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Complete Reversal of Chronic Ethanol Polydipsia by Schedule Withdrawal[1]

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TANG, M., C. BROWN AND J. L. FALK. *Complete reversal of chronic ethanol polydipsia by schedule withdrawal.* PHARMAC. BIOCHEM. BEHAV. **16**(1) 155–158, 1982.—Rats exposed to daily 3-hr intermittent food delivery sessions (binging) chronically ingested excessive amounts of either H_2O or 5% EtOH (mean of 7.1 g/kg/3-hr). Withdrawing the intermittency of the feeding schedule once every 10 days (single-ration probe session) resulted in reduction of fluid intakes (both H_2O and EtOH) to the level of animals always given daily single-ration sessions. This complete dependence of elevated fluid intake levels on the intermittent feeding schedule was unaffected by either the number of probes previously administered (0 to 11) or the duration the feeding schedule was maintained before introduction of the first probe session (29 or 109 days). The results of the probe sessions demonstrated that a history of ethanol overindulgence was not a sufficient condition for the maintenance of overdrinking. Continued overindulgence required the continued presence of the original inducing conditions. Ethanol-polydipsic animals exposed to periodic probe sessions also developed a slow rise in binge session intake. No such increase was observed in the water-polydipsic animals.

Schedule-induced polydipsia Chronic alcohol intake Overdrinking

EXPOSING food-limited rats to intermittent-food-delivery schedules (schedule-induction condition) has been established as a useful method for generating excessive, oral self-administration of various psychoactive drugs: e.g., pentobarbital, morphine and chlordiazepoxide (for a review see [5]). Recent work has extended the use of this technique to induce excessive intakes of etonitazene [11], phencyclidine [3] and phenobarbital [20]. Germane to the present study, schedule induction also has been used to induce excessive ethanol intakes in various species, such as the rat [4, 6, 7, 9, 12], mouse [15], rhesus[13] and squirrel [2] monkeys, as well as under various physiological (e.g., pregnancy [17]) and environmental (see review by Gilbert, [5]) conditions.

A common assumption in the area of drug abuse, and within alcohol overdrinking investigations in particular, is that drug-taking often is initiated by extraneous environmental factors, such as social reinforcement, and is then gradually maintained by environmental stimulus control and the accruing pharmacological consequences of overindulgence. These latter variables, then, serve to maintain and perhaps increase the chronic overdrinking. This assumption was explored in the present experiment by using the schedule-induction technique to induce and maintain chronic ethanol overindulgence; then on several occasions only the intermittent-schedule aspect of the situation was removed, leaving all else constant: the physical situation and the total food available in experimental sessions. These schedule-removal probes were used to ascertain whether overindulgence begins to evolve so that it comes under the control of the drinking situation and the pharmacological consequences of chronic drinking, thus becoming emancipated from the original inducing conditions.

METHOD

Animals

Sixteen male, albino, Holtzman rats with a mean starting weight of 357 g (range: 314–387 g) were used. They were housed individually in Acme stainless-steel cages in a temperature-controlled room with 12-hr light-dark cycle.

Procedure

All animals were gradually reduced to 80% of their body weights by limiting food rations (Purina Lab Chow, pelleted) over a 2-week period. Water was freely available. After they had reached their 80% weight they were moved to a room with continuous lighting. Each animal was housed in a Plexiglas chamber (30×26×23 cm) that was equipped with a stainless-steel food pellet receptacle and a fluid source on one wall of the chamber consisting of a stainless-steel, ball-bearing spout attached to a Nalgene graduated cylinder.

The sixteen animals were divided into four equal groups (N=4). Three groups received daily 3-hr schedule-induction (binge) sessions during which a 45-mg Noyes food pellet was automatically delivered into the pellet receptacle once every 60 sec (180 pellets/session). Ethanol (5% v/v) was the sole session fluid for 2 groups (EtOH-binge I and II) and water for the third group (H_2O-binge). Water was the only available fluid during the remaining 21 hr. Both groups EtOH-binge I

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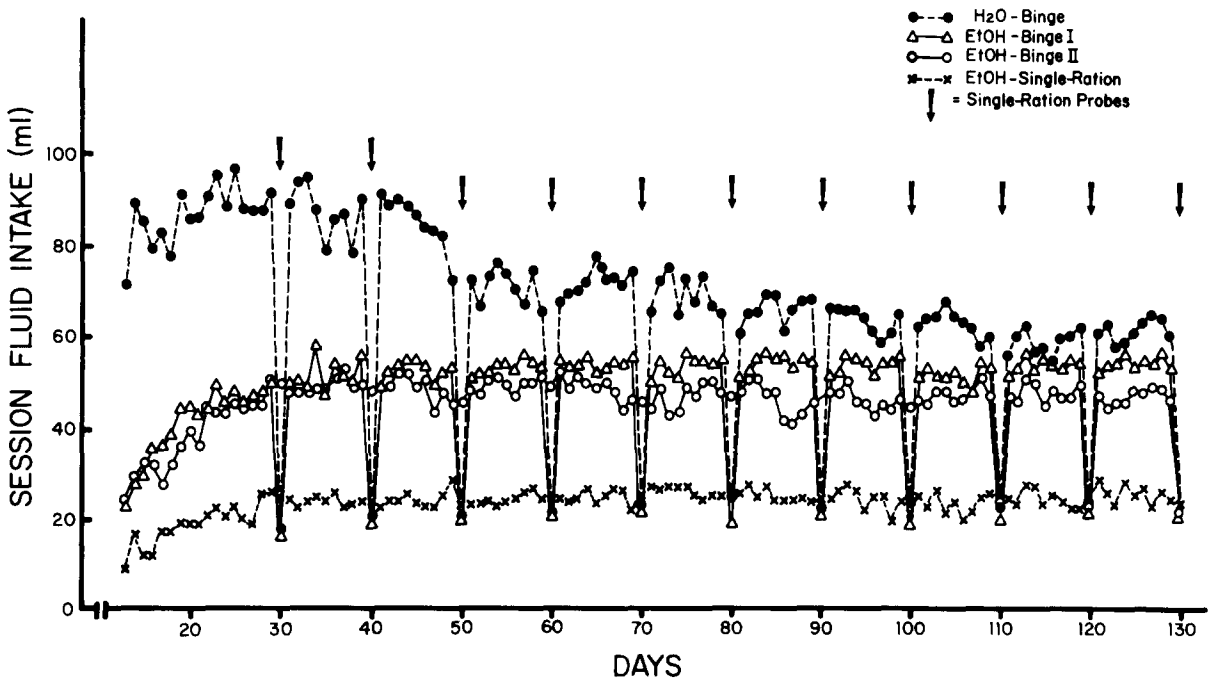

FIG. 1. 3-hr session intake (ml) of groups (N=4) of rats drinking either water (H_2O-Binge group) or 5% ethanol (all other groups). Session food-pellet schedule was fixed-time one minute. Arrows indicate single sessions for which food (180 pellets) was given as a single ration rather than on the fixed-time schedule.

and H_2O-binge were given 17 daily binging sessions. The 18th session was a single-ration probe session which consisted of giving the animals 180 pellets all at once at the beginning of the session. The animals were still allowed the same 3-hr opportunity to ingest fluid. Thus, a probe session was identical to a binge session in all ways except one: absence of the schedule-induction condition. Following this single probe session regular daily binging was resumed the very next day. A total of 11 probe sessions were administered, each separated by 9 days of regular binging. Group EtOH-binge II only received the last 3 probe sessions (9th, 10th, and 11th). This group was necessary to ensure that any change in the level of ethanol drinking over successive probes that might occur in the EtOH-binge I group would not be explicable simply in terms of an increased physical dependence on ethanol developing over time. A Single-ration group was also included in the present study to control for changes in ethanol intake that could occur over successive probe sessions independent of the schedule-induction phase between probes. Briefly, animals in this group were given daily probe sessions without ever being exposed to the schedule-induction condition. Ethanol was the 3-hr session fluid and water was the fluid available for the post-session 21-hr period.

At 1000 hr each day, overnight water was removed and intakes recorded. Each animal was weighed, session fluid was placed on the chambers, and the session was started immediately after the necessary single rations were given. At the end of the 3-hr period, session fluid intakes were recorded and the fluids removed from the cages. Water was replaced and any food supplements necessary to maintain the animals at 80% of their body weights were given.

RESULTS

Figure 1 shows the mean session fluid intakes for all four groups of animals. The session intakes for all three ethanol groups remained stable throughout the duration of the experiment; in contrast, the H_2O-binge group had a substantially higher mean intake during the initial phase, but the high intake decreased gradually over time to about 70% of its original level by the end of the experiment. Within the three EtOH groups, ethanol intakes for the two binge groups were persistently higher (mean for last 5 binge sessions=7.62 g/kg for group I and 6.33 g/kg for group II) than that of the single-ration control group (3.66 g/kg) during the same 3-hr period. A brief summary of mean body weights and session intakes at 4 time periods are presented in Table 1. An overall analysis of variance on the mean of the last 5 binge-session intakes shows that the fluid volumes ingested by the 4 groups were significantly different from each other, $F(3,12)=5.78$, $p<0.05$. Neither days nor interaction effects were significant. Individual comparisons between the 4 group means using the Newman-Keuls procedure [22] reveal that the Single-ration group had significantly lower mean session intakes than any of the other three groups ($p<0.01$ for all 3 tests); the H_2O-binge group's intake was higher than that of the 2 EtOH-binge groups ($p<0.05$ for both tests), and the difference between the two EtOH-binge groups also reached statistical significance ($p<0.05$).

Absence of the schedule-induction condition during the 3-hr session (probes) drastically reduced session intakes in all three binge groups to a level that approximated that of the Single-ration controls (see Fig. 1). A two-way analysis of variance (probes × group) was performed on the session

TABLE 1

MEAN MONTHLY BODY WEIGHT (g), 3-HR SESSION 5% ETHANOL OR WATER (ml) AND ETHANOL (g/kg) INTAKES FOR ALL 4 GROUPS OF RATS

Groups (N=4 for each)	Mean Body Weight (g) Month				Mean Session Fluid Intake (ml) (g EtOH/kg) Month			
	1st	2nd	3rd	4th	1st	2nd	3rd	4th
EtOH-binge I	288± 4.9	287± 4.7	288± 4.4	289± 4.6	43.2 ±2.0 (5.97±0.38)	50.3 ±1.9 (6.94±0.22)	51.1 ±2.0 (7.06±0.28)	50.5 ±2.1 (6.98±0.28)
EtOH-binge II	290± 8.0	290± 8.0	290± 7.8	289± 7.6	42.6 ±1.5 (5.83±0.07)	48.7 ±0.5 (6.65±0.51)	46.7 ±0.5 (6.38±0.74)	45.5 ±1.5 (6.21±0.74)
EtOH single-ration	280±14.9	280±14.9	280±14.7	280±14.7	20.5 ±0.8 (2.97±0.55)	24.4 ±0.3 (3.52±0.71)	24.7 ±0.4 (3.54±0.67)	24.7 ±0.4 (3.59±0.56)
H_2O-binge	285± 5.2	285± 5.0	285± 4.8	285± 5.0	82.6 ±3.4	69.5 ±3.3	62.3 ±2.5	57.8 ±2.3

intakes obtained during each of the 11 probe days. No statistically significant differences were obtained either between probes or between groups (EtOH-binge I, H_2O-binge and Single-ration groups). A separate analysis on the intakes from the 3 probe sessions of EtOH-binge II and that from the last 3 probe sessions of EtOH-binge I also did not yield significant group, probes or interaction effects.

DISCUSSION

The present study utilized a 3-hr schedule-induction situation to produce daily ethanol overdrinking (binging) in the rat at a level more than twice that of the non-schedule animals (Single-ration group). Furthermore, this high level of schedule-induced drinking remained stable throughout the duration of the experiment in spite of interruptions in the schedule (probes), and consequently the intake levels, once every ten days.

Temporary increases in ethanol intake have been reported following interruptions in the continuous access to ethanol (e.g., [1, 8, 16, 18, 19, 21]). In the present experiment, periodic removal of the schedule-induction condition resulted in the development of a small but sustained increase in session ethanol intake (compare the two EtOH-binge groups in Fig. 1). It is interesting to note that in this case, no actual interruption in ethanol availability was imposed; rather, it was a periodic, self-imposed reduction in the level of ethanol intake, precipitated by the absence of the schedule-induction condition, that generated the elevated intakes. This elevation in the EtOH-binge I group's intake does not seem to be related to a general increase in the level of drinking behavior since similar increases were not observed in the H_2O-binge group. In fact, the level of intake by the latter group declined slowly but steadily over the 4-month experimental period.

In agreement with an earlier study [14], maintenance of ethanol polydipsia depended solely on the presence of the schedule-induction condition: removal of the feeding schedule intermittency (single-ration probe) drastically reduced intake levels of both Ethanol-binge groups so that they approximated the Single-ration group's level. Meisch and Henningfield found that monkeys, however, retained the polydipsic level of ethanol intake when the feeding schedule was gradually removed from the session [10]. This same laboratory also reported that the levels of schedule-induced oral intake of phencyclidine [3] and etonitazene [11] both remained fairly intact after the feeding schedule was removed. In the present study, no sign of any carry-over effect from binge to probe sessions was observed. Furthermore, dependence of the session ethanol overindulgence on the feeding schedule was not weakened either by the number of probes the animals had already been exposed to or by the duration the animals had been on the schedule-induction condition before the first probe session was introduced.

It is generally believed that the pharmacological consequences of excessive alcohol intake is a sufficient condition for biasing one towards continued alcohol overindulgence. The present lack of probe session intake differences between the EtOH-binge and H_2O-binge groups, however, do not lend support to a notion that a strong, pharmacological determinant accounts for the maintenance of alcohol overindulgence. Instead, it appears that the presence of an environmental generating condition is necessary for maintaining current overindulgence; a history of chronic ethanol overindulgence alone is inadequate to sustain overdrinking.

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