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Effect of Taste Aversion Learning on Ethanol Self-Administration

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CANNON, D. S. AND L. E. CARRELL. *Effect of taste aversion learning on ethanol self-administration.* PHARMACOL BIOCHEM BEHAV **28**(1) 53–56, 1987.—Ethanol (EtOH) oral self-administration studies using rats have had inconsistent outcomes: studies in which rats are fluid deprived report decreasing EtOH intake over trials, whereas studies not employing fluid deprivation report increasing intake over trials. The present study supports the hypothesis that differential taste aversion learning may account for some of this discrepancy. This study indicates that taste aversion learning is maximized under fluid deprivation conditions and that "latent inhibition," i.e., exposure to non-intoxicating amounts of the EtOH solution prior to conditioning, reduces taste aversion learning. It is suggested that the effect of fluid deprivation on taste aversion resulting from EtOH self-administration may be at least in part due to the development of latent inhibition in non-deprived animals during initial exposure to the EtOH solution.

Ethanol self-administration Taste aversion learning Neophobia Latent inhibition

STUDIES in which rats are given repeated opportunities to drink ethanol (EtOH) solutions have had inconsistent outcomes. In some studies EtOH ingestion increases over drinking trials [3, 4, 14, 16, 17, 19, 23] but in others intake decreases [6–11, 24]. Typically, animals are not fluid-deprived in studies in which they consume increasing amounts of EtOH, but they are fluid-deprived in those studies yielding decreasing consumption.

The decreasing consumption of fluid-deprived animals may be due to greater taste aversion learning resulting from higher rates of EtOH self-administration [1]. Rate of administration could affect taste aversion learning in two ways. One is that higher rate of administration could produce a more effective unconditioned stimulus (US) due to higher blood EtOH levels (BELs). The effectiveness of EtOH as a US is dose-dependent [3], presumably as a function of peak BEL. This possibility is consistent with the finding of weaker taste aversions and lower BELs in rats that consumed a fixed dose of EtOH over 6 drinking periods distributed throughout the day than in rats that drank the same dose in one 10 min interval [10]. The other possibility is that the lower initial rate of EtOH self-administration by non-fluid-deprived rats produces "latent inhibition" to the taste of the EtOH solution. "Latent inhibition" results from unreinforced initial exposure to a conditioned stimulus (CS), and its effect is to reduce the associability of the CS when it is subsequently paired with a US [2,12]. Thus, if initial EtOH intake were at non-intoxicating levels, latent inhibition to its taste (i.e., the CS) would develop that would attenuate the conditioning effects of later intake at rates that do lead to intoxication.

Three previous studies have shown that fluid-deprived rats will drink enough of an EtOH solution to acquire an aversion to it [6, 9, 10]. The former study [6] found decreased EtOH preference following consumption of a 10% (v/v) EtOH-water solution in fluid-deprived rats but not in rats on ad lib intake. The decreased intake by fluid-deprived rats was suggested to be due either to a "biochemical imbalance" that changed the palatability of EtOH or to a learned aversion to the smell and taste of EtOH. In neither of the latter two studies [9,10] was the effect of latent inhibition to the taste of the solution or the effect of fluid deprivation investigated.

In the present experiment, familiarity with the taste of the EtOH solution was manipulated to assess the effect of latent inhibition on EtOH self-administration in fluid-deprived rats. Further, two conditioning groups differing in fluid deprivation were compared to test the effect of level of deprivation during conditioning on taste aversion learning.

METHOD

Subjects were 57 naive male Long-Evans rats weighing between 266 and 476 g at the beginning of the experiment. Animals were housed individually in 18×18×24 cm stainless steel cages in a room with a 12 hr light/dark cycle, and Teklad rodent chow was available ad lib throughout the study. The EtOH solution employed, a 10% (w/v) rum and cola mixture, was selected on the basis of its relative palatability to rats in pilot work in our laboratory. All fluids were presented in 50 ml nalgene tubes with rubber stoppers and metal

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TABLE 1
EXPERIMENTAL PROCEDURES BY DAY AND GROUP

Day	Group L-A	L-C	N-A	N-C	Ad Lib
1–4	rum-cola	rum-cola	water	water	—
5	rum-cola	rum-cola	water	water	water
6	total fluid	deprivation	———	>	water
7	rum-cola	water	rum-cola	water	water
8	total fluid	deprivation	———	>	rum-cola
9	rum-cola	water	rum-cola	water	rum-cola
10	water	(ad lib)	———	>	
11	water	deprivation	(18 hr)	———	>
12	rum-cola	posttest	(20 min)	———	>

Note: The latent inhibition groups (i.e., Groups L-A and L-C) were given 5 ml of rum-cola and the naive groups (i.e., Groups N-A and N-C) received 5 ml of water for 5 min at 1000 hr on Days 1–5. The aversion groups (i.e., Groups L-A and N-A) were given rum-cola and the control groups (i.e., Groups L-C and N-C) were given water for 90 min on Days 7 and 9. Group Ad Lib was given water ad lib on Days 5–7 and rum-cola ad lib on Days 8–9.

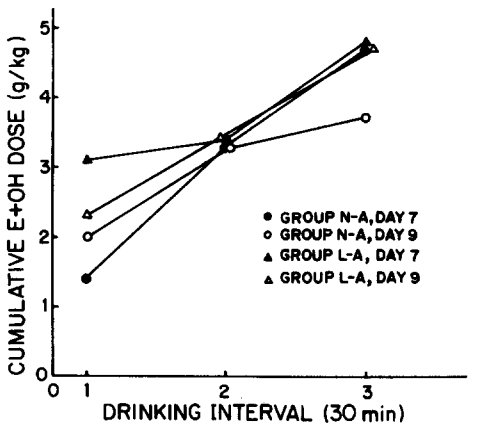

FIG. 2. Cumulative ethanol dose (g/kg) for Groups N-A and L-A over three 30 min drinking periods on Days 7 and 9.

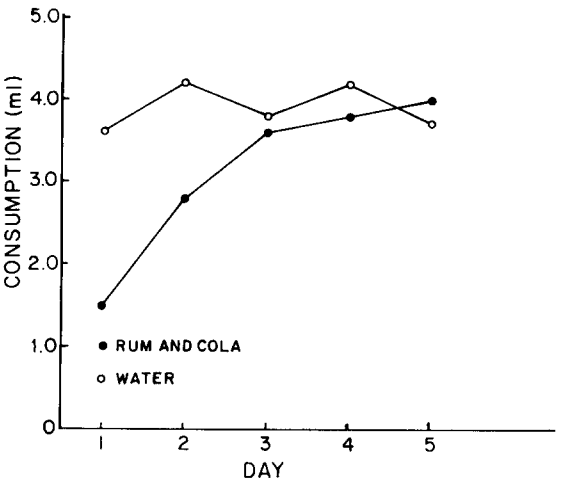

FIG. 1. Mean preexposure consumption (ml) of rum-cola (Groups L-A and L-C combined) and water (Groups N-A and N-C combined) over 5 days. Rats were given 5 ml of rum-cola or water for 5 min.

spouts. Intakes were determined by weighing the bottles before and after each drinking period.

Except where otherwise noted, rats were given water 20 min/day at 1400 hr, beginning 13 days prior to the start of the experiment. Mean daily water intake was 16.1 ml at the beginning of the study, with no significant difference between groups. Conditioning and testing began at 1400 hr on specified days.

Experimental procedures by day and group are described in Table 1. On experimental Days 1–5, Groups L-A (N=10) and L-C (N=10), the latent inhibition groups, were given 5 ml of rum-cola for 5 min at 1000 hr to familiarize animals with the taste of the solution. These small doses resulted in no observable signs of intoxication. Groups N-A (N=18) and N-C (N=10), the groups naive to EtOH at the beginning of conditioning, were given 5 ml of water for 5 min at 1000 hr on Days 1–5. To increase deprivation during conditioning on Days 7 and 9, animals in these four groups were given no fluids on Days 6 and 8. On Days 7 and 9, the aversion groups (Groups N-A and L-A) were given rum-cola while the control groups (Groups N-C and L-C) were given water. Fluids were presented for three 30 min periods separated by 15 min intervals during which bottles were weighed and refilled. Spillage was collected in petri dishes placed beneath the cages and was weighed following each drinking period. Group Ad Lib was given water ad lib on Days 5–7, and rum-cola was presented ad lib on Days 8–9 (rum-cola spillage was collected and weighed daily). Water was presented to all animals ad lib for 24 hr beginning on Day 10 and then was removed for 18 hr beginning on Day 11. On Day 12, the test day, all groups were given water for 10 min at 1000 hr and rum-cola for 20 min at 1400 hr.

Group Ad Lib and half the subjects in Group N-A were run after the other groups had been run. As there was no significant difference in the results of the two cohorts of Group N-A on the posttest, the data of all rats was combined into one analysis of posttest intake. All other analyses involving Group N-A include only the animals run concurrently with other deprivation groups.

RESULTS

Mean intakes during the 5 min preexposure periods on Days 1–5 of animals given rum-cola (Groups L-A and L-C combined, N=20) and water (Groups N-A and N-C combined, N=19) are shown in Fig. 1. Mean water intake was near the maximum available (5 ml/day), but rum-cola intake was low on Days 1–2. Statistical analyses indicate the reliability of this observation. A Flavor by Day repeated measures analysis of variance (ANOVA) resulted in a significant Flavor by Day interaction, $F(4,148)=13.7$, $p<0.001$. One-way ANOVAs comparing intakes of the two flavors were significant for Days 1 and 2, $Fs(1,37)\geq 17.8$, $ps<0.001$, but were not significant for Days 3–5.

Cumulative EtOH dose (g/kg) over the three 30 min drinking periods on conditioning days is shown in Fig. 2 for Groups N-A and L-A. On Day 7, there was a significant Group by Interval interaction, $F(2,34)=18.2$, $p<0.001$.

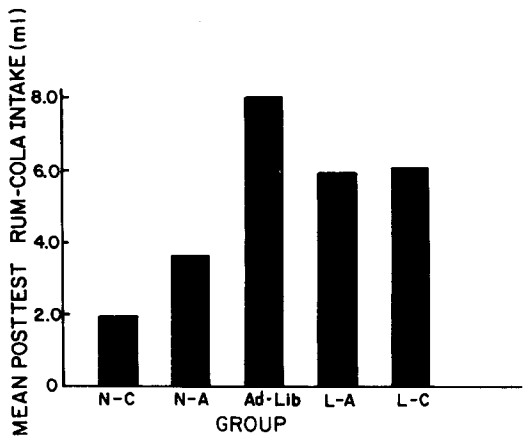

FIG. 3. Mean posttest consumption (ml) of rum-cola. All groups were tested for 20 min.

One-way ANOVAs indicated Group L-A drank more than Group N-A during the first 30 min, $F(1,17)=24.1$, $p<0.001$, and less than Group N-A during the second 30 min interval, $F(1,17)=20.0$, $p<0.001$. There was no difference in mean intake during the third interval nor in mean total intake for the day (Group N-A=4.7 and Group L-A=4.8 g/kg). On Day 9 there were no significant differences between Group N-A and Group L-A in mean EtOH intake (3.7 and 4.8 g/kg, respectively) nor in the way intakes were distributed across drinking intervals. Gross behavioral signs of intoxication, including ataxia and increased somnolence, were observed following EtOH ingestion on Days 7 and 9. The mean EtOH dose self-administered by Group Ad Lib on Days 8 and 9 was 8.6 and 9.5 g/kg/day, respectively.

Posttest rum-cola consumption, shown in Fig. 3, was reliably different across groups, $F(4,53)=12.7$, $p<0.001$. Newman-Keuls tests indicated Groups N-A and N-C both drank less than the other three groups, $ps<0.05$. No other group comparisons were significant.

DISCUSSION

These results are consistent with previous reports of conditioned taste aversions resulting from EtOH self-administration in fluid-deprived rats [6, 9, 10]. Fluid-deprived, ethanol-naive rats (Group N-A) allowed to drink an EtOH solution during conditioning drank less of the solution on a posttest than did animals familiar with the taste of the solution but not with the effects of EtOH (Group L-C). As in previous research [6], non-fluid-deprived rats (Group Ad Lib) did not learn aversions to the taste of the EtOH solution. The failure of Group Ad Lib to learn an aversion cannot be attributed to inadequate daily EtOH dose during conditioning. Daily EtOH doses in the range observed in this study have been reported to produce EtOH dependence in rats after 1–2 weeks and are high for self-administration studies [13]. The difference in taste aversion learning between Groups N-A and Ad Lib observed in this study supports the hypothesis that greater taste aversion learning occurs under fluid deprivation and thus the observation that fluid-deprivation is a critical procedural difference between those EtOH self-administration studies that find increasing amounts of intake and those that find decreasing amounts of intake over repeated trials [1].

Further, the results indicate that latent inhibition to the taste of an EtOH solution attenuates taste aversion learning. Rats latently inhibited to the CS prior to conditioning (Group L-A) did not learn an aversion to the taste of the solution even though they drank amounts of it during conditioning that produced aversions in naive animals (Group N-A). Data have been reported that further support the importance of the contingency between the taste of EtOH and the effects of EtOH in conditioning EtOH taste aversions [18]. Rats given 12 unpaired presentations of the taste of an EtOH-saline solution and IP EtOH injections (2.5 g/kg) separated by 24 hr failed to learn a taste aversion when the taste was paired in a single trial with an EtOH injection. Rats given only the single paired trial did learn a taste aversion. This finding could in part be due to latent inhibition developed during the unpaired trials. It could also be, in part, due to the unpaired EtOH injections since preconditioning US experience is known to disrupt taste aversion learning [5].

The demonstration of a latent inhibition effect in Group L-A strengthens support for the interpretation that Group N-A consumed relatively little on the posttest due to taste aversion learning rather than to some non-associative effect of rapid EtOH ingestion as has been suggested [6]. Since Groups N-A and L-A self-administered comparable amounts of EtOH during conditioning, non-associative EtOH effects cannot account for the difference observed between them on the posttest.

As described earlier in this paper, it has been argued that fluid deprivation increases taste aversion learning during EtOH self-administration by increasing the rate of administration, which would increase peak BEL (i.e., US intensity) and also would decrease the opportunity for the taste of the solution to become latently inhibited [1]. Both possibilities received indirect support. Since BELs were not measured, this study does not provide conclusive data on relative US intensity in deprived and non-deprived rats. However, since Group N-A consumed in 2 hr almost half the EtOH dose consumed by Group Ad Lib in 24 hr, it is likely the peak BEL (and so, peak US intensity) was greater in Group N-A.

Latent inhibition was demonstrated, but the design of the study does not permit a test of the hypothesis that latent inhibition is more likely to develop in the absence of fluid deprivation. However, the results suggest a mechanism, "neophobia," whereby non-deprived rats would be more likely to develop latent inhibition to an EtOH solution. "Neophobia" is the well-documented reluctance of animals to ingest large amounts of novel substances [15]. Neophobia was manifested by the low intakes of rum-cola by latent inhibition groups on Days 1–2, by Group N-A relative to Group L-A during the first 30 min interval on the first conditioning trial (Day 7), and by Group N-C on the posttests. Indeed, intake by EtOH-naive animals (Group N-C) was as low on the posttest as that of conditioned animals (Group N-A). Repeated experience with non-intoxicating amounts of EtOH resulted in increased EtOH self-administration across Days 1–5 in Groups L-A and L-C. We attribute this finding to extinction of neophobia. It is possible that neophobia reduces initial EtOH intake of non-deprived animals sufficiently to permit development of latent inhibition to the taste of the solution, which would attenuate taste aversion learning later when administration rate increased.

Since neophobia to cola alone was not assessed in this study, it could be argued rats were neophobic to cola rather than to rum. However, unpublished work in our lab makes such an interpretation unlikely. Rats given cola alone display little or no neophobia.

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