the next 5 weeks (3).

Endogenous opioid systems are also known to be involved in the regulation of alcohol intake. Alcohol-preferring mice (17) and rats (26) have a lower endogenous opioid tone as estimated in the hot plate test. Blockade of opioidergic transmission with opioid antagonists results in suppression of alcohol intake in a dose-dependent manner (15), whereas reports regarding stimulation of this system are more controversial. Some publications claim the ability of opioid agonists (e.g., morphine 2.5 mg/kg) or inhibitors of enkephalinase (e.g., thiorphan, 30 mg/kg) to increase voluntary alcohol intake in rats and mice (14,24), whereas others have demonstrated that morphine at doses of 7.5–60 mg/kg (22,23,40–43), the selective mu-receptor opioid agonist [D-Ala^2,MePhe^4,Met(O)^5-ol]-enkephalin and enkephalinase inhibitor ketalorphan decrease alcohol consumption in alcohol-preferring animals (13,17). There are also reports suggesting that even a single injection of a high dose (30–60 mg/kg) of morphine may substantially decrease voluntary alcohol intake in rats. This effect is robust and lasts for about a week, long after the drug is washed out of the system (40,41).

Assessment of the effect that sweet substances may have on the voluntary alcohol intake is an even more difficult task. When sweets are given in the same fluid with alcohol, they dramatically increase alcohol intake, presumably because they camouflage the bitter taste of alcohol. This phenomenon has been used to develop the so-called "fading procedure," which induces animals to increase their alcohol intake (39). On the other hand, when palatable substances are given to animals as an alternative to alcohol (25,29), they dramatically decrease alcohol intake, although some authors claim that such reduction in alcohol intake may be seen in rats only before they develop physical dependency upon ethanol (6). Availability of sweet substances also reduces the self-administration (oral or intravenous) of other drugs of abuse such as amphetamine (27), morphine (28), the synthetic opioid etonitazene (8), and phencyclidine (7). In a recent study, confirmation that the effect of saccharin ingestion may last after discontinuation of the access to saccharin has been reported. Exposure of alcohol-preferring rats on alternative days to saccharin and decreasing doses of opioid antagonists results in the significant suppression of ethanol intake, which continues after the treatment period (45).

The limited human data also provide some indication that the eating of sweets may interfere with alcohol craving. In the book *Alcoholics Anonymous: Living Sober* (1), which summarizes the experience of recovering alcoholics, it is emphasized that "many of us—even many who said they had never like sweets—have found that eating and drinking sweets allays the urge to drink." There is also a clinical report indicating that alcoholics who stay sober in treatment for more than 30 days consume significantly more sucrose than people who do not remain sober for the 30 days (47). These reports suggest that the interaction between consumption of the sweet substances and alcohol may include mechanisms other than simple taste preference.

In conclusion, the present findings demonstrate that exposure to saccharin induced a relatively prolonged attenuation of alcohol intake in two different strains of alcohol-preferring rats. Although the mechanism of action is not fully understood, it is speculated that saccharin exerts its inhibitory effect on alcohol consumption by modulating the opioid system in the brain, which seems to be deficient in alcohol-preferring animals (17,26) and in humans with a high risk for development of alcoholism (19). This is the first indication that artificial sweetener may suppress alcohol craving. If these results are confirmed in human studies, special diets for recovering alcoholics and addicts that will help to reduce the craving might be developed.

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