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BRIEF COMMUNICATION

Schedule-induced Ethanol Polydipsia: Enhancement by Saccharin[1]

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SAMSON, H. H. AND J. L. FALK. *Schedule-induced ethanol polydipsia: enhancement by saccharin.* PHARMAC. BIOCHEM. BEHAV. 2(6) 835–838, 1974. The effect of adding sodium saccharin to a 5% ethanol solution on intake was examined. One set of animals were maintained at 80% of their free-feeding weight, in their home-cages with either 5% ethanol, or 5% ethanol–0.25% sodium saccharin as the only fluid available for three months (home-cage condition). A second set of animals were maintained in cages with automatic food dispensers that provided a 24 hr feeding regimen known to produce ethanol overdrinking (schedule-induced condition). These animals had 5% ethanol as their only available fluid for one month, followed by the 5% ethanol–0.25% sodium saccharin mixture for two months. No significant differences in ethanol intake were found between the 2 home-cage conditions (5% ethanol = 11.6 g ethanol/kg/day; 5% ethanol in 0.25% sodium saccharin = 11.7 g ethanol/kg/day). However, the addition of saccharin in the schedule-induced condition produced a marked increase in ethanol intake (5% ethanol = 13.1 g ethanol/kg/day; 5% ethanol in 0.25% sodium saccharin = 15.1 g ethanol/kg/day). The home-cage animals showed no sign of an abstinence syndrome upon substitution of water for ethanol. In the schedule-induced group, severe tonic-clonic seizures occurred as a result of ethanol withdrawal.

Ethanol Physical dependence Withdrawal Schedule-induced polydipsia Saccharin

RECENTLY, we described a chronic preparation in which ethanol overdrinking resulted in physical dependence [1]. A feeding regimen that produces schedule-induced polydipsia was used, but a 5% ethanol solution instead of water was provided as the only available fluid and animals drank 13.1 g ethanol/kg/day. Increases in ethanol intake have been obtained when ethanol was mixed with various flavored solutions, but these increases were not sufficient to produce ethanol dependence [4]. The following study was performed to determine if larger daily ethanol intakes could be obtained by using flavored ethanol solutions in the polydipsic situation, which already produced markedly elevated ethanol intakes.

METHOD

Animals

Seventeen adult, male albino rats (Holtzman strain) were used. Four animals were maintained in a schedule-induced polydipsia situation. Thirteen animals were maintained in a home-cage situation. Five of these animals had 5% ethanol solution (v/v) as the only available drinking fluid, while the remaining 8 had the 5% ethanol in a 0.25% sodium saccharin solution vehicle as the only available fluid. At the start of the experiment the mean free-feeding weight for the schedule-induced group was 350 g ± 9 g. The mean free-feeding weight of the 5 home-cage animals that had only 5% ethanol as their drinking fluid, was 340 g ± 10 g. The remaining 8 home-cage animals had a mean free-feeding weight of 377 g ± 9 g.

Experimental Environment

Schedule-induced condition. The basic environment has been previously described [1,2]. Briefly, the animals were housed in individual Plexiglas chambers each of which had an automatic food dispenser (Ralph Gebrands Co.) and a ball-point drinking tube (Ancare, TD-300) attached. There was 24-hr fluorescent lighting and the temperature was maintained at 75°C ± 3°.

Home-cage condition. The animals remained individually housed in standard stainless steel rat cages for the duration

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of the experiment. Fluids were available from the same type of drinking tube as in the schedule-induced condition. Daily food rations were provided once a day, at the same time each day. The temperature and lighting were the same as the schedule-induced condition.

Procedure

Schedule-induced condition. The animals were slowly reduced to 80% of their free-feeding body weights by limiting food intake. The experimental procedure was the same as that previously described [1]. The animals received a 45 mg Lab rat food pellet (P. J. Noyes Co.) every 2 min for 1 hr. Then, for the next 3 hr no food was delivered. These 1-hr food-delivery, 3-hr no-food delivery periods alternated continuously so that there were 6 feeding periods daily with a 3 hr interval between each food delivery period.

For the first month, the only available fluid was 5% ethanol. After this, a 5% ethanol in 0.25% sodium saccharin solution was the only fluid source. Each day, following the midmorning feeding session, the animals were weighed, their fluid intakes recorded, fluid reservoirs refilled, and a food supplement given if body weight was below 80% of free-feeding level.

Following a total time of three months, the animals were withdrawn from ethanol by placing water instead of the ethanol-saccharin mixture in their drinking tubes. After 8 hr of withdrawal, the animals were observed for general withdrawal reactions. They were then subjected to key shaking to determine sensitivity to and severity of induced seizures in order to compare the state of dependence to that previously described in which 5% ethanol alone was used [1,2].

Home-cage conditions. In these conditions the animals had either 5% ethanol (v/v) or 5% ethanol in 0.25% sodium saccharin available as their only drinking fluid. After slowly (about two weeks) reducing them to 80% of the free-feeding weight by limiting food rations, the experiments were begun. They were weighed at the same time daily, the fluid intakes recorded and the reservoirs refilled. A food supplement was then given to maintain the animals at the 80% body weight level. After 90 days, the animals were withdrawn by substituting water for the ethanol solution in the drinking tubes. They were observed for signs of an abstinence syndrome as were the schedule-induced animals. After 8 hr of no ethanol intake, they were subjected to key shakes to determine their sensitivity to seizures.

RESULTS

Home-cage Controls

The animals that had 5% ethanol as their only available drinking fluid averaged over the last 30 days an intake of 78 ml/day (Fig. 1). This is equal to an ethanol dose of 11.6 ± 0.15 g/kg/day. Over the total three months, their last 30 days were not significantly different from the preceding two months (first month = 11.4 ± 0.34 g/kg/day; second month = 11.2 ± 0.32 g/kg/day). Upon substitution of water for the ethanol after the three months of ethanol intake, no

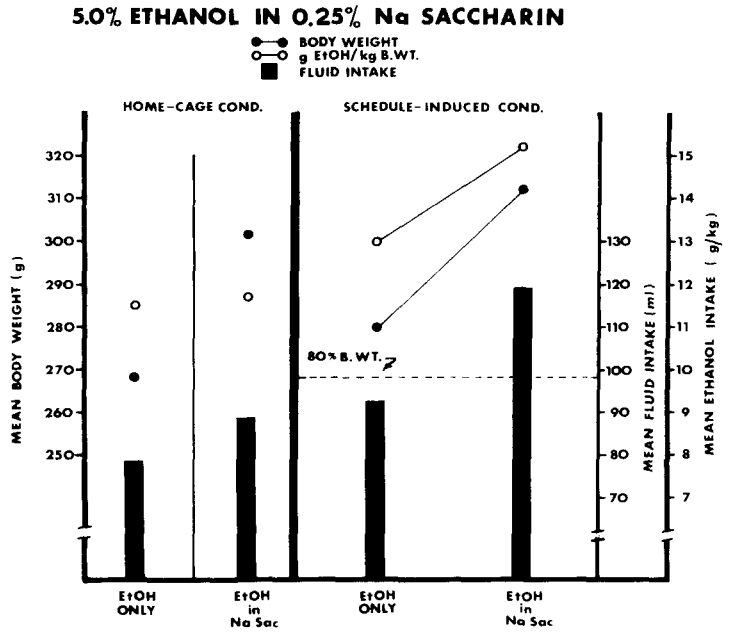

FIG. 1. Effect of addition of sodium saccharin to 5% ethanol intake in both the home-cage and schedule-induced conditions. In the home-cage condition, one group of animals received 5% ethanol as their only drinking fluid (EtOH only; N = 5) while another group received the 5% ethanol–0.25% saccharin mix (EtOH in NaSac; N = 8) for the entire experimental period. In the schedule-induced condition (N = 4), 5% ethanol was available for the first month (EtOH only) and was replaced by the ethanol-saccharin mixture for the following two months (EtOH in NaSac). (All data are means for the last 30 days in each condition. The body weights for the two home-cage conditions are the mean 80% weight levels.)

signs of withdrawal were observed. The animals appeared normal and were not hyperactive when handled. A brief shaking of keys (up to 15 sec) failed to elicit any seizures and no preconvulsive behaviors were noted.

The home-cage condition that received the ethanol–saccharin mix, while having a greater mean daily intake (88 ml/day), also had a larger 80% body weight level, and thus took in 11.7 ± 0.11 g/kg/day, which was not significantly different from the other home-cage condition. Upon withdrawal, there were no observable effects suggesting an abstinence syndrome nor any response to the brief key shaking exposure.

Schedule-induced Condition

During the first month of ethanol drinking, during which only 5% ethanol was available, the mean intake was 92.2 ml/day (13.1 ± 0.87 g/kg/day). Upon the addition of the 0.25% sodium saccharin to the 5% ethanol, the intakes increased substantially and for the last 30 days were 119.0 ml/day (15.1 ± 0.15 g/kg/day).

After one month of 5% ethanol–0.25% saccharin drinking, one animal died. Up until this time there were no indications of illness. Body weight and fluid intake remained stable until the sudden demise. Gross autopsy revealed no apparent pathological changes.

On one occasion 2 animals decreased their intakes to approximately 35% of the previous stable intake levels for 3–4 days and then returned to their previously high levels.

Upon withdrawal, all animals showed signs of extreme hyperactivity and a key-shaking stimulus (less than 5 sec) produced severe tonic-clonic seizures in all animals similar to those previously described [1,2].

DISCUSSION

The addition of saccharin to the ethanol in the schedule-induced condition produced a longterm, excessive, daily ethanol intake greater than under any other condition examined. The addition of saccharin in the home-cage condition did not result in a daily ethanol dosage increase. Neither ethanol nor the ethanol–saccharin mix were ingested at the level of ethanol alone in the schedule-induced condition. Thus, the addition of saccharin in the schedule-induced condition did enhance intakes, while failing to have an effect in the non-schedule controlled condition of the home-cage. It should be pointed out that the increased intake of the ethanol–saccharin solution in the schedule-induced condition was stable and persisted over the two months; thus the phenomenon can not be attributed to some novel stimulus effect. If the basis of this enhanced intake were the reduction of some negative gustatory aspect of the ethanol, then an enhanced intake in the home-cage conditions should also have resulted. If the enhancement were due to some perceived addition of calories (i.e., sweet = calories), then the same argument applies and an increase under the home-cage condition should have been found, as these animals were under a more severe food deprivation state (i.e., held to 80%) than the schedule-induced animals.

The animal that was found dead showed no sign prior to his demise. His intake was 14.2 g/kg the preceding day, which was approximately his daily mean for the preceding two-week period (15.0 g/kg/day). He had only drunk 5 ml since the prior morning refilling of the reservoir, and perhaps if for some reason the drinking spout had blocked, he possibly could have gone into withdrawal and had a lethal convulsion. However, no physical signs of this were apparent, and the length of time the animal had been dead before detection made exact determination impossible.

Two animals during the second month of ethanol–saccharin drinking decreased their intakes for a three to four day period to approximately 35% of what they had been drinking daily. There were no obvious experimental changes (i.e., equipment malfunction, weight change, temperature change, etc.) to account for the observed decrease. Both animals decreased at different times, which would indicate that the reason for intake decrement was due to individual variables, rather than to some external environmental condition. Self-imposed withdrawal has been found in human subjects [3] and with monkeys that were self-administering ethanol [7]. Thus, it is possible that these animals were voluntarily self-withdrawing and after a few days of this self-imposed withdrawal, as in the human case, returned to their usual high ethanol intakes.

One possible contaminant of the results could be the effects of saccharin intake alone in producing physiological changes that were seen upon withdrawal. There is evidence that saccharin produces lower blood sugar levels [6] under some intake conditions. However, if rats are maintained on a diet which does not produce weight loss, no effects of saccharin on blood sugar levels could be found [5]. Since our animals were found to be increasing in weight, and showed no nutritional evidence of dietary inadequacy (normal fur appearance, no skin or other external signs of nutritional deficiency), it seems unlikely that any of the observed withdrawal signs could be attributed to the saccharin itself, and that the withdrawal syndrome was due to the large, daily ethanol intake resulting from the combination with saccharin. The lack of seizures in the home-cage condition, under which large quantities of saccharin were also consumed lend further support to this contention.

The increased ethanol intakes occurred within 3–4 days following the addition of saccharin to the ethanol. This indicates that the resultant intake was not due to some physiological damage resulting from saccharin, but most likely to a changed gustatory acceptability. Since the increase was not found in home-cage animals which had the saccharin mix, the schedule-induction procedure was a necessary component for enhancing the overdrinking after the addition of saccharin.

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