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Rat Strain Differences in Ethanol Self-Administration and Taste Aversion Learning

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CANNON, D. S. AND L. E. CARRELL. *Rat strain differences in ethanol self-administration and taste aversion learning.* PHARMACOL BIOCHEM BEHAV **28**(1) 57–63, 1987.—Taste aversion learning was investigated in two inbred strains of rats known to differ in amount of ethanol (EtOH) they will self-administer orally. The "low EtOH preference" strain, WKYs, acquired an aversion to an EtOH solution during self-administration; but a "high preference" strain, M520s, did not. It was shown that a lower dose of EtOH will condition saccharin aversion in WKYs than in M520s, suggesting EtOH is a more effective US in the low preference strain. Analysis of patterns of EtOH self-administration indicates the pattern of the low preference strain is more likely to result in taste aversion learning. The implications of these results for the presumed relation between EtOH preference and other EtOH-related phenotypes is discussed.

Inbred rat strains Ethanol self-administration Taste aversion learning Neophobia Latent inhibition

ONE approach to the investigation of genetic determinants of behavioral and pharmacological responses to ethanol (EtOH) has been to study inbred strains of rats [13]. Among the EtOH-related phenotypes for which rats have been successfully bred are two variables related to EtOH self-administration, viz., EtOH intake (g/kg/day) and EtOH "preference," defined as EtOH intake relative to water intake. A principal components analysis of EtOH-related phenotypes indicates that EtOH intake shares common variance with rate of EtOH metabolism and with behavioral sensitivity to acute EtOH administration [e.g., sleep time, blood EtOH level (BEL) at recovery of righting reflex] [15].

The behavioral processes that mediate the relation between EtOH self-administration and other EtOH-related phenotypes have not been extensively investigated. One behavioral variable that may affect EtOH self-administration is taste aversion learning [1]. It is known that EtOH can function as both an unconditioned stimulus (US) [2, 4, 8] and a conditioned stimulus (CS) [12] in taste aversion learning paradigms and that EtOH aversion is produced, at least under some conditions, by oral EtOH self-administration [4a,5]. It is not known, though, whether there are strain differences in taste aversion learning following self-administration that may account for strain differences in consumption rate and/or EtOH preference. EtOH preference and daily intake are usually assessed only after 2–3 weeks of ad lib EtOH intake [16], so taste aversion learning that may occur during initial EtOH ingestion has not been observed.

The present series of studies investigates differences in taste aversion learning between two strains of rats reported to differ in EtOH preference. The "low preference" strain was the Wistar Kyoto (WKY), and the "high preference" strain was the Marshall (M520). M520s, relative to WKYs, have a higher EtOH preference ratio and daily EtOH intake (g/kg/day) when both water and 10% EtOH are available ad lib [9], have a shorter sleep time following a 3.5 g/kg dose [15], metabolize EtOH more rapidly [8], and have lower BELs 1 hr following a 3.0 g/kg dose [15].

EXPERIMENT 1

Conditioned aversions have not been demonstrated previously in ad lib EtOH self-administration studies [4a,5]. However, the hypothesis that low EtOH preference is mediated by taste aversion learning requires that low preference strains, but not high preference strains, develop such aversions. The first experiment investigates whether WKYs and M520s differ in conditioned aversion to the taste of an EtOH solution following ad lib consumption. Since our previous work [4a] indicates rats are reluctant to drink EtOH initially, control rats were familiarized with the taste of the solution but not with the effects of EtOH prior to the posttest. On the posttest, conditioned taste aversion in experimental animals was assessed relative to same-strain control animals. Since the occurrence of taste aversion learning following EtOH self-administration is central to the present

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TABLE 1

DAILY EtOH INTAKE (g/kg) PER STRAIN, EXPERIMENTS 1a–1b

Conditioning Day	Strain			
	WKY		M520	
	Experiment 1a	Experiment 1b	Experiment 1a	Experiment 1b
1	8.7	8.8	8.4	7.0
2	9.3	9.2	11.5	11.5
3		9.7		9.7

series of studies, Experiment 1 was conducted twice with minor variations.

METHOD

Subjects

In Experiment 1a, 21 WKYs (11 males and 10 females) and 24 M520s (8 males and 16 females) served as subjects. The WKYs were obtained from Harlan Sprague Dawley, and the M520s were born in our lab of brood stock obtained from the National Institutes of Health. Both strains were approximately 180 days old at the beginning of the study. They had served previously in a taste aversion study (Experiment 3a) but were naive to EtOH and cola.

In Experiment 1b, 20 WKYs (10 males and 10 females) and 17 M520s (7 males and 10 females) served as subjects. They were first generation descendents of the subjects in Experiment 1a. They had been used as control animals in another study (Experiment 2) but were naive to EtOH and cola. Subjects were approximately 120 days old at the beginning of the study.

Procedure

Animals were housed individually in 18×18×24 cm stainless steel cages in a room with a 12 hr light/dark cycle, and Tekland rodent chow was available ad lib throughout the study. Intakes were determined by weighing fluid bottles before and after each drinking period. EtOH was presented as a rum-cola solution (10% EtOH, w/v) because pilot work in our laboratory indicates this solution is relatively palatable to rats.

Experiment 1a. Animals first were adapted to a 20 min/day drinking schedule for 8 days. Watering occurred at approximately 1400 hr daily. Within each strain, rats were randomly assigned to an experimental or control group counterbalanced with respect to sex. Sample sizes for WKYs were experimental group, N=10; control group, N=11. There were 12 M520s per group. For 5 consecutive days, control animals were given 5 ml of rum-cola for 5 min at 1000 hr to familiarize them with its taste but not with its pharmacological effects. No signs of intoxication were observed following these small doses (approximately 0.1 g/kg). Experimental animals were given 5 ml of water for 5 min at the same time. Rats were then placed on water ad lib for 3 days prior to conditioning. On 2 conditioning days, experimental animals were given rum-cola ad lib while control animals were given water ad lib. After the conditioning phase, animals were placed on the 20 min/day watering schedule again for 3 days, and then all animals were given a 20 min rum-cola posttest.

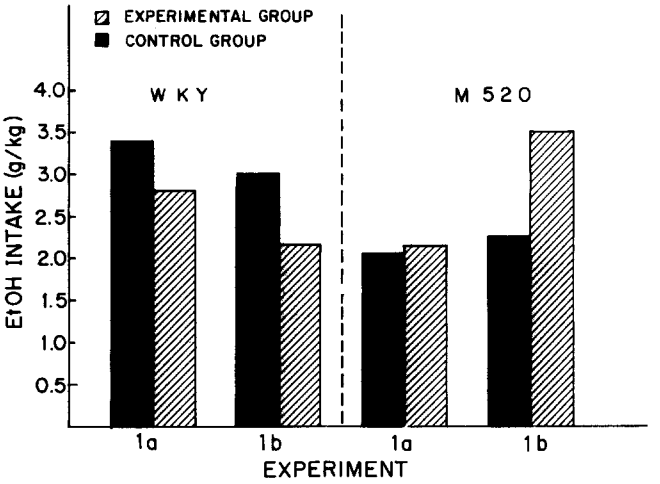

FIG. 1. Mean posttest rum-cola intake (g/kg of EtOH) per strain in Experiments 1a and 1b. Experimental groups had been given rum-cola (10% EtOH, w/v) for 2–3 days ad lib. Control animals were familiar with the taste of the solution but not with the pharmacological effects of EtOH.

Experiment 1b. In unspecified regards, the procedure of Experiment 1b was the same as that of Experiment 1a. There was no flavor preexposure or fluid deprivation prior to conditioning, but animals had had experience with the deprivation schedule in an earlier study. On 3 conditioning days, control animals (WKY N=10, M520 N=9) were given 5 ml of rum-cola from 0800–1200 hr and water ad lib the rest of the day. Experimental animals (WKY N=10, M520 N=8) were given rum-cola ad lib on these 3 days. All animals were then given water ad lib for 1 day before being placed on a 20 min/day drinking schedule for 3 days prior to the rum-cola posttest.

RESULTS

The design of Experiment 1a permits comparison of initial acceptance of rum-cola by control subjects with water intake by experimental subjects on the flavor familiarization days. On the first familiarization day, mean intakes were as follows: WKY water=3.5 ml, WKY rum-cola=3.4 ml, M520 water=4.5 ml, and M520 rum-cola=2.4 ml. These results indicate an interaction between strain and fluid (i.e., rum-cola or water), $F(1,41)=20.9$, $p<0.001$. This interaction is due to a difference in mean intake of the 2 fluids by the M520s, $F(1,22)=59.9$, $p<0.001$, while there was no difference in intake by the 2 WKY groups. On the rest of the

familiarization days, rum-cola intake by both strains was comparable to water intake (i.e., near the maximum possible).

Daily mean EtOH intake (g/kg) on conditioning days by experimental animals is shown in Table 1. Across both experiments combined, the M520s drank more on the second conditioning day than did the WKYs, $F(1,37)=5.5$, $p<0.05$. There were no strain differences on any other conditioning day.

Mean rum-cola intake (ml) on the posttest is shown in Fig. 1. In both experiments, WKYs given rum-cola ad lib developed aversions to the solution relative to same-strain controls familiar with the taste of the solution but naive to the effects of EtOH: Experiment 1a, $F(1,19)=6.9$, $p<0.05$; Experiment 1b, $F(1,18)=11.4$, $p<0.01$. There was not a statistically significant difference between M520 groups in either study.

DISCUSSION

The results support the hypothesis that low preference, but not high preference, strains develop aversions to the taste of EtOH solutions during ad lib consumption. In 2 studies, WKYs acquired aversions to rum-cola during ad lib consumption, but M520s did not. This strain difference in taste aversion learning cannot be attributed to differences in EtOH dosage during conditioning because the only difference observed in daily dosage was that the strain not acquiring an aversion drank more than the one that did on the second conditioning day.

The finding of an aversion in the WKYs is the first report to date of a taste aversion conditioned by ad lib EtOH self-administration. Previous studies have found learned aversions only in fluid-deprived animals [4a,5].

The reluctance of M520 control animals to drink rum-cola on the first flavor familiarization day of Experiment 1a is interpreted as "neophobia," i.e., the well-documented reluctance of animals to ingest novel substances [12]. Neophobia to rum-cola has been found previously with Long-Evans rats, [4a]. Neophobia was extinguished by the second flavor familiarization day. The possible significance of the greater EtOH neophobia of M520s for taste aversion learning is investigated in Experiment 4.

EXPERIMENT 2

Experiment 1 found that a low preference, but not a high preference, rat strain learned an aversion to an EtOH solution after 2–3 days of self-administration. Experiment 2 investigates the possibility that this finding is the result of strain differences in the aversiveness of EtOH as an US. It has long been known that EtOH administered non-orally will produce a dose-dependent aversion to a flavor with which it is paired [2,8]. In the present study, dose-response curves for EtOH-induced saccharin aversion are compared across strains. If the taste aversion observed in WKYs in Experiment 1 is the result of greater aversiveness of EtOH's pharmacological effects, WKYs should manifest saccharin aversion at a lower EtOH dose.

METHOD

Subjects

Forty WKYs (20 males and 20 females) and 35 M520s (16 males and 19 females) served as subjects. They were the first generation descendents of the subjects used in Experiment 1a and were experimentally naive. Subjects in both strains were approximately 60 days old at the beginning of the study, but the WKYs were significantly larger. The mean body weight of WKYs was 225.6 g; of M520s, 175.5 g, $F(1,76)=22.9$, $p<0.001$. Thus, between-strain comparisons were made using analyses of covariance with body weight or the previous day's water consumption as the covariate.

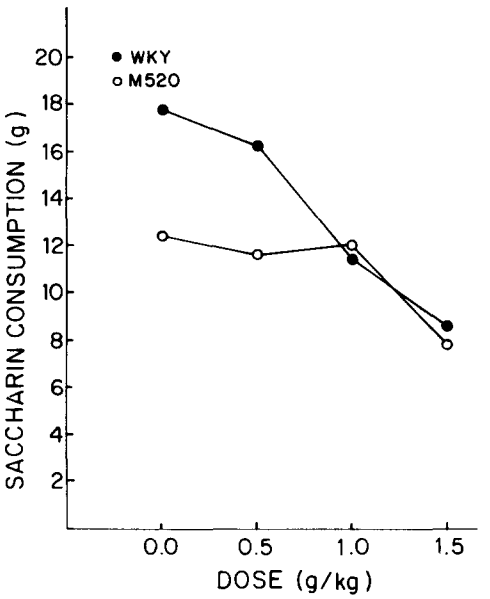

FIG. 2. Mean posttest saccharin (0.1%, w/v) intake (ml) per strain following one conditioning trial with either a 0.0, 0.5, 1.0 or 1.5 g/kg dose of EtOH (22.5%, w/v, IP) as the unconditioned stimulus in Experiment 2.

Procedure

Subjects were individually housed and fed as in Experiment 1. They were given water 20 min/day at 1400 hr for 12 days prior to the start of the study and were maintained on that schedule throughout the experiment. Subjects within each strain were randomly assigned to 4 EtOH dosage groups (0.0, 0.5, 1.0, and 1.5 g/kg) counterbalanced with respect to sex. For WKYs, there were 10 subjects per group. For M520s the Ns were, respectively, 10, 9, 8, and 8 subjects per group.

At 1000 hr on the conditioning day, all rats were given a 0.1% (w/v) saccharin-water solution for 20 min and were given an injection within 1 min of removal of the bottle. Rats in the 0.0 g/kg groups were given 3 ml of 0.9% (w/v) saline, and rats in the other groups were given appropriate amounts of a 22.5% (w/v) EtOH-water solution. Two days later, all animals were given the saccharin solution for 20 min at 1000 hr.

RESULTS

There was a strain difference in saccharin neophobia on the conditioning day. Mean saccharin intake of the WKYs was 15.9 ml; of M520s, 13.2 ml. Using water intake on the preconditioning day as a covariate, an analysis of covariance indicated a significant strain effect, $F(1,71)=4.3$, $p<0.04$. Mean saccharin intake per group on the posttest is shown in

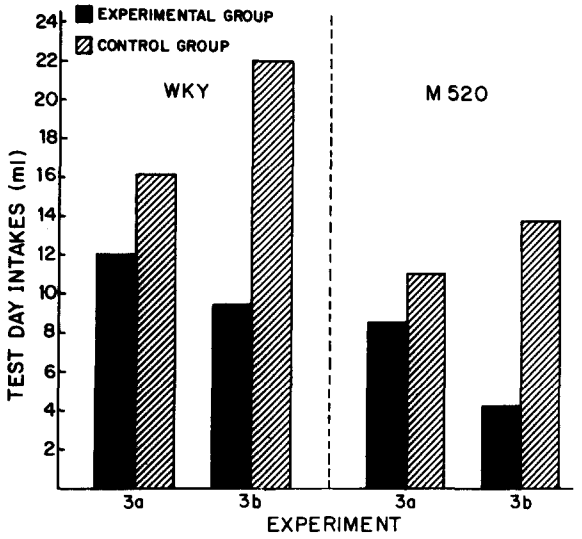

FIG. 3. Mean posttest conditioned stimulus (CS) intake (ml) per strain following one conditioning trial with a 1.2% of body weight dose of 0.075 M LiCl as the unconditioned stimulus. In Experiment 3a, the CS was saccharin (0.1%, w/v); and in Experiment 3b, saline (0.9%, w/v).

Fig. 2. As can be seen, there was a steeper dose-response curve for the WKYs than for the M520s. A strain by dosage analysis of covariance in which body weight was the covariate confirms this observation: there was a significant strain by dosage interaction, $F(3,66)=5.7$, $p<0.002$. Within-strain analyses of the dosage effect was significant for both strains: WKY, $F(3,36)=17.3$, $p<0.001$; M520, $F(3,31)=7.4$, $p<0.001$. Newman-Keuls post-hoc comparisons indicate that, for the M520s, only the 1.5 g/kg dose was effective in producing a saccharin aversion, $p<0.01$. For the WKYs, though, both the 1.0 and 1.5 g/kg doses produced aversions, $ps<0.01$.

DISCUSSION

The results of Experiment 2 support the hypothesis that EtOH is a more effective US for WKYs than for M520s. A 1.5 g/kg dose produced an aversion in both strains, but a 1.0 dose was effective only for the WKYs. Thus it is possible that the greater aversiveness of EtOH is one reason WKYs, but not M520s, developed aversions to an EtOH solution following self-administration in Experiment 1.

The difference in saccharin neophobia observed in this study suggests the greater rum-cola neophobia of M520s in Experiment 1 may not be specific to EtOH solutions. Rather, M520s may be more neophobic in general. This possibility will be explored further in Experiment 3.

EXPERIMENT 3

An alternative interpretation of the results of Experiment 2 is that M520s do not learn taste aversion as readily as do WKYs regardless of the US employed. This interpretation assumes strain differences in conditionability rather than in the aversiveness of EtOH. This possibility is investigated in Experiment 3 in two studies using LiCl as the US. In Experiment 3a saccharin was the CS, and in Experiment 3b saline was the CS. In both studies, a relatively low LiCl dose was used to try to avoid floor effects that would mask any possible strain differences.

METHOD

Subjects

Twenty-two WKYs (11 males and 11 females) and 24 M520s (8 males and 16 females) served as subjects in Experiment 3a. They were 120 days old and were experimentally naive. In Experiment 3b, 20 WKYs (10 males and 10 females) and 17 M520s (8 males and 9 females) served as subjects. They were in the experimental groups of Experiment 2 but were naive to saline and LiCl.

Procedure

In both Experiments 3a and 3b, experimental and control groups were counterbalanced with respect to sex. In Experiment 3a, 11 WKYs and 12 M520s were assigned to both groups. In Experiment 3b, there were 10 WKYs per group; for M520s, there were 8 experimental and 9 control subjects. In both experiments, subjects were adapted to a 20 min/day watering schedule prior to conditioning. Watering occurred at approximately 1400 hr throughout the studies. On the conditioning day, subjects were presented the CS (i.e., a 0.1% saccharin-water solution in Experiment 3a and 0.9% saline in Experiment 3b) for 20 min at 1000 hr. Immediately after the CS presentation, half the subjects in each strain were given 1.2% body weight of 0.075 M LiCl IP. Control subjects were injected with 3 ml of normal saline. Two days later, subjects were given a 20 min posttest at 1000 hr with the CS used in conditioning.

RESULTS

Conditioning day intakes of strains were compared using analyses of covariance in which preconditioning day water intake was the covariate. In both studies, these analyses suggest the M520s had more neophobia to the CS than did the WKYs: Experiment 3a, $F(1,43)=62.0$, $p<0.001$; Experiment 3b, $F(1,33)=4.3$, $p<0.05$.

Mean saccharin and saline intakes on the posttests are shown in Fig. 3, which shows that both strains learned aversions to both CSs. For saccharin intake in Experiment 3a, there was a significant difference due to strain, $F(1,42)=22.2$, $p<0.001$, and experimental condition, $F(1,42)=14.0$, $p<0.001$, but no interaction between strain and condition. Likewise, in Experiment 3b there was a significant difference in saline intake due to strain, $F(1,33)=23.5$, $p<0.001$, and experimental condition, $F(1,33)=62.8$, $p<0.001$, but no interaction between strain and condition. In both experiments, within-strain analyses were significant for both strains, $ps<0.001$.

DISCUSSION

These data do not support the suggestion that M520s failed to learn an aversion to rum-cola in Experiment 1 and had a more gradual dose-response curve in Experiment 2 because they have a deficit in taste aversion learning ability. They acquired aversions to saccharin and saline as readily as did WKYs when LiCl was the US. Of course, it is possible that a strain difference might be evident under a different set of parametric conditions. M520s were more neophobic to both saccharin and saline in these studies, supporting the suggestion that they are generally more neophobic than are WKYs.

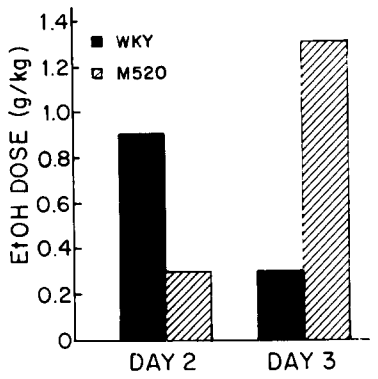

FIG. 4. Mean rum-cola intake (g/kg of EtOH) per strain during the first 2 hr of EtOH availability on the first and second EtOH days in Experiment 4. The rum-cola solution was 10% EtOH (w/v).

EXPERIMENT 4

In addition to EtOH being a more effective US for WKYs, it is possible that strain differences in drinking pattern influence taste aversion learning during EtOH self-administration. Of particular importance would be the amount of EtOH consumed during initial exposure to the EtOH solution. One reason that taste aversions to EtOH solutions may not be readily acquired during self-administration by non-fluid-deprived rats is that "latent inhibition" develops during an initial neophobia period [1]. "Latent inhibition" to a CS results from non-reinforced presentation of the CS prior to conditioning, and its effect is to reduce associability of the CS during subsequent conditioning trials [10]. Neophobia would be expected to result in latent inhibition because a period of low administration rate would constitute a non-reinforced CS presentation. In support of this hypothesis, it is noted that preconditioning ingestion of non-intoxicating amounts of rum-cola attenuates taste aversion learning during rum-cola self-administration in fluid-deprived rats [4a]. Further, M520s have been found to be more neophobic than WKYs in the present series of studies.

Another variable of potential significance is amount consumed per drinking episode. Rats that consume EtOH in a few, relatively large episodes would be expected to develop more aversion than rats that distribute their drinking over many small episodes because the few large episodes would result in a more aversive US per CS exposure. It has been shown that a given dose of EtOH is more effective in conditioning taste aversions if administered all at once than if given in several small doses spaced over 6 hr [6].

In Experiment 4, drinking was continuously recorded to determine whether there are strain differences in neophobia and/or amount consumed per drinking episode during ad lib consumption.

METHOD

Subjects

Experimentally naive, male WKYs (N=5) and M520s (N=5) served as subjects. They were first generation descendents of the subjects in Experiment 1a and were all born within 5 days of one another. Within strains, one male per litter was randomly selected from 5 different litters. Rats were 60 days old when the study began, but since it was necessary to run subjects one at a time and each subject took a week to run, the last subject was 130 days old when studied. Subjects were studied in alternating order across strains. Since body weight increased over the course of the study and was correlated with fluid consumption in ml, comparisons of water intake were based on a weight adjustment, i.e., g water/kg body weight.

Procedure

When studied, animals were individually housed in a room with a 12 hr light/dark cycle in a 24×28×27 cm cage with two clear Plexiglas sides, two metal sides, and metal rods for a floor. Drinking was measured using a Coulbourn "Lickometer" that detected licks by means of a photoelectric beam broken by the rat's tongue. Licks were integrated by a Grass Model 7 polygraph to provide a cumulative record of drinking. Polygraph pen deflection during each 10 min period was measured, and total fluid intake for each 24 hr period was determined by weighing the fluid bottle. The weight of collected spillage was subtracted from total fluid intake. The amount consumed during each 10 min interval was computed to be proportional to the amount of pen deflection that occurred during the interval.

Fluids and food were available ad lib throughout the study. Rats were given 2 days to habituate to the recording cage, and then continuous recordings of fluid intake were made, as described above, on Days 1–3. Water was given on Day 1, and rum-cola was given on Days 2–3. Bottles were refilled and rats were weighed at 0800 hr daily.

RESULTS

Mean daily EtOH consumption (g/kg/day) was as follows: on the first EtOH day, WKY=6.6 and M520=6.5; on the second EtOH day, WKY=5.3 and M520=9.3. An analysis of variance of total daily dose by strain and day resulted in a significant interaction, $F(1,8)=5.5$, $p<0.05$. There was no difference between strains in total intake on Day 2, but M520s drank more than WKYs on Day 3, $F(1,8)=22.2$, $p<0.01$.

A question of primary importance in the present study is whether the strains differ in neophobia. To first rule out strain differences in water drinking at the same time of day rum-cola was first presented, weight-adjusted water consumption during the first 2 hr of Day 1 was compared, and there was not a significant strain difference (WKY=1.0 g/kg, M520=0.67 g/kg). Analysis of mean EtOH intake (g/kg) during the first 2 hr of Days 2 and 3, shown in Fig. 4, suggests greater neophobia in M520s. As can be seen, there was a significant interaction between strain and day, $F(1,8)=6.5$, $p<0.05$. On Day 2, WKYs drank more than M520s during the first 2 hr, Mann-Whitney $U=4$, $p<0.05$, one-tailed test; but on Day 3 M520s drank more than the WKYs, Mann-Whitney $U=4$, $p<0.05$, one-tailed test. During minutes 11–40 of Day 2, the WKYs drank 0.5 g/kg while the M520s drank 0.1 g/kg, Mann-Whitney $U=2$, $p<0.05$, two-tailed test.

The results also indicate a strain difference in amount consumed during each drinking episode on the first EtOH day. For this analysis, a drinking episode was defined as any drinking period of at least 1 min duration not interrupted by 10 min or more of no drinking. Mean consumption (g/kg) per episode was computed daily for each rat. On Day 2, WKYs drank 0.45 g/kg/episode and M520s drank 0.23 g/kg/episode, Mann-Whitney $U=4$, $p<0.05$, one-tailed test. There was no difference in EtOH intake per episode on Day 3 or in

weight-adjusted water intake per episode on Day 1. As would be expected from the findings that total EtOH intake of the two strains was comparable on Day 2 while intake per episode by WKYs was greater, WKYs drank during fewer episodes on Day 2 than did M520s, Ms=15.4 and 33.8 intervals, respectively, $F(1,8)=22.9$, $p<0.01$. There was not a significant difference between strains in number of drinking intervals on Day 1, and on Day 3 the difference approached significance, Ms=12.4 intervals for WKYs and 21.6 intervals for M520s, $F(1,8)=4.7$, $p<0.10$.

DISCUSSION

As in Experiments 1a and 1b, total EtOH intake was comparable across strains on the first EtOH day and was greater by M520s on the second EtOH day. However, the present study reveals strain differences in the distribution of drinking on the first EtOH day that may affect taste aversion learning. The first such difference is greater neophobia, and thus possibly greater latent inhibition, in the high preference strain. Consistent with the finding of greater neophobia by M520s in earlier studies in this series, the M520s had a much lower rate of EtOH self-administration during initial rum-cola presentation. The dose self-administered by M520s during the first 2 hr (i.e., 0.3 g/kg) was less than the 0.5 g/kg dose administered IP in Experiment 2 that failed to condition a taste aversion in either strain. Thus, the initial taste experience would have been an unreinforced CS presentation for the M520s that could have attenuated any conditioning that would have otherwise resulted from subsequent drinking at higher rates. Supporting this interpretation is the finding that even a brief non-reinforced CS preexposure can disrupt taste aversion learning for up to 4 hr [3]. On the other hand, the amount self-administered by WKYs during the first 2 hr may have been somewhat aversive. The amount drunk in the first 2 hr (0.92 g) was comparable to the 1.0 g/kg dose administered IP that conditioned an aversion in WKYs in Experiment 2, although oral administration over two hours would result in a lower BEL than the same amount administered in a single injection.

The second strain difference in drinking pattern that may have affected taste aversion learning is rate of administration. It appears that the pattern of EtOH ingestion on Day 2 by WKYs would result in a more aversive US for them than the M520s' pattern would: the WKYs drank greater amounts per episode in fewer episodes than did the M520s. Further research investigating peak BELs per drinking episode is necessary to confirm this possibility.

GENERAL DISCUSSION

The present series of studies support the hypothesis that EtOH-induced taste aversion learning is associated with rat strain differences in EtOH preference. WKYs, a low preference strain, acquired aversions to an EtOH solution following ad lib self-administration, but M520s, a high preference strain, did not. This difference is at least in part due to greater aversiveness of acute EtOH effects in WKYs as evidenced by their steeper dose-response curve for EtOH-induced saccharin aversions. The specific effects of EtOH responsible for taste aversion learning are not known, but the fact these strains differ in behavioral sensitivity to acute EtOH effects [15] suggests EtOH's aversiveness in a conditioning paradigm may be correlated with behavioral sensitivity in inbred rat strains. However, as Petersen [14] has cautioned, since the genotype of inbred strains is fixed entirely by chance, one cannot assume causality from correlations between phenotypes.

The strain difference in taste aversion learning observed in Experiment 1 cannot be attributed entirely to differential aversiveness of EtOH as a US. Strain differences in neophobia to rum-cola observed before either strain had experienced the pharmacological effects of EtOH may have also affected taste aversion learning. It is significant that this difference in neophobia is not specific to rum-cola. The difference in EtOH intake per drinking episode observed in Experiment 4 also cannot be attributed to difference in behavioral sensitivity to EtOH since it was the more sensitive strain that ingested more per drinking episode. These results caution against the unqualified attribution of differences in EtOH preference in inbred strains to any other EtOH-related phenotype without first investigating behavioral differences that are not EtOH-specific but that may affect taste aversion learning.

The finding that the high preference strain is more neophobic is at variance with the report that C57BL mice, a high preference strain, are less neophobic to EtOH than BALB/c mice, a low preference strain [12]. There were a number of procedural differences between that study and these studies that might account for this discrepancy (e.g., they used an EtOH-water solution and mice had a choice between water and the EtOH solution), but the discrepancy does suggest that neophobia and EtOH preference are not always positively correlated. One would not expect they would be if their association on the same genotype were due to chance.

Another strain difference that may have affected taste aversion learning in Experiment 1 is the effectiveness of the EtOH solution as a CS. It has been reported that C57BL mice do not acquire LiCl-induced aversions to an EtOH CS as readily as do BALB/c mice but show no such deficiency when other flavors are employed as CSs [12]. This possibility was not investigated in this series of studies but should be in future research.

As a final caveat, it should be acknowledged that the differences observed in these studies between WKYs and M520s may not generalize to other inbred strains bred for EtOH preference and have unknown relevance for strains selected for other phenotypes such as reactivity to EtOH [14]. However, the present studies do encourage consideration of the role taste aversion learning may play in EtOH ingestion by other strains.

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