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Ethanol Interoceptive Cue and Sleep-Time Duration in HAS and LAS Selectively Bred Rats[1]

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KRIMMER, E. C. *Ethanol interoceptive cue and sleep-time duration in HAS and LAS selectively bred rats.* PHARMACOL BIOCHEM BEHAV **36**(2) 255–260, 1990.—The drug discrimination paradigm was used to evaluate the effects of selective breeding for differential sensitivity to the hypnotic effects of ethanol. Tenth generation high alcohol sensitive (HAS) and low alcohol sensitive (LAS) rats were trained to discriminate between ethanol (0.6 g/kg, IP) and saline vehicle on a VR-5 schedule of reinforcement. The animals were tested with 0.15, 0.3, and 0.9 g/kg ethanol following 40, 50, and 60 training sessions. Sleep-time, tested before and following discrimination training, did not change for the HAS and LAS animals. Dose-response functions showed differences between the HAS and LAS phenotypes after 40 training sessions but not after 50 sessions or after 60 sessions.

Ethanol Drug discrimination Selective breeding HAS LAS Alcohol Sleep-time Exteroceptive cue

GENERALLY it is accepted that a predisposition to develop alcoholism is under genetic influence in humans and therefore may be inherited (5). Rats can be selectively bred for preference or nonpreference for ethanol versus water. Thus, a preferring (P) phenotype is genetically predisposed to voluntarily consume sufficient quantities of ethanol to elevate blood alcohol concentration, whereas the nonpreferring (NP) phenotype prefers water to ethanol (10). The P rats will intragastrically self-administer as much as 9.4 g/kg ethanol per day, suggesting that they consume ethanol for its pharmacological properties, whereas the NP rats self-administered only 0.7 g/kg/day (20). Animals have also been selectively bred for differences in sensitivity to the sedative effect of ethanol (13). Sleep-time, measured by the interval from loss to recovery of the righting response (RR) following an hypnotic dose of ethanol is an accepted method for determining sensitivity to ethanol.

Drug discrimination is a procedure in which pharmacological effects of a drug serve as stimuli in an operant conditioning task. Animals are trained to make differential responses solely on the basis of perceived drug-induced interoceptive cues (2). Alcohol has frequently been used in this paradigm (4,14). The advantage when studying the pharmacological effects of ethanol is that drug discrimination does not presuppose either the reinforcing properties proposed for self-administration (SA) or the aversive properties suggested to function in conditioned taste aversion (CTA).

Ethanol drinking preference has also been used to selectively breed other lines of alcohol accepting (AA) and alcohol nonaccepting (ANA) rats (8). When ethanol (1.0 g/kg) was used for drug discrimination training with these animals, the ANA rats achieved the criterion level of performance sooner than the AA rats and maintained a superior level of performance throughout the experiment (23). These results suggest that animals with a low ethanol drinking preference (ANA) may have a greater sensitivity for perception of the ethanol cue. The length of time that AA rats stayed on the rotarod following saline was nearly twice that for the ANA rats, however, ethanol produced similar impairment in both groups. The author suggests that the cue saliency for ethanol could not be attributed to differences in alcohol-induced motor impairment between the two groups (23).

The present study used rats bred for differential sensitivity to an hypnotic dose of ethanol. The high alcohol sensitive (HAS) animals sleep longer than the low alcohol sensitive (LAS) animals (18). The animals were tested for sensitivity to an hypnotic dose of ethanol before and after discrimination training. The purpose was to compare the differential sleep-time sensitivity of these 2 lines with their sensitivity to recognize the ethanol discriminative cue. This article discusses the rate at which these animals learned the ethanol discrimination and describes differential levels of performance and activity at various stages of drug discrimination training.

METHOD

Animals

Twenty-four male rats were received from the Alcohol Re-

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search Center, University of Colorado Health Science Center. The rats were the result of selective breeding to develop separate phenotypes with high alcohol sensitivity (HAS) and low alcohol sensitivity (LAS). These rats were also the third through fifth littermates as ranked by an alcohol sleep-time screening test conducted by the supplier. The first and second littermates were retained by the supplier as the best phenotype representatives for breeding purposes. Sensitivity was determined by the duration of loss of righting reflex (LRR) following parenteral administration of alcohol (18). The original animals were the N/Nih heterogeneous strain (HS) that is presently maintained by the National Institutes of Health (NIH) Animal Resource Center (9). The animals (12 HAS and 12 LAS) used in this report represent the tenth generation of selective breeding. They were approximately 475 days old at the time of arrival and had a mean body weight of 341.4 g (range 291–423).

Upon receipt the animals were individually housed in suspended metal cages with wire floors and cage fronts and given free access to food (Purina Lab Chow) and water. Twenty-four-hour fluid intake from two graduated drinking cylinders was measured.

Vivarium facilities had an ambient temperature of 20–22°C and were maintained on a 12:12 light:dark cycle with lights on at 0600. The animals were weighed 6 times during a 3-week acclimation period that preceded the initial alcohol sleep-time test.

Ethanol Sleep-Time Tests

Ethanol (15% w/v solution in saline) was administered intraperitoneally in a dose of 3.0 g/kg of body weight. The time of LRR was taken as zero time and the time until the animal regained RR was recorded. The criterion for regaining the righting reflex was the ability of the animal to recover from lying on its back on a flat surface and place all four feet under it, three times in 60 sec. The sleep-time test was repeated one week later and the averages of the two scores were calculated and rank ordered for all animals. The 10 animals with the longest sleep-time averages were selected to represent the HAS subgroup, and the 10 animals with the shortest averages to represent the LAS subgroup. The remaining 4 animals underwent all conditions of the study but are not included in any further analysis.

A third sleep-time test was conducted 17 days later, 12 days after the animals had been placed on a food restricted diet. The purpose of the food restriction diet was to reduce their weight to 90–95% of their free-feeding weight as preparation for drug discrimination training. Daily food rations were given at approximately 1100 hr each day.

Following 14 days of the food restriction diet the tap water in one drinking cylinder for each animal was replaced with ethanol. Half of the animals (5 HAS, 5 LAS) received 3% (w/v) ethanol in tap water and the remaining animals received a 6% (w/v) ethanol solution. Ethanol drinking preference was measured during the next 38 days and this data will be reported in a forthcoming article.

A fourth sleep-time determination was conducted 7 days after the completion of 64 drug discrimination training sessions and 3 series of test sessions.

Drug Discrimination Training

Following the test for ethanol drinking preference the subjects were permitted 9 days to stabilize again to the tap-water and restricted food diet conditions. Fluid intake was not recorded during drug discrimination training. The experimental space consisted of standard rodent operant test cages and computer interface (Med Associates Inc., East Fairfield, VT). Each chamber was equipped with two operant levers and a food receptacle located equidistant between the two levers. The test environment was contained in a ventilated sound-attenuated cubicle equipped with a house light. All test parameters and data collection used a modified version of the software package described by Emmett-Oglesby *et al.* (7) and Spencer and Emmett-Oglesby (17).

Half of the animals (5 HAS, 5 LAS) received ethanol 0.6 g/kg (10% w/v in saline solution) and the other half received an equal volume of saline during the first training session. The drug condition was administered intraperitoneally (IP) and the animal was returned to its home cage. Following a 10-minute period to allow for maximal drug action the animal was placed into the test chamber and the house light turned on to signal the beginning of a 10-minute training session. Depending on whether the animal had received ethanol or saline, it obtained reinforcements by pressing either the designated ethanol lever or saline lever respectively. A food pellet (45 mg Noyes pellets) was delivered following each correct lever press (FR 1). Pellets were also delivered when necessary by the experimenter following the technique of successive approximation during hand shaping sessions. All animals were responding at the end of 6 sessions (3 drug, 3 saline). Responses on the incorrect lever were recorded, but produced no programmed consequence.

In subsequent training sessions the drug conditions randomly alternated between ethanol and saline with the restriction that the same drug condition not be administered on more than 2 consecutive training sessions. To control for possible position preference, lever assignments were ethanol left, saline right for half of the HAS and half of the LAS animals and ethanol right, saline left for the other half. These assignments remained constant throughout the experimentation.

A variable ratio schedule of 2 (VR 2) was introduced for sessions 7 and 8 and increased to VR 5 (SD = 1) for session 9 and thereafter. An extinction period of 15 seconds, at the beginning of the 10-minute training session, was also introduced on session 8. During an extinction period lever presses were recorded but no reinforcements were delivered. During training sessions 8–30, the extinction duration alternated randomly between a 15-second delay and a zero delay. The only restriction was that the two extinction durations (0 and 15 sec) occurred with equal frequency with each drug condition. A reinforcement was delivered on the first and each subsequent completions of the VR-5 schedule that occurred following any extinction period. The inclusion of 60-sec extinction periods on some training sessions began with session 31. The animals were trained between 800 and 1000 hr 5 days each week.

Following 40 training sessions (20 with each drug condition) tests with novel ethanol doses were alternated with maintenance training sessions. A test session began exactly as a training session with a 60-sec extinction period, however, the animal was removed immediately from the test chamber and returned to its home cage following the 60-sec extinction period and without receiving reinforcement. Tests with ethanol 0.15, 0.3, and 0.9 g/kg were conducted at this time (Series I). The same test doses were repeated following training session 50 (Series II) and again following session 60 (Series III).

Data Analyses

Drug lever choice was expressed as the percentage of total responses made on the ethanol designated lever during 60-sec extinction periods. Total responding (combined presses on either lever) was also assessed. Both percent drug choice and total responding were analyzed using repeated measures analysis of variance (ANOVA) across doses for each animal with phenotype as the independent grouping factor. In those cases when ethanol

TABLE 1

SLEEP-TIME AVERAGES (MIN) AND RANGES FOR HAS AND LAS ANIMALS ADMINISTERED ETHANOL (3.0 g/kg, IP)

	HAS		LAS	
Test No.	Mean	Range	Mean	Range
1 (*)	195.9	157–272	12.6	0–50
2 (*)	231.5	98–345	33.9	0–89
3 (*)	199.8	0–307	34.9	0–72
4 (*)	229.4	150–330	44.3	23–70

*$p<0.0001$ for phenotype differences.

completely suppressed responding, that animal contributed a score of zero to the response rate average. A percent drug choice score cannot be calculated in that instance and thus the animal does not contribute a score to the analysis with ANOVA. One-way analysis of variance was used to analyze dose effects for each phenotype separately followed, when appropriate, by post hoc Scheffe's tests for comparisons with the saline control results. A $p<0.05$ was taken to indicate a significant difference. A computer-generated formulation of Litchfield-Wilcoxon analysis (19) yielded ED_{50} values and confidence levels for ethanol dose response curves.

RESULTS

Ethanol Sleep-Time Test

The group averages for sleep-time tests are presented in Table 1. The overall averages for test 1 and 2 conducted during the free-feeding period were 213.7 min for the 10 HAS animals and 23.2 min for the 10 LAS animals, $t(18)=12.01$, $p<0.0001$. The sleep-time averages following 12 days of food restriction were 199.8 min for the HAS group and 34.9 min for the LAS group. The single HAS animal with a zero sleep-time (Table 1) was probably the result of a poorly placed injection, as the next lowest sleep-time for an animal in this group was 131 min. A fourth sleep-time test was performed 7 days after Series III drug discrimination tests while the animals were still in a food deprivation condition and indicated mean sleep-times of 229.4 and 44.3 min for the HAS and LAS lines respectively. The results overall are quite uniform for averages and ranges of both lines. HAS and LAS selected animals continued to be 2 very distinct groups of animals with no overlap of scores.

Ethanol Discrimination

Percent drug choices (left-hand side) and response rates are graphically portrayed in Fig. 1 for the 3 dose-response probes designated as Series I, II, and III. Both measures were analyzed for differences that were the result of phenotype differences or of the ethanol treatment during each of the 3 series.

Series I Analyses

The percentage of total responses made on the drug lever during Series I were 71.2% for 0.6 g/kg ethanol and 34.2% for saline by the HAS animals and 67.4% for ethanol and 30.5% for saline by the LAS animals. These baseline data were averages obtained from 2 training sessions (37 and 38) with 60-sec extinction periods immediately before and 2 sessions (43 and 44) immediately after the test series. The selection of the drug lever was dose related for larger and smaller doses (Fig. 1, left side). Thus, an ethanol dose of 0.9 g/kg evoked 87.8% and 80.1% drug lever choice respectively for the HAS and LAS animals. A significant effect of phenotype on the overall response to ethanol doses was found, $F(3,45)=23.08$, $p<0.0001$. No interaction between dose and phenotype was found, $F(3,45)=0.33$, $p=0.80$.

The ED_{50} values equal 0.181 g/kg with a 95% confidence interval of 0.081–0.403 for the HAS animals and 0.302 g/kg with 95% confidence interval of 0.166–0.552 for the LAS animals. These ED_{50} values reflect the overall phenotype difference found with ANOVA for the two groups, but the ED_{50} values do not differ.

The response rates (Fig. 1, right side) are total presses measured during the 60-sec extinction periods of the 4 baseline sessions and total presses obtained during the 60-sec tests with novel ethanol doses. Application of a repeated measures ANOVA showed no effect of phenotype on the response rates, $F(18)=3.58$, $p=0.075$, during dose function determination. There was an overall effect of ethanol dose, $F(3,54)=22.12$, $p<0.0001$. The highest dose of ethanol (0.9 g/kg) tested depressed response rates below the rates for the training dose (0.6 g/kg) in both HAS ($p<0.0001$) and LAS animals ($p<0.005$). A phenotype-dose interaction did not occur, $F(3,54)=1.31$, $p=0.282$.

Series II Analyses

Series II dose response determinations were made after 50 training sessions. Baseline training data are the averages for sessions 47, 48, 53, and 54. Percent drug responses were 80.5% for ethanol (0.6 g/kg) and 40.1% for saline by the HAS animals and 66.4% for ethanol and 36.4% for saline by the LAS animals (Fig. 1). A repeated measures ANOVA showed no effect of phenotype on the overall responses to ethanol doses, $F(1,17)=1.26$, $p=0.28$, but an overall effect of ethanol dose was significant, $F(3,51)=21.01$, $p<0.0001$. No interaction between dose and phenotype was found, $F(3,51)=0.99$, $p=0.4063$. The ED_{50} values equal 0.231 g/kg with 95% confidence interval of 0.121–0.442 for the HAS animals and 0.213 g/kg with 95% confidence interval of 0.082–0.555 for the LAS animals.

Application of ANOVA to Series II response rates (Fig. 1) indicated no phenotype effect, $F(1,18)=3.17$, $p=0.092$. There was, however, an overall effect of ethanol dose, $F(3,54)=4.93$, $p=0.004$. A dose-phenotype interaction was not found, $F(3,54)=1.25$, $p=0.300$.

Series III Analyses

The Series III dose response determinations followed a total of 60 training sessions. Baseline training data are averages from sessions 58, 59, 63, and 64. Percent drug choices were 78.3% following ethanol and 46.2% following saline by the HAS animals and 64.5% for ethanol and 27.5% for saline by the LAS animals (Fig. 1). A repeated measures ANOVA showed a significant effect of phenotype on the overall response to ethanol doses, $F(1,17)=5.64$, $p=0.030$, as well as an overall effect of ethanol dose, $F(3,51)=29.51$, $p<0.0001$. A dose-phenotype interaction was not indicated, $F(3,51)=0.09$, $p=0.963$. The ED_{50} values were 0.191 g/kg with 95% confidence interval of 0.095–0.382 for the HAS animals and 0.356 g/kg with 95% confidence interval of 0.181–0.703 for the LAS animals.

A tendency toward random responding, following saline (46.2% drug choice), by the HAS group (Fig. 1, Series III), raised an issue that a bias of unexplained nature was influencing the lever choice in favor of a drug lever choice. Thus, a repeated measures analysis of covariance was made with the saline scores as the covariate constant over the levels of dose. An effect of phenotype on percent

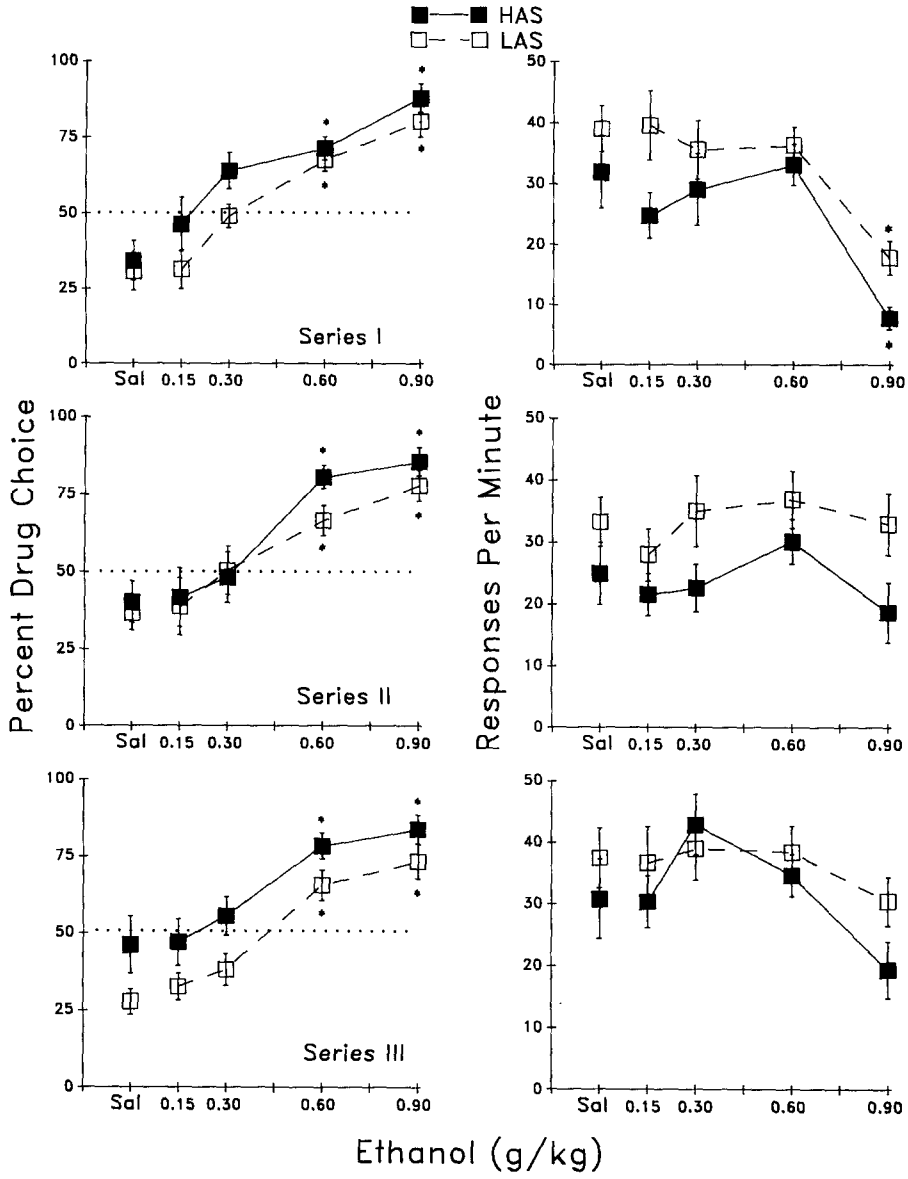

FIG. 1. Percent ethanol appropriate responding (left frames) and total responses per minute (right frames) during Series I, II and III. The Sal and 0.6 g/kg data points are baseline averages for training sessions. Points are means ± S.E.M. for HAS ■ and LAS □ lines. *Significant difference between ethanol result and saline baseline ($p<0.001$).

drug choice was not found with the analysis of covariance, $F(1,16)=2.58$, $p=0.128$. It was recalled that results with Series I had also shown a significant interaction of phenotype with percent drug choice. Although the saline results in Series I did not suggest a similar bias for drug choice, the data were analyzed again using an analysis of covariance. The results continued to suggest an effect of phenotype on percent scores, $F(1,14)=4.81$, $p=0.046$.

Application of a repeated measures ANOVA to Series III response rates showed no phenotype effect during the ethanol dose function test, $F(1,18)=0.61$, $p=0.446$. There was an overall effect of dose, $F(3,54)=10.29$, $p<0.0001$.

Generally the results of the 3 series of dose response determinations (Fig. 1) show that for both strains the percent drug choice for ethanol 0.6 and 0.9 g/kg by both phenotypes always differed from the same measurement following saline. The percent drug choice following 0.6 g/kg ethanol for both the HAS and LAS animals differed from chance responding (50%) during all 3 series. The HAS and LAS lines responded differentially to the discriminative effects of ethanol only during the Series I dose function. Ethanol 0.9 g/kg significantly depressed the response rates below the response rates for the ethanol training dose in HAS and LAS animals during Series I.

DISCUSSION

The individual averages for the first 2 sleep-time tests served as the basis for selection of animals to the HAS and LAS subgroups and no overlap of sleep-time ranges occurred between the selected subgroups. The decision to select subgroup animals on the basis of

2 sleep-time tests in this laboratory was because the animals had originally been rejected as breeders by the supplier as well as a desire to enhance the reliability of results for this study.

The 3.0 g/kg ethanol dose used during the selection process for generations 1–8 (18) was the same dose as chosen for sleep-time tests of this study. Differential ethanol doses (3.0 g/kg for HAS, 3.6 g/kg for LAS) were adopted by the supplier to select breeders for generations 9 and 10. This was done in order to adjust for the shifting sensitivity of the two phenotypes (Dr. Laura Draski, personal communication). The intent of the present study was to treat all animals in an identical manner when possible and to insure that all animals would still survive an ethanol dose that induced LRR in most animals. The results of the third sleep-time test, averages obtained during food deprivation, are quite similar to those obtained earlier during the free-feeding series. A fourth sleep-time test, following 60 drug discrimination training sessions, was remarkably similar to previous sleep-times.

The results of this study show that the original sensitivity to an hypnotic dose of ethanol apparently was not altered by any of 4 factors that accumulated during drug discrimination training: a) exposure to ethanol during volitional intake tests, b) exposure to repeated, although infrequent (5 times each 2 weeks), low doses of ethanol during discrimination training, c) 60 sessions of training specific to distinguish between 0.6 g/kg ethanol and the nondrug condition, and d) changes associated with aging. Regarding this last factor, old (18–20 month) rats sleep longer than younger (2–3 and 11–12 month) groups (1). Age-related differences are probably due to metabolic changes, CNS sensitivity shifts and changes of ethanol distribution in body fluid compartments.

The sleep-times for these tenth generation HAS/LAS rats show the continued segregation of the two lines that are descendants of the N/Nih strain. The HS parent strain was developed from 8 inbred lines that had an overall sleep-time range of 27–352 minutes (6) when tested with ethanol (3.5 g/kg). That range is comparable to the overall sleep-time range of 0–345 minutes reported here (Table 1, all tests for both lines) using the slightly lower dose of 3.0 g/kg. Sleep-time averages for the HS rats were 161 min for males and 149 min for females. The averages for combined sexes of generations 7 and 8 HAS and LAS rats were 117 and 34 minutes respectively (18), whereas the averages for the first 2 tests of these tenth generation males were 213 and 23 (Table 1) minutes respectively. This appears to be a greater jump toward line separation than might have been expected to occur in 2 generations. It should be noted, however, that the HAS and LAS subgroups in the present study were each intentionally selected as the best representatives of their respective phenotype group. This selection, which had the effect of removing marginal animals, eliminated overlapping sleep-times scores. The overall results generally agree with those of Spuhler *et al.* (18) and demonstrate that 10 generations of selective breeding have produced two phenotypes which have little overlapping of sleep-times.

Overton (12) suggested a direct relationship between increasing dosage and increasing stimulus strength of a drug. Barry and Krimmer (3) reviewed drug discrimination studies with ethanol and concluded that the average number of training sessions required to establish discriminative responding decreases with increasing training doses. Overton (11) showed that fewer than 5 sessions were required to the beginning of the criterion for learning (8 correct choices in 10 consecutive session) with doses of 2.0–3.0 g/kg. Barry and Krimmer (3), however, concluded that doses of 1.0–1.2 g/kg were close to the minimum at which discrimination can be learned fairly easily. Winter (21) trained rats to discriminate the low ethanol dose of 0.63 g/kg from saline, whereas Schechter (15) showed that a dose of 0.6 g/kg was capable of controlling discriminative responding in rats. The dose of 0.6 g/kg however required an average of 37 training sessions to an 8 correct choices in 10 consecutive sessions criterion. Additionally, these sessions were preceded by approximately 20 sessions to develop lever-pressing behavior and achieve an FR-10 schedule of reinforcement for the two drug conditions (16). York (22) trained separate groups of rats to discriminate ethanol 990, 660 or 333 mg/kg from saline. The 2 highest doses required 30–40 training sessions to learn the discrimination, however, the lowest dose required 80–100 training sessions.

The ethanol dose (0.6 g/kg) used in this study was specifically chosen so that learning might occur over a moderately extended training period (4). Learning progress was monitored with dose response determinations at 3 stages of training. It was also anticipated that the level of performance would neither quickly become asymptotic with this low training dose nor would animals achieve 100 percent drug lever selection following the ethanol training dose. The regimen used in this study thus would allow for performance to improve over a series of training sessions as well as provide latitude for responding differentially to interspersed lower and higher ethanol doses. An additional consideration for using the lower dose was to minimize the exposure to the animals to ethanol which might alter their response to ethanol over time.

Series I dose response results obtained following 40 training sessions indicate that discrimination learning occurred with both the HAS and LAS strains. The percentage drug responses (71.2% for HAS, 67.4% for LAS) during ethanol training sessions are somewhat below the frequently reported criterion of 80 percent correct responding. However, the percentages obtained with 0.9 g/kg (87.2% for HAS, 80.1% for LAS) do meet this criterion and established a significant dose response relationship for both HAS and LAS animals. The phenotype difference found during Series I tests indicates that the HAS animals tended toward greater sensitivity to the discriminative properties of ethanol as well as greater sensitivity to the hypnotic effect for which they were selectively bred. The differential did not exist during Series II and III. There is no explanation for the apparent loss of sensitivity but the intervening and repeated exposure to ethanol should be considered and it should be noted that the difference was marginal.

Analysis of the response rates clearly shows a depressant effect of ethanol 0.9 g/kg in both HAS and LAS rats, but an influence of phenotype was not found. An absence of a phenotype effect on response rates during Series I contrasts with the presence of a phenotype effect on sensitivity to the discriminative effects during the same series and suggests that drug discrimination was not based on the depressant effects of ethanol. The same conclusion was reached by York (23) for the AN and ANA rats. The results of this study do contrast those for the ANA animals which achieved the criterion level of performance sooner than the AA rats and maintained a superior level of performance (23). This would suggest that ethanol drinking preference is more closely related than sleep-time to the discriminative ethanol effect. The present results further suggest that mechanisms for depression of response rates with the relatively low ethanol dose (0.9 g/kg) differs qualitatively or neurophysiologically from the depression of a high dose (3.0 g/kg). That is, the animals were bred for high and low sensitivity to the hypnotic effect of ethanol but the phenotype separation was not apparent for response rate depression in the drug discrimination task.

Additional studies with the HAS/LAS lines will benefit from an increased availability of these animals. The use of younger animals will also permit the observation of changes during early development as well as to make it possible to test over a long period of time. The longer experimental life of younger animals will also allow extended drug-free periods after training in order to test for any return to original differential sensitivities. Additional studies will also benefit from the use of the CAS control animals for the HAS and LAS lines. The P and NP lines bred for volitional

ethanol intake (9) might provide even more relevant results toward understanding the relationships between alcohol consumption, genetics and the subjective effects of alcohol.

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