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# Differences in Response to the Aversive Properties of Ethanol in Rats Selectively Bred for Oral Ethanol Preference

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FROEHLICH, J. C., J. HARTS, L. LUMENG AND T.-K. LI. *Differences in response to the aversive properties of ethanol in rats selectively bred for oral ethanol preference.* PHARMACOL BIOCHEM BEHAV 31(1) 215–222, 1988.—A conditioned taste aversion (CTA) paradigm was used to determine whether aversion to the pharmacological effects of ethanol, apart from orosensory cues, can contribute to genetic differences in voluntary ethanol consumption. Four doses of ethanol, administered IP, were paired with the consumption of a 0.1% saccharin solution in rats from the alcohol-preferring (P) and alcohol-nonpreferring (NP) lines. Repeated pairings of saccharin and ethanol in a dose of 1.0 g/kg produced stronger and more prolonged aversion to saccharin in NP rats, compared with P rats, at comparable blood ethanol levels. A low dose of ethanol (0.25 g/kg) produced transient conditioned facilitation of saccharin consumption in P rats, but not in NP rats, at comparable blood ethanol levels. The results suggest that rats of the NP line find the postingestional effects of high-dose ethanol more aversive, and low-dose ethanol less reinforcing, than do rats of the P line. Genetic differences in voluntary ethanol consumption may be due, in part, to differences in aversion to the postingestional effects of ethanol.

Genetics Aversive/rewarding properties of ethanol Conditioned taste aversion

BOTH orosensory and postabsorptive factors have been postulated to contribute to the initiation and maintenance of high voluntary ethanol consumption which are characteristic of human alcoholism. An examination of the relative importance of these two factors in controlling ethanol drinking using laboratory animals has been limited by the lack of suitable animal models. Most animals either avoid unadulterated ethanol solutions or limit their ethanol consumption to amounts that produce very low blood ethanol levels. Therefore lower animal species, unlike humans, typically do not become voluntarily intoxicated or physically dependent on alcohol.

Selective breeding in our laboratory has resulted in the derivation of two rat lines which differ widely in voluntary ethanol consumption. Rats of the alcohol-preferring or P line consume alcohol in quantities sufficient to produce acute intoxication, tolerance and dependence (12, 27, 28). Rats from the P line will also work for the opportunity to consume ethanol (23). By contrast, rats of the alcohol-nonpreferring or NP line consume very little ethanol (19). This genetic difference in voluntary ethanol consumption could be due to differences in preference for, or aversion to, either the orosensory properties or the postabsorptive effects of ethanol. We have previously demonstrated that rats of the P line self-administer significant quantities of ethanol intragastrically (26). This indicates that the postabsorptive effects of ethanol, rather than its taste or smell, are reinforcing for rats of the P line. It remains to be determined whether ethanol consumption by rats of the NP line is limited by aversion to the orosensory or postabsorptive effects of ethanol.

Aversion to ethanol, administered IP, was examined in rats from the P and NP lines using a conditioned taste aversion (CTA) paradigm. Saccharin consumption was paired with four doses of ethanol in different groups of rats from the P and NP lines. Two procedures were used to increase the sensitivity for detecting ethanol aversion. First, repeated pairings of saccharin and ethanol, instead of single pairing, were used during conditioning to increase the strength of association between the flavor of saccharin and the

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postabsorptive effects of ethanol. Second, rats were presented with a free-choice between saccharin and water during postconditioning tests rather than forcing the consumption of saccharin by presenting saccharin alone. Following aversive conditioning and testing, blood ethanol concentrations and elimination rates were monitored in rats from the P and NP lines following IP administration of each of the four doses of ethanol used during conditioning in order to identify the blood ethanol level capable of producing conditioned suppression of saccharin consumption.

## METHOD

### *Subjects*

The P and NP rat lines were developed by selectively breeding rats which drink high or low amounts of a 10% (v/v) ethanol solution during four weeks of continuous free-choice between ethanol and water (19). Food was freely available during free-choice drinking. Fifty female rats from the P line and 46 females from the NP line were randomly chosen from the 25th selected generation prior to routine ethanol preference testing. Therefore, all rats were ethanol-naive at the beginning of aversive conditioning. Rats, weighing 200–300 grams, were housed individually in a temperature and humidity controlled room with a 12 hour light-dark cycle (lights on from 0700–1900 hours). Rats were weighed daily and food was available ad lib throughout all phases of the experiment.

### *Design and Procedure*

*Conditioned taste aversion.* During the first 4 days of preconditioning, ad lib water intake was monitored daily to establish baseline fluid consumption in all groups. During the last 8 days of preconditioning and during conditioning and postconditioning, fluid access was limited to 10 minutes per day. On each of the last 8 days of preconditioning, water alone was presented in two 100-ml Richter tubes for 10 minutes per day until water intake stabilized. On the last day of preconditioning, rats in each of the P and NP lines were divided into two groups, matched on the basis of average water consumption during the prior four days of preconditioning, and were assigned to either the ethanol or the saline treatment groups.

During conditioning, saccharin consumption was paired with one of four doses of ethanol (0.25, 0.50, 1.00 or 1.87 g/kg body weight, IP), or an equal volume of saline, in rats from the P and NP lines. Each conditioning trial consisted of 10-minute access to a normally preferred saccharin solution (0.1%) presented in one Richter tube, with the other tube empty, followed immediately by an IP injection of either ethanol (group 1) or saline (group 2). Each of the four doses of ethanol was administered to a separate group of rats in order to eliminate effects of prior ethanol exposure. The concentration of ethanol in saline, injected at each dose, did not exceed 14% (v/v), in order to minimize concentration-induced differences in ethanol absorption rates and tissue irritation at the site of injection (2,18). A total of 5 conditioning trials were given, one every other day. On intervening days, water alone was presented for 10 minutes in one of the two Richter tubes, with the other tube empty, in the absence of injections. The development of conditioned aversion to saccharin results in a progressive decrease in saccharin consumption over the course of conditioning. Access to water alone on intervening days prevents dehydration which can occur if conditioning trials are presented daily. The position of the tube containing saccharin was rotated on each conditioning trial and fluid consumption was recorded at the end of the 10-minute drinking period on conditioning (saccharin) and intervening (water) days.

During postconditioning, rats were presented with a free-choice between water in one tube and saccharin (0.1%) in the other tube for 10 minutes per day for 10 consecutive days in the absence of injections. The position of the tube containing saccharin was rotated daily. Animals were weighed and the amounts of water and saccharin solution consumed were recorded daily at the end of the 10-minute, free-choice period.

*Blood ethanol elimination.* Blood ethanol elimination rates were determined in 18 rats from the P line and 17 rats from the NP line. Immediately following completion of aversive conditioning and testing, rats were given ad lib access to food and water for 12 days, followed by 1 day of water deprivation (day 13). On day 14, rats were given access to water for 10 minutes and were then injected IP with the same dose of ethanol that they received during aversive conditioning (0.25, 0.5, 1.0, or 1.87 g/kg). Blood samples (0.1 ml) were collected from the retro-orbital sinus in heparinized capillary tubes at 15, 30, 60 and 180 minutes after ethanol administration. Blood was centrifuged and the plasma stored at −20°C until assayed for plasma ethanol concentration by direct injection of 1.0 μl of plasma into a Hewlett-Packard 5730A gas chromatograph equipped with a flame ionization detector and a 3380A integrator. The glass columns were packed with Poropak Q (80/100 mesh) and the oven temperature was 150°C. Isopropanol was used as the internal standard.

*Testing for oral ethanol preference.* Following completion of conditioned taste aversion testing and estimation of blood ethanol elimination rates, all rats were tested for oral ethanol preference using the procedures and criteria which are routinely used in the breeding and selection of the P and NP rat lines (19). Briefly, ethanol preference testing consisted of 4 days of access to a 10% (v/v) ethanol solution followed by four weeks of free-choice between the ethanol solution and water. Ethanol consumption was calculated for each rat during the 4-week free-choice period and was expressed as 1) grams of ethanol/kg b.wt./day, 2) ml of 10% ethanol/day and 3) ratio of ml 10% ethanol:ml water. The criteria for selection of alcohol-preferring (P) and -nonpreferring (NP) rats have previously been reported (19). To qualify as an alcohol-preferrer, a rat must consume in excess of 5 g ethanol/kg b.wt./day or more than 18 ml of 10% ethanol/day, and must demonstrate a 2:1 preference ratio of ethanol to water. To qualify as an alcohol-nonpreferrer, a rat must consume less than 1.5 g ethanol/kg b.wt/day or less than 2 ml of 10% ethanol/day, and must exhibit a preference ratio which does not exceed 0.2:1 of 10% ethanol to water. Ten of the 96 rats tested for ethanol preference failed to meet at least two of the three criteria used for designation as alcohol-preferring (P) or -nonpreferring (NP) and hence did not demonstrate a clear oral preference or nonpreference for ethanol. Only those rats which met the criteria for designation as alcohol-preferring or -nonpreferring were included in the data analysis.

### *Data Analysis*

Data from the preconditioning phase of the experiments, at each ethanol dose, were analyzed with a two-way analysis of variance using line and day as factors, with repeated measures on the day factor (29). Data from the conditioning

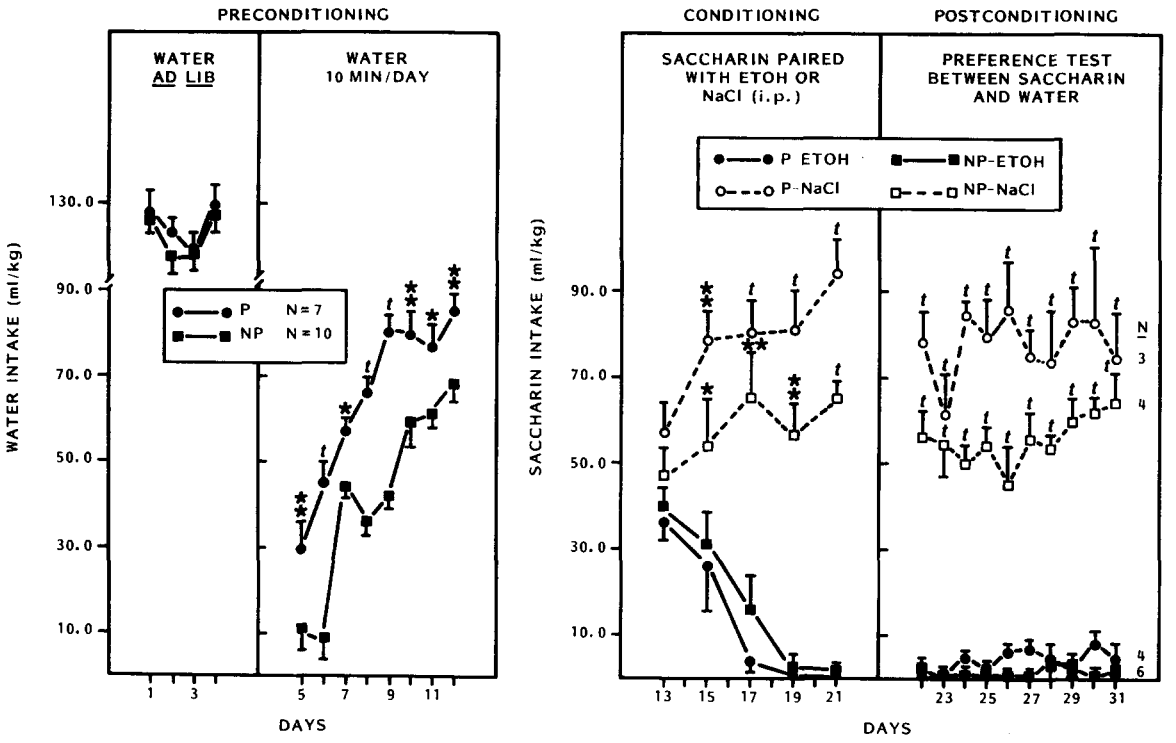


FIG. 1. Water intake during preconditioning (panels 1 and 2) and sacchrin intake during conditioning (panel 3) and postconditioning (panel 4) in rats of the P and NP lines receiving 1.87 g ethanol/kg (solid lines) or saline (broken lines) paired with saccharin during conditioning. Between-line comparisons of water intake during preconditioning and within-line comparisons of saccharin intake during conditioning and postconditioning: $*p<0.05$; $**p<0.01$, $^{\dagger}p<0.001$.

and postconditioning phases of the experiment, at each ethanol dose, were analyzed with a three-way analysis of variance using line, treatment and day as factors with repeated measures on the day factor (29). Post-hoc comparisons of differences between group means were made using *t*-tests for simple main effects.

During preconditioning, comparisons of water intake were made between rats of the P and NP lines. During conditioning and postconditioning, comparisons of saccharin intake were made between rats which received saccharin paired with ethanol, and those which received saccharin paired with saline, within each rat line.

## RESULTS

During the first four days of preconditioning, ad lib water intake (ml/kg b.wt.) was higher in rats from the NP than from the P line ($p<0.01$) on certain test days in 2 of the 4 groups (panel 1, Figs. 2 and 4). During the last 8 days of preconditioning, when water access was limited to 10 minutes per day, this pattern of water intake was reversed, with P rats consuming more water than NP rats on some of the test days (panel 2, Figs. 1–4). A sustained difference in water consumption between the lines during preconditioning was seen only in those rats receiving 1.87 g ethanol/kg (panel 2, Fig. 1). To control for differences in water consumption, rats assigned to the ethanol and saline groups within each line were matched on water consumption prior to conditioning. This procedure produced groups of rats within each line which did not differ in fluid consumption on day 1 of conditioning. The small differences in fluid consumption seen between and within the P and NP lines on day 1 of conditioning at the 1.87 g/kg dose (panel 3, Fig. 1) were not significant. These differences resulted from the post-hoc elimination of 3 rats from the NP line and 1 rat from the P line because they failed to exhibit a clear preference or nonpreference for oral ethanol during subsequent preference testing.

Administration of ethanol in a dose of 1.87 g/kg produced sedation and resulted in the development of strong conditioned aversion to saccharin in rats from both the P and NP lines (Fig. 1). It should be noted that ethanol-induced inactivity was not responsible for suppression of saccharin consumption during conditioning since access to saccharin preceded the administration of ethanol. The acquisition of aversion to saccharin was very rapid with significant suppression of saccharin consumption discernable in rats from both the P and NP lines after a single conditioning trial (P line, $p<0.01$; NP line, $p<0.05$). Four additional pairings of saccharin and ethanol during conditioning enhanced conditioned aversion to saccharin in rats from both lines. Saccharin consumption in both lines was completely suppressed following the fourth conditioning trial and remained suppressed during all 10 days of postconditioning. The absence of extinction of the conditioned response in both lines reflects the strength of aversion to the pharmacological effects of ethanol in a dose of 1.87 g/kg. Suppression of saccharin consumption was accompanied by a compensatory increase in water intake on the intervening days during conditioning and during postconditioning in rats from both the P and NP lines. Consequently, body weights within each line remained stable throughout conditioning and postconditioning.

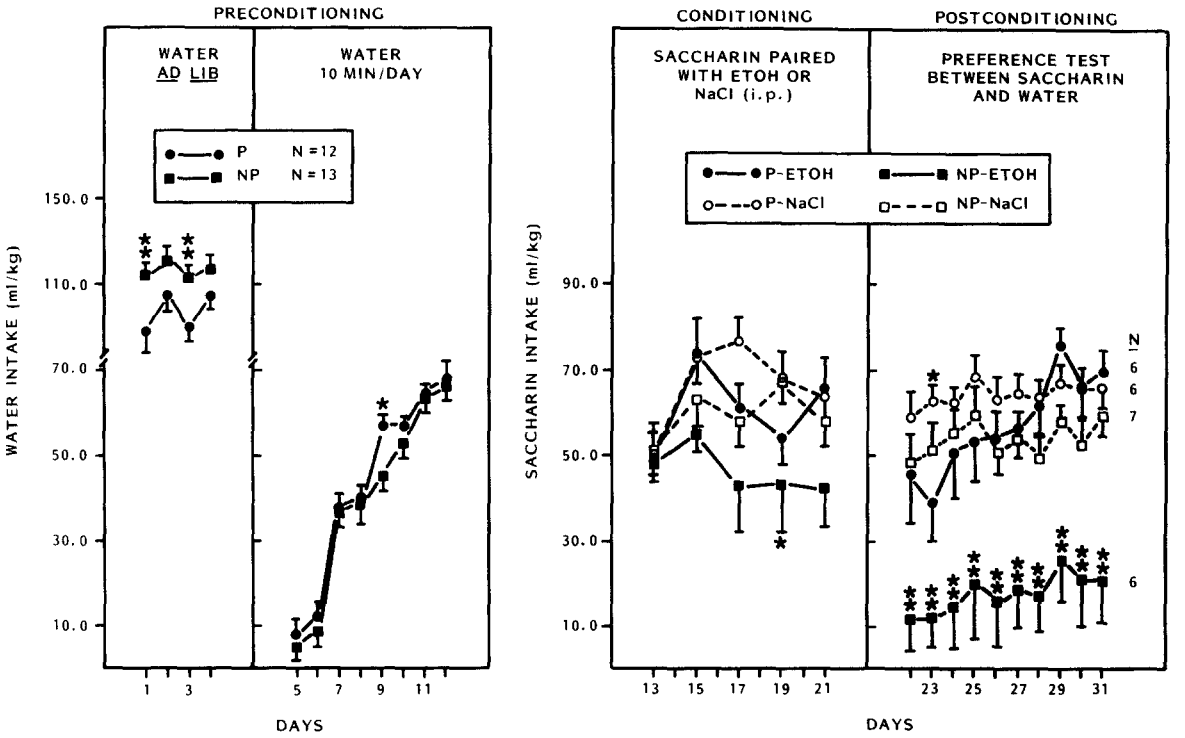


FIG. 2. Water intake during preconditioning (panels 1 and 2) and saccharin intake during conditioning (panel 3) and postconditioning (panel 4) in rats of the P and NP lines receiving 1.0 g ethanol/kg (solid lines) or saline (broken lines) paired with saccharin during conditioning. Between-line comparisons of water intake during preconditioning and within-line comparisons of saccharin intake during conditioning and postconditioning: $*p<0.05$, $**p<0.01$.

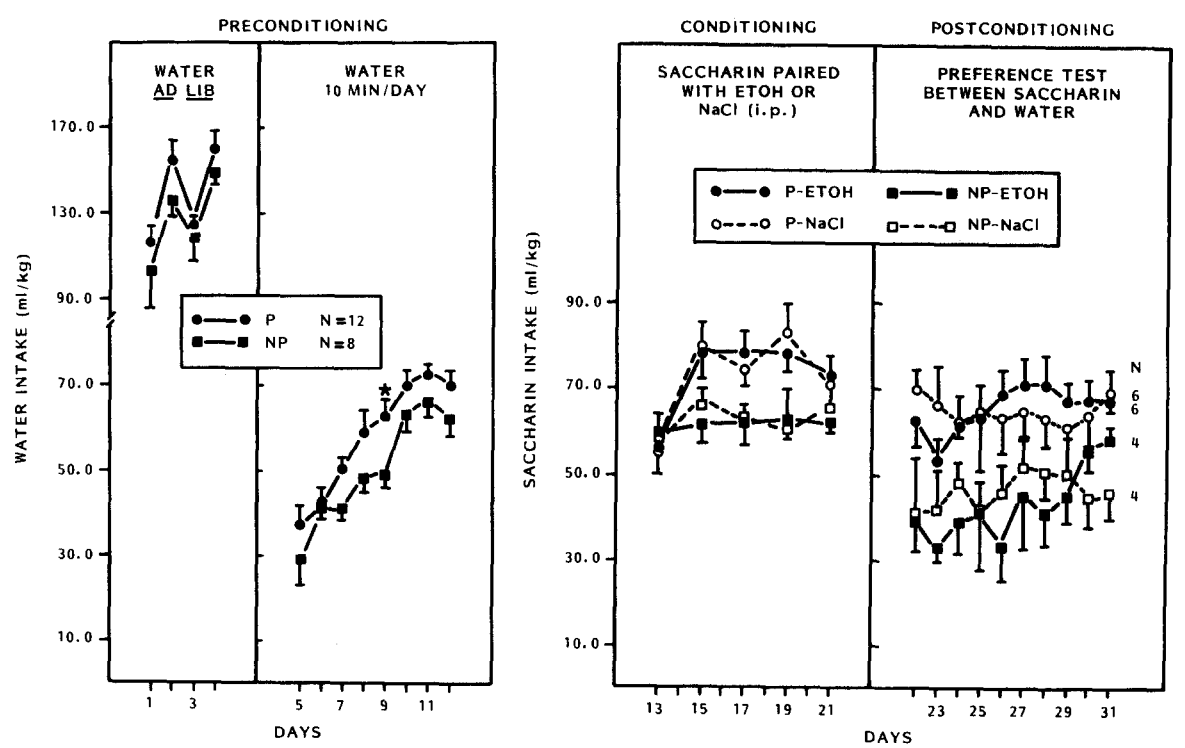


FIG. 3. Water intake during preconditioning (panels 1 and 2) and saccharin intake during conditioning (panel 3) and postconditioning (panel 4) in rats of the P and NP lines receiving 0.5 g ethanol/kg (solid lines) or saline (broken lines) paired with saccharin during conditioning. Between-line comparisons of water intake during preconditioning and within-line comparisons of saccharin intake during conditioning and postconditioning: $*p<0.05$.

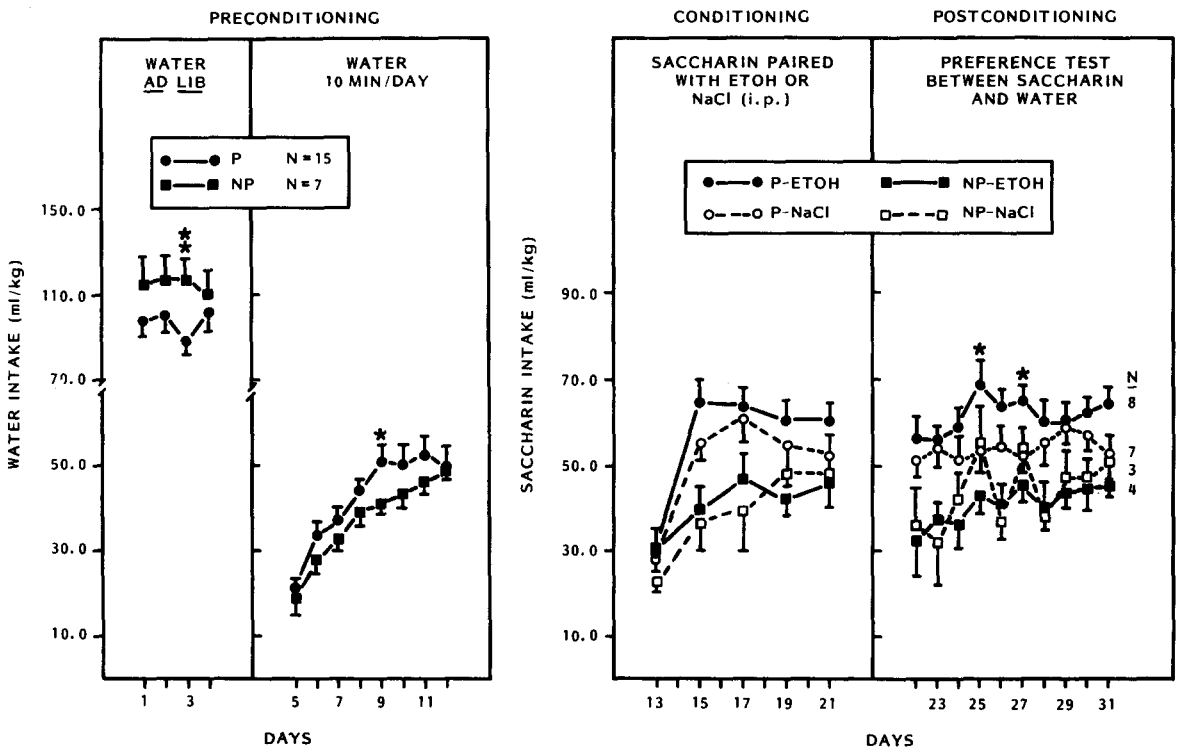


FIG. 4. Water intake during preconditioning (panels 1 and 2) and saccharin intake during conditioning (panel 3) and postconditioning (panel 4) in rats of the P and NP lines receiving 0.25 g ethanol/kg (solid lines) or saline (broken lines) paired with saccharin during conditioning. Between-line comparisons of water intake during preconditioning and within-line comparisons of saccharin intake during conditioning and postconditioning: $*p<0.05$, $**p<0.01$.

Ethanol in a dose of 1.0 g/kg produced visible signs of intoxication including lethargy and motor instability in rats from both the P and NP lines. As illustrated in Fig. 2, this dose of ethanol produced strong aversion to saccharin in rats of the NP line, as evidenced by a significant suppression of saccharin intake on the 4th day of conditioning ($p<0.05$) and on all 10 days of postconditioning ($p<0.01$). In contrast to this finding, no significant decrease in saccharin consumption was seen in rats of the P line during conditioning or during 9 out of the 10 days of postconditioning. Suppression of saccharin consumption in the NP line was accompanied by a compensatory increase in water consumption on the intervening days during conditioning and during postconditioning. Again, body weights did not change throughout conditioning or postconditioning in either line.

Ethanol in a dose of 0.5 g/kg produced no visible signs of intoxication and no conditioned aversion to saccharin in rats from either the P or the NP lines (Fig. 3). Instead, this moderate dose of ethanol produced a slight increase in saccharin consumption in rats of the P line on the 5th through the 9th day of postconditioning, although this increase was not significant.

Administration of ethanol in a dose of 0.25 g/kg produced no visible signs of intoxication in rats from the P or NP lines. This low dose of ethanol tended to elevate saccharin consumption in the P line during the 10 days of postconditioning with significant increases in consumption ($p<0.05$) becoming apparent on the 4th and 6th day of postconditioning (Fig. 4). By contrast, no significant ethanol-induced facilitation of saccharin consumption was seen in rats of the NP line during conditioning or postconditioning.

As illustrated in Fig. 5, rats from the P and NP lines did not differ in blood ethanol concentrations or ethanol elimination rates following the IP administration of ethanol in doses of 0.25, 0.5, 1.0 or 1.87 g/kg.

## DISCUSSION

Conditioned taste aversion paradigms are often used to determine whether the physiological effects of a drug are aversive. Conditioned taste aversion involves pairing the consumption of a distinctly flavored solution with the administration of a drug. Subsequent suppression of consumption of the flavored solution is used as an indicator of the extent of aversion to the drug. CTA paradigms have previously been effectively used to index aversion to ethanol (1, 6–8, 17, 25).

In the present study we have examined the acquisition and extinction of conditioned taste aversion to saccharin paired with various doses of ethanol in rats that differ in their genetic predisposition towards voluntary ethanol consumption. The results indicate that genetic differences in voluntary ethanol drinking may be determined, in part, by differences in preference for, and aversion to the postingestional effects of ethanol.

Ethanol in a dose of 1.87 g/kg, which resulted in 15-minute blood ethanol levels of approximately 250 mg%, produced equally strong conditioned aversion to saccharin in

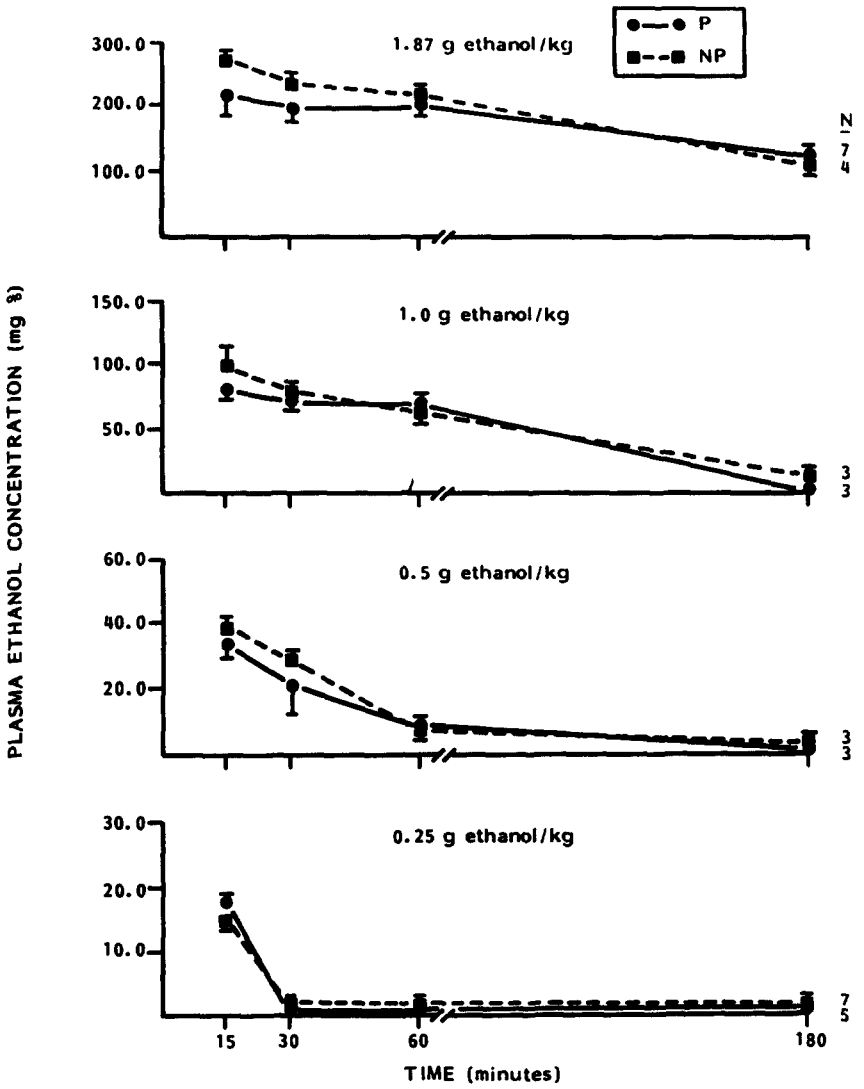


FIG. 5. Plasma ethanol concentration in rats of the P (solid lines) and NP (broken lines) lines following administration of ethanol in doses of 1.87 g/kg (top panel), 1.0 g/kg (second panel), 0.5 g/kg (third panel) or 0.25 g/kg (bottom panel).

rats from both the P and NP lines. It is unlikely that physiological stress, due to the IP injections per se, produced conditioned taste aversion to saccharin since no aversion was seen when saccharin consumption was paired with IP injections of saline. In addition, the observed decreases in saccharin consumption cannot be attributed to ethanol-induced sickness or anorexia for several reasons. First, a progressive decrease in saccharin consumption on alternate days during conditioning was accompanied by a compensatory increase in water intake on intervening days. Second, suppression of saccharin consumption during postconditioning was accompanied by increased daily water consumption. Consequently, total fluid intake and body weights remained stable within each group throughout conditoning and postconditioning.

A difference in the strength of aversion to ethanol between rats of the P and NP lines became apparent in groups receiving 1.0 g ethanol/kg b.wt. This moderate dose of ethanol produced significantly stronger and more prolonged suppression of saccharin consumption in the NP rats than in the P rats. This difference between the lines was not due to differences in the pharmacokinetics of ethanol. It has previously been demonstrated that the NP rats are more sensitive to ethanol and less able to develop acute tolerance to the sedative-hypnotic effects of ethanol than are the P rats (20,28). It is possible that increased sensitivity to the sedative-hypnotic effects of ethanol in NP rats contributes to the development of conditioned taste aversion.

Differences in the strength of aversion to ethanol appear to be associated with genetic differences in volutary ethanol consumption. The results suggest that strong aversion to the pharmacological effects of ethanol, apart from orosensory cues, may serve to limit voluntary ethanol drinking in rats of the NP line. It has previously been demonstrated that the P rats voluntarily consume ethanol in quantities sufficient to produce blood ethanol levels in excess of 100 mg% when

given unrestricted access to ethanol and water (22). In the present study, strong aversion to ethanol was seen in NP rats at blood ethanol levels of 100 mg%. It seems likely that ingestion of even moderate quantities of ethanol by NP rats would result in aversive postingestional effects which would lead to a reduction in subsequent ethanol intake. Whether aversion to the taste of ethanol also serves to limit voluntary ethanol drinking in rats of the NP line, as has recently been demonstrated in rats of the Wistar Kyoto strain (3), remains to be determined. The conditioned aversion to saccharin observed in the P and NP rats receiving moderate to high doses of ethanol is consistent with aversions produced by comparable doses of ethanol in unselected rat populations (4, 5, 9, 21).

Doses of ethanol below 1.0 g/kg, which resulted in no visible signs of intoxication, did not produce conditioned aversion to saccharin in rats from either the P or NP line. Instead, the lowest dose of ethanol (0.25 g/kg) produced transient conditioned facilitation of saccharin consumption in rats from the P but not the NP line. This demonstration of increased preference for saccharin paired with low dose ethanol in rats of the P line is surprising in view of the fact that many previous attempts to induce conditioned taste preferences with drugs have been unsuccessful (15). In the present paradigm, saccharin was presented daily for a limited interval which resulted in a very high rate of baseline saccharin drinking as was seen in the saline-injected control rats from both lines. This paradigm is optimal for demonstrating response suppression which results from the development of conditioned aversion to saccharin. However, this paradigm is less than optimal for demonstrating response facilitation which would be expected to result from the development of conditioned preference for saccharin. Given that the paradigm employed does not allow for a clear demonstration of response facilitation, it is not surprising that conditioned saccharin preference in the P line within this paradigm was not pronounced.

The presence of transient conditioned facilitation of saccharin consumption in P but not in NP rats suggests that the postabsorptive effects of low dose ethanol may be more reinforcing for rats of the P line than for those of the NP line. Preference for the postabsorptive effects produced by low doses of ethanol may be a factor which facilitates high voluntary ethanol consumption in rats of the P line. It is likely that ingestion of small amounts of ethanol by the P rats produces reinforcing pharmacological effects which increase the probability of subsequent drinking. Weaker aversion to the pharmacological effects of high doses of ethanol would also allow rats of the P line to drink more ethanol than those of the NP line before the postingestional effects become aversive. We have previously demonstrated that rats of the P line become tolerant to ethanol more quickly than those of the NP line (20,28). Rapid induction of tolerance to repeated bouts of voluntary ethanol drinking, as well as persistence of acute tolerance in the P rats (13), might then serve to maintain high ethanol consumption by these animals.

Many drugs that are known to act as positive reinforcers are also capable of producing conditioned taste aversions. For instance, rats will self-administer alcohol, morphine, amphetamines and barbiturates, all of which are capable of producing conditioned taste aversions (10). This apparent "paradox" in drug action has been reviewed by a number of investigators (10, 11, 14–16, 24). It has been suggested that a number of factors are capable of influencing the extent to which a drug is perceived as "rewarding" or "aversive." These factors include route of administration of the drug, the extent to which the subject is capable of predicting and/or controlling drug administration, the multiplicity of drug action, rate of onset and duration of drug action, and the subject's drug history. Our results suggest that genetic factors may also be important in determining whether a given dose of a drug, such as ethanol, will be perceived as "rewarding" or "aversive."

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