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Chronic Ethanol Consumption Produces Genotype-Dependent Tolerance to Ethanol in LS/Ibg and SS/Ibg Mice

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ERWIN, V. G., R. A. RADCLIFFE AND B. C. JONES. *Chronic ethanol consumption produces genotype-dependent tolerance to ethanol in LS/Ibg and SS/Ibg mice.* PHARMACOL BIOCHEM BEHAV 41(2) 275-281, 1992.—It is well known that chronic ethanol administration produces tolerance to the sedative-hypnotic and hypothermic effects as well as low-dose locomotor inhibitory effects of ethanol. We report herein characterization of a convenient method of producing genotype-dependent functional tolerance to ethanol-induced locomotor inhibition. Mice, LS/Ibg (LS) and SS/Ibg (SS), which differ markedly in acute effects of ethanol on locomotor activity, hypothermia, and hypnotic sensitivity, were required to consume solutions of ethanol in water as the sole source of liquid. Mice were provided lab chow ad lib. and the following regimen of ethanol in water, v/v: 10% for 4 days, 15% for 4 days, 20% for 7 days, followed by 15% for periods longer than 2 weeks. Control animals received water only or were pair-fed sucrose (isocaloric with ethanol) solutions plus lab chow; both control and ethanol-consuming (15 g ethanol/kg/24 h) mice maintained similar body weights for up to 4 weeks. Blood ethanol concentrations from 10-200 mg% were obtained during a 12 L:12 D cycle. At 6 h following withdrawal, LS and SS mice showed differential dose-dependent tolerance to locomotor inhibitory effects of ethanol. However, low-dose locomotor activation was unaltered in either line of mice, and results indicate that an apparent sensitization in SS mice is secondary to development of tolerance to locomotor inhibition. Maximum tolerance to locomotor inhibition was observed after 2 weeks of chronic ethanol consumption, with responses returning to control values within 1-2 weeks after withdrawal. Rates of acquisition of tolerance were similar in LS and SS mice. LS but not SS mice developed tolerance to ethanol-induced hypothermia, but neither line acquired tolerance to the hypnotic effects of ethanol. While LS mice acquired some metabolic tolerance, tolerance to locomotor inhibition or hypothermia was not mediated by alterations in ethanol elimination rates indicating marked neuroadaptation, that is, changes in CNS sensitivity. Only slight hypothermia and zero scores for handling-induced seizures were observed after withdrawal from 2-4 weeks of chronic ethanol intake. The results indicate that different genotype-dependent mechanisms may mediate or modulate hypnotic effects and activating or inhibitory effects of subhypnotic doses of ethanol and that these processes respond differentially to chronic ethanol intake. It is proposed that this ethanol intake model will be valuable in examining neurochemical processes hypothesized to mediate neuroadaptation to locomotor inhibitory effects of ethanol.

LS and SS mice Tolerance Sensitization Chronic ethanol

CHRONIC functional tolerance to ethanol has been the subject of intensive investigation [see (18,30)], and development of tolerance to the intoxicating effects of ethanol has been suggested to be an important feature of alcoholism (29). Many studies have demonstrated functional tolerance to ethanol-induced hypothermia and narcosis and to low-dose effects of ethanol. Chronic tolerance has been demonstrated following voluntary ethanol consumption in alcohol-preferring rats (10). Both genetic and environmental factors influence acquisition of chronic tolerance to high- and low-dose effects of ethanol (1,2,19,23,28). Many of these studies have reported contradictory results regarding acquisition of functional tolerance to ethanol and the relationships between initial sensitivity and acquisition of tolerance (2,15,20,28,31).

Subhypnotic, intoxicating doses of ethanol produce a well-known biphasic behavioral effect, characterized in many animal studies by locomotor activation, and depression, demonstrated by impaired performance such as locomotor inhibition (25). Marked genetic differences have been observed in the locomotor-activating actions of acute ethanol administration (3,5,7,9,26). In these studies, locomotor activity in C57BL mice is either unchanged or inhibited at doses producing activation in DBA mice. Similarly, LS/Ibg (LS) mice are depressed by doses of ethanol that cause stimulation of locomo-

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tor activity in SS/Ibg (SS) mice. It has been reported that chronic administration of subhypnotic doses of ethanol produces tolerance to inhibitory but not excitatory effects of ethanol in mice (3,22,31). Crabbe et al. (3) reported that chronic administration of low doses of ethanol produced an apparent sensitization of DBA but not C57BL mice to locomotor-activating effects of ethanol. In this study, C57BL mice acquired tolerance to ethanol-induced inhibition of activity. Since LS were similar to C57BL and SS were similar to DBA mice in initial sensitivity to locomotor effects of ethanol, it was of interest to determine whether the LS and SS mice, like C57BL and DBA mice, differed in acquisition of tolerance or sensitization to ethanol-induced locomotor activity following chronic ethanol administration. We report in the present study characterization of a method of chronically administering low doses of ethanol that produces tolerance to locomotor inhibition in both LS and SS mice without altering locomotor activation or hypnotic sensitivity.

METHOD

Animals

Male SS and LS mice were obtained from the Institute for Behavioral Genetics, University of Colorado (Boulder, CO). These lines of mice were selectively bred for differences in hypnotic sensitivity to ethanol and have been shown to differ markedly in sensitivity to effects of ethanol on thermoregulation and motor activity (5,6,9). All experiments were conducted with mice (60–80 days of age) that were maintained in a constant temperature (22°C), humidity (20%), and light (12 L:12 D) environment.

Locomotor Activity and Rectal Temperature

Spontaneous locomotor activity was measured by immediately placing animals, which had received injections of saline or doses of ethanol in saline (15% v/v), in an Omnitech Activity Monitor (Omnitech Electronics, Inc., Columbus, OH). The activity monitors were enclosed in ventilated, wooden containers, and activity data were collected under reduced lighting for 30 min by means of an IBM-PC. Rectal temperatures were measured with a telethermometer (Bailey Instruments, Saddle Brook, NJ) immediately prior to, and at 30 min after, injections of saline or ethanol solutions. The ambient temperature of testing was maintained at 22°C.

Chronic Ethanol Administration

Since we have previously shown that isolated housing alters CNS sensitivity of LS and SS mice to ethanol (17), animals received ethanol solutions in groups of five mice/cage. Mice were provided lab chow ad lib. and were required to drink ethanol solutions in water (% v/v) in the following regimen: 10% for 4 days; 15% for 4 days; 20% for 7 days; and 15% for exposure beyond 15 days. Animals used to determine blood ethanol concentrations (BEC) at various times during the 24-h light:dark cycle were not used in behavioral testing. Blood samples were collected in 25-μl microcapillary tubes from the retroorbital sinus, and ethanol concentrations in the blood were measured spectrophotometrically (21). Two sets of control animals were studied: group housed (five mice/cage) with access to water and lab chow ad lib and group housed with lab chow ad lib and receiving sucrose solutions (2–5% w/v) isocaloric and equivalent in volume to that consumed by ethanol-drinking animals. After the various times of chronic ethanol consumption, indicated in the table and figure legends, mice were withdrawn by replacing ethanol solutions with water. Animals withdrawn for indicated periods of time were tested for withdrawal symptoms, hypothermia (27), and handling-induced seizures (14); subsequently, they received a challenge dose of ethanol or saline and were placed in an activity monitor. All animals were kept in a separate colony room until 6 h prior to testing, when they were transported to the behavioral testing room. Animals were completely naive to the ethanol administration and behavioral test procedures.

Data Analysis

Data from each experiment were analyzed by appropriate analysis of variance (ANOVA) to assess effects of between-subjects variables (mouse line, ethanol dose, or treatment condition) and within-subjects variables (time) as needed. Where appropriate, posthoc tests are noted. As noted in figure legends, values represent means ± SEM and degrees of freedom represent number of cages or mice as indicated.

RESULTS

Figure 1a, b, and c shows volumes of ethanol solutions and water consumed (ml/g body weight/24 h), body weights (g), and quantities of ethanol consumed (g/kg body weight/24 h) by LS and SS mice. Over the first 4 days (10% ethanol) and in subsequent days (15 and 20% ethanol), the mean volume of fluid intake was approximately 0.12 ml/g/24 h in both LS and SS mice; mean volumes of water intake in control mice were higher (0.15–0.175 ml/g/24 h). Body weights of ethanol-consuming LS and SS mice remained constant relative to initial weights, whereas water-drinking LS or SS mice gained 10–15% in weight over a 2-week period. At 15 and 20% ethanol, both LS and SS mice consumed approximately 15 g ethanol/kg body weight. This level of ethanol consumption achieves significant BEC's as shown in Table 1. Both LS and SS mice achieve blood levels of 100–200 mg%, levels known to produce pharmacological effects (9) in these lines of mice. There was a circadian influence on BEC's with values being lower (10.8–30 mg%) during the light hours and higher during the dark (37.5–207.3 mg%). After 15, 21, and 28 days of chronic ethanol intake, mice were withdrawn by replacing ethanol solutions with water. At 2, 4, 6, and 8 h after withdrawal, mice were tested for withdrawal hypothermia or handling-induced seizures. It is of interest that neither LS nor SS mice displayed significant signs of withdrawal; seizure scores were zero and rectal temperatures following withdrawal were 37.1 ± 0.3, similar to control animals.

Results presented in Fig. 2 show the effects of chronic ethanol intake on locomotor activity following a challenge dose of ethanol (2.5 g/kg, IP) or saline. Water controls (0 time) and pair-fed, isocaloric sucrose controls (data not shown) were virtually identical in their locomotor response to saline or ethanol administration. In both sets of controls, SS mice are slightly activated, whereas LS mice are completely inactivated by this dose of ethanol. Chronic ethanol intake for 7, 15, 21, or 28 days did not significantly alter locomotor activity following saline administration in either SS or LS mice, indicating that the chronic ethanol intake procedure had little or no effect on excitability of these mice. However, chronic ethanol produced an apparent enhancement of locomotor-activating effects of ethanol in SS mice; ethanol-induced (2.5 g/kg) locomotor activation was increased significantly after 15, 21, or 28 days of chronic ethanol intake. The

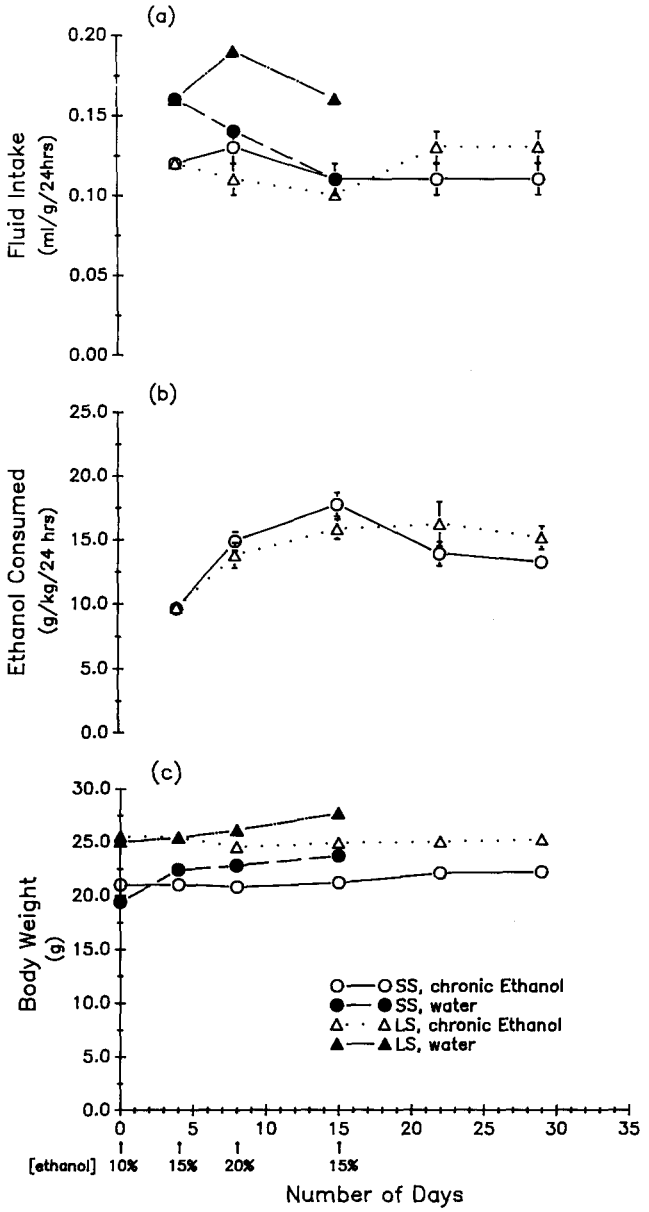

FIG. 1. (a) Water and (b) ethanol consumption and (c) body weights of LS and SS mice. Animals were required to drink ethanol solutions or water as described in the text and as shown in the figure. At the times indicated (mean ± SEM), ethanol and water consumption (ml/g/24h) and body weights were calculated using the following number of cages with five mice/cage: (n = 6 for water, n = 8 for 15 days ethanol, n = 5 for 21 days ethanol, n = 4 for 28 days ethanol). Water vs. ethanol intake (ml/g/24h) differed significantly in LS mice, $F(1,13) = 11.19, p < 0.01$.

inhibitory effects of ethanol on locomotor activity in LS mice was reversed by chronic ethanol intake (Fig. 2b), indicating essentially complete tolerance.

The data in Fig. 3 demonstrate differential dose-response relationships for the effects of ethanol on locomotor activity in control LS and SS mice. These data are similar to those previously reported (5,9) and show that LS and SS mice are similarly activated at doses of 1.0 and 1.5 g/kg; moreover,

TABLE 1

BLOOD ETHANOL CONCENTRATIONS DURING A 24-H LIGHT: DARK CYCLE IN MICE CHRONICALLY CONSUMING ETHANOL

Time of Day	n	LS (mg%)	SS (mg%)
0600	5	45.6 ± 24.4	44.4 ± 15.6
1200	5	10.8 ± 3.8	30.0 ± 9.7
1800	5	22.1 ± 14.2	17.8 ± 2.3
2100	5	101.4 ± 24.2	76.0 ± 14.3
2400	5	108.8 ± 33.3	37.5 ± 11.9
0300	5	103.0 ± 27.1	207.3 ± 33.9

LS and SS mice were required to consume ethanol solutions as described in the text and in Fig. 1. During the last day (day 7) of consumption of the 20% ethanol solution, blood samples were collected at the times indicated. Values represent (mean ± SEM) blood ethanol concentrations in mg/dl; n = 5 for each line at each time.

chronic ethanol treatment did not alter low-dose locomotor activation in either line. LS are markedly inhibited at doses above 2 g/kg; indeed, a dose of 2.8 g/kg produces loss of righting response in LS mice (8). Control SS mice are activated at doses up to 3.0 g/kg and inactivated at 4.0 g/kg (Fig. 3a). It is of interest that after 15 days of chronic ethanol intake LS mice were tolerant to locomotor-inhibitory effects of ethanol up to 3.0 g/kg (Fig. 3b). Activity in the chronic ethanol-treated LS mice receiving 3.0 g/kg was observed within the first few minutes of the test period, prior to loss of righting response. Chronically treated LS mice were significantly activated at 2.0 g/kg, indicating an unmasking of activation by acquisition of tolerance to inhibitory effects of ethanol. The results in Fig. 3a show that chronic ethanol induced an enhancement of locomotor activity in SS mice at intermediate challenge doses (2.0–3.0 g/kg) of ethanol and produced tolerance to an inhibitory dose of 4.0 g/kg.

Experiments were performed to determine whether the observed tolerance might be due to chronic ethanol-induced changes in ethanol elimination rates or alterations in blood/brain levels of ethanol following a challenge dose of ethanol (Fig. 4). The data clearly show that SS and LS control mice and those exposed to chronic ethanol intake for 2–4 weeks did not differ in BEC's 30 min after a 2.5-g/kg (IP) ethanol dose. Consistent with previous reports (6,11), BEC's tended to be higher in LS mice than SS mice when comparable doses are administered. The slight decrease in BEC's in LS mice withdrawn from chronic ethanol is not sufficient to account for the marked tolerance observed within 5–15 min after a challenge dose of ethanol. However, it is indicative of an increased elimination rate and consistent with the effects of chronic ethanol intake on sleep time as shown in Fig. 5a. Following administration of hypnotic doses of ethanol, a significant reduction in sleep time was observed in LS (4.0 g/kg) but not SS (6.0 g/kg) mice, indicative of some metabolic tolerance. The results in Fig. 5b show that LS and SS mice did not develop CNS tolerance to the hypnotic effects of ethanol because the BEC's at regaining righting response for chronic ethanol and control animals were virtually identical within lines.

The LS and SS mice have been shown to differ in sensitivity to ethanol-induced hypothermia (9). The data in Fig. 5c show that differential doses (SS, 6 g/kg; LS, 4 g/kg) of ethanol administered to control mice produced similar losses (ca. 5°C)

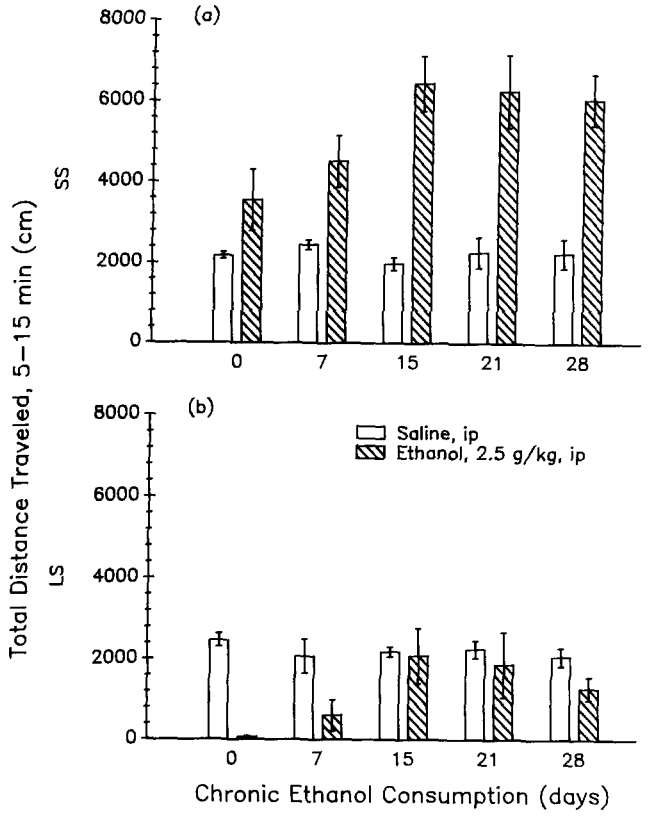

FIG. 2. Effects of chronic ethanol consumption on locomotor activity of LS and SS mice following a challenge dose of saline or ethanol. LS and SS mice were required to consume ethanol or water (0 time) as indicated in the figure and as described in the text and in Fig. 1. On the days indicated, animals were withdrawn at 0600 h and locomotor activity determined at 1200 h immediately following injections of 15% v/v ethanol (2.5 g/kg) or saline as described in the text. Values represent distance traveled (cm/10 min) from 5–15 min after injection. The 0- to 5-min activity was not used because the blood ethanol level is rapidly rising and peaking during this time period. Five to nine each of SS and LS mice were used in each treatment group. Mice in each treatment group represented a minimum of four different litters to avoid litter and cage (similar housing) effects. This precaution was taken in all subsequent experiments. ANOVA showed no significant overall line or treatment effect for saline-injected animals. Significant effects, $p < 0.01$, of chronic ethanol consumption, time of consumption and treatment by time interactions were obtained in both LS and SS mice; for example, SS mice, $F(1,74) = 79.54$, $F(4,74) = 3.32$, and $F(4,74) = 3.96$, respectively.

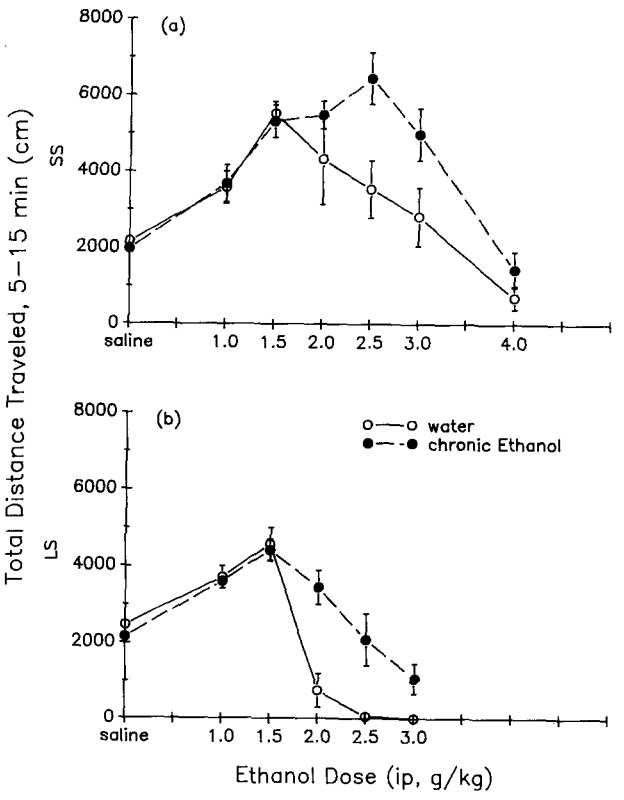

FIG. 3. Effects of chronic ethanol intake on locomotor activity in LS and SS mice as a function of ethanol challenge dose. These experiments were conducted with chronic ethanol and control mice as described in Fig. 2 and in the text. Mice received ethanol for 15 days prior to withdrawal. Six hours after withdrawal, mice received injections (IP) of challenge doses of ethanol as shown in the figure. Six to 10 mice were used for each line at each ethanol dose. ANOVA shows significant, $p < 0.001$, dose and treatment effects in both LS and SS lines: LS, $F(4,87) = 35.52$ and $F(1,87) = 20.45$; SS, $F(5,101) = 23.90$ and $F(1,101) = 12.39$.

in rectal temperature. Temperatures were taken at the times of regaining righting response, and both lines of mice developed significant chronic tolerance to hypothermia produced by the respective hypnotic doses of ethanol. Tolerance was greater in LS than in SS mice.

Results presented in Fig. 6 show the effects of chronic ethanol intake on hypothermia following low doses of ethanol. Rectal temperatures were taken immediately before and 30 min after challenge doses of 2.5 and 3.0 g/kg in control and chronic ethanol mice used to generate data in Fig. 3. These doses of ethanol produced significant losses in rectal temperatures of both SS and LS control mice. After chronic ethanol, neither line displayed significant hypothermia with 2.5 g/kg doses of ethanol, indicating development of toler-

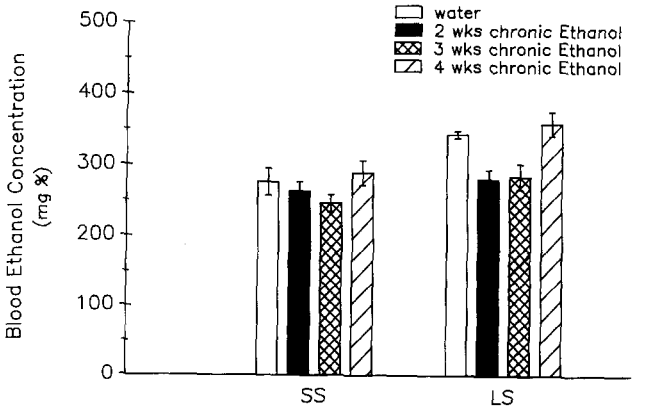

FIG. 4. Blood ethanol concentrations in LS and SS mice 30 min after a challenge dose of ethanol. Experiments were performed as described in Fig. 2 and in the text. Values represent (mean ± SEM with $n = 6$ for each group of LS and SS mice) blood ethanol concentrations in mg/dl 30 min after ethanol 2.5 g/kg IP. Water control groups were after 2 weeks.

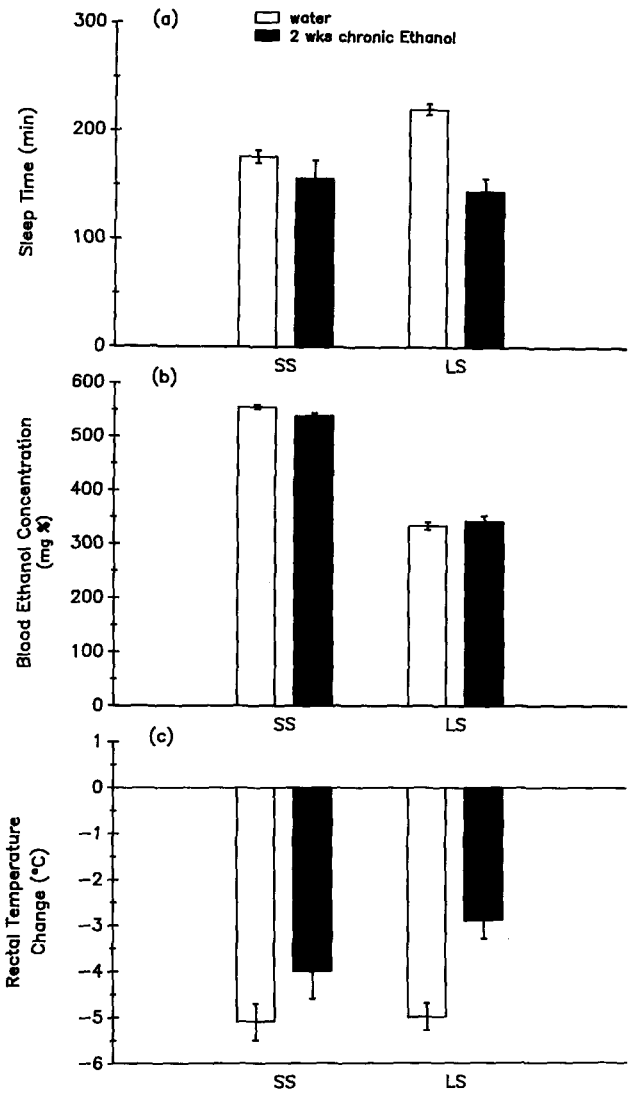

FIG. 5. Effects of chronic ethanol consumption on sleep time, blood ethanol concentrations, and hypothermia after a hypnotic dose of ethanol in LS and SS mice. Animals were chronically administered ethanol for 15 days as described in Fig. 2. Blood ethanol assays were performed as described in the text. After withdrawal, mice were injected with 4.0 g/kg (LS) and 6.0 g/kg (SS) ethanol. Values in the figure represent mean ± SEM for (a) sleep time (time of loss of righting response), (b) BEC at regaining righting response, and (c) hypothermia (rectal temperature loss from immediately prior to ethanol injection to regain of righting response); n = 5-7 animals per each group of LS and SS mice. Significant effects, $p < 0.001$, of chronic ethanol consumption on sleep time and on hypothermia were observed in LS mice, $F(1,14) = 18.4$ and $F(1,14) = 15.87$, respectively, but not in SS mice.

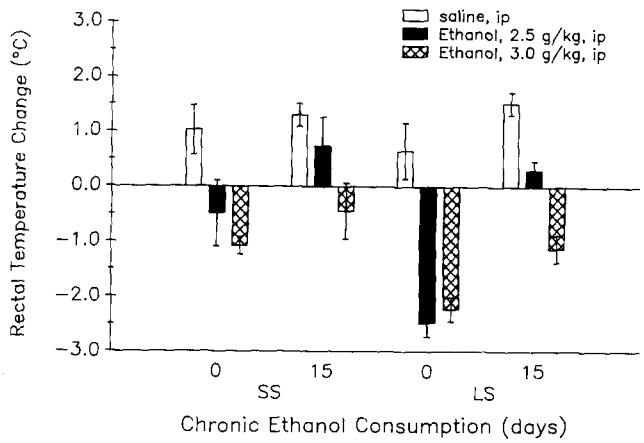

FIG. 6. Effects of chronic ethanol consumption on hypothermia after challenge doses of ethanol. Data were obtained from control and chronic ethanol-treated animals receiving challenge doses of 2.5 or 3.0 g/kg described in Fig. 3. Rectal temperatures were taken immediately before and at 30 min after IP injections of ethanol or saline. Values represent mean ± SEM; n = 6-10 animals per injection group per line. ANOVA shows significant effects, $p < 0.001$, of chronic ethanol consumption on ethanol-induced hypothermia in LS mice but not in SS mice: LS, $F(1,10) = 16.80$ and $F(1,14) = 10.93$ for 2.5 and 3 g/kg, respectively.

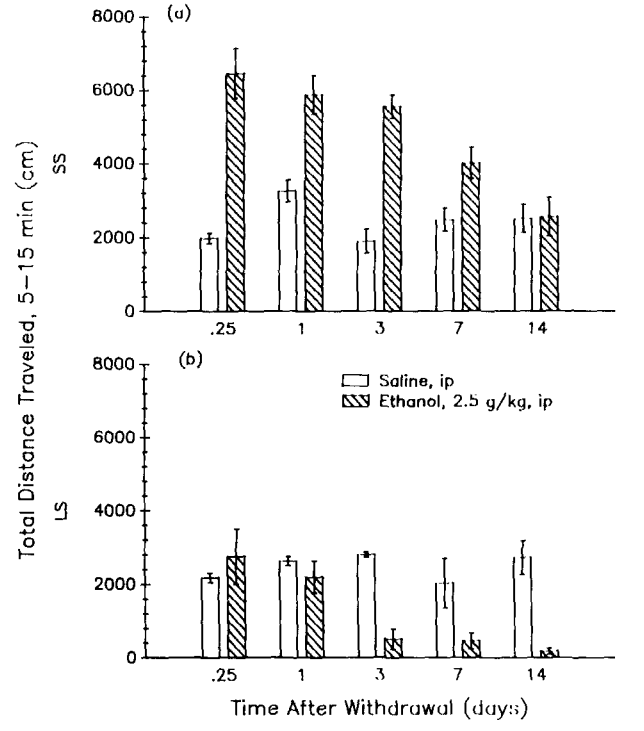

FIG. 7. Decay of chronic ethanol-induced changes in locomotor activity following withdrawal. Animals chronically treated with ethanol for 15 days were withdrawn for the times indicated in the figure. A challenge dose of ethanol (2.5 g/kg) was injected (IP) and locomotor activity was determined as described in the text and in Fig. 2. Values represent mean ± SEM; n = 6-10. ANOVA showed a significant effect, $p < 0.01$, of time after withdrawal in ethanol-induced locomotor activity in both LS and SS; $F(4,26) = 3.76$ and $F(4,29) = 9.32$, respectively.

ance. These results are in contrast to the results in Fig. 5 where LS but not SS showed tolerance to hypothermia at relatively high hypnotic doses.

Time courses for the disappearance of enhanced locomotor activation in SS (thought to be due to acquisition of tolerance to inhibitory effects of ethanol; see Fig. 3 and the Discussion section) and tolerance to locomotor inhibition in LS mice are shown in Fig. 7. Chronic ethanol-treated SS mice returned to

control locomotor sensitivity in 14 days, and LS mice fully recovered from tolerance to inhibitory effects of ethanol in 7–14 days. The data indicate similar rates of loss of tolerance in the LS and SS mice.

DISCUSSION

In reviewing the literature for procedures used in producing chronic tolerance to low-dose intoxicating effects of ethanol, it became clear that a method was needed that would minimize environmental cues (23) and stress associated with chronic ethanol administration. Indeed, contradictory reports in the literature regarding the relationships between initial sensitivity and acquisition of tolerance (2,15,20,28,31) are probably due in part to differences produced by chronic ethanol administration via injections, oral intubations, liquid diets, or vapor inhalation. The present study utilized an oral, self-administration (albeit intake was required) procedure for chronic ethanol exposure followed by single injections of challenge doses of ethanol to assess sensitivity to ethanol in a novel environment. These procedures minimize the potential effects of stress and environmental cues. It should be noted that this method of chronically administering ethanol achieved pharmacological blood levels of ethanol, and after 4 weeks of chronic ethanol intake animals were as healthy in appearance as control mice. Another positive feature of this method is that stress of isolated housing (17) is eliminated. Further, it is of interest that locomotor activities after saline administration (IP) were not significantly altered in chronic ethanol-treated compared with control mice. The method appears not to require pair-fed (sucrose solutions made isocaloric with ethanol and administered in equal volumes) control animals because such animals responded to saline and ethanol in a manner identical to water controls. Characterization of this method of chronic ethanol administration is of interest in that acquisition of tolerance to behavioral depressant effects of low intoxicating doses of ethanol may be relevant to human alcoholism (12).

A number of studies have shown dissociation of chronic functional tolerance from withdrawal symptoms (32), and the present study clearly demonstrates that chronic ethanol intake produces marked genotype-dependent changes in response to ethanol without overt withdrawal signs, for example, handling-induced seizures or hypothermia. These results support the hypothesis that tolerance and dependence are mediated in part by different mechanisms, albeit additional studies are needed to prove this conclusion. For example, this chronic ethanol treatment procedure may produce enhanced CNS excitability as measured by chemical or audiogenic seizure threshold.

In other studies, Tabakoff et al. (33) found that SS and LS mice rapidly develop tolerance to the hypnotic effects of ethanol following chronic hypnotic doses. However, LS and SS mice differed little in rates of acquisition of tolerance to hypnotic sensitivity to ethanol. In the present studies, LS mice acquired tolerance to low-dose effects of ethanol (locomotor inhibition and hypothermia; Figs. 3, 5, and 6) but not to hypnotic sensitivity to ethanol. These results suggest possible similarities in some mechanisms mediating neuroadaptation to locomotor inhibition and hypothermia but not to hypnotic effects of ethanol. It has been proposed that tolerance is mediated by decreased sensitivity of molecular mechanisms responsible for the acute effects of ethanol (13); thus, results of the present study suggest that different molecular processes mediate or modulate acute hypnotic, hypothermic, and locomotor effects of ethanol. This conclusion is supported by recent studies of DeFries et al. (4) and Erwin et al. (7) using LS × SS recombinant inbred (RI) strains of mice. These authors found low to nonsignificant genetic correlations between ethanol effects on locomotor activity, hypothermia, and hypnotic sensitivity. Results with the LS × SS RI strains showed mean values for ethanol-induced locomotor activation to differ by five-fold, and genetic analysis yielded four "effective" loci to account for differences in ethanol activation. The number of loci estimated to mediated differences in hypothermia and hypnotic sensitivity were four and seven, respectively. While these may not represent the exact number of genes, the results suggest that polygenic systems (multiple mechanisms) mediate excitatory or inhibitory effects of ethanol in LS and SS mice. Results of the present study are strikingly similar to observations of Crabbe et al. (3), who found that C57BL and DBA mice differ in acquisition of tolerance to ethanol-induced locomotor activation. C57BL mice developed tolerance to locomotor inhibition, whereas DBA mice displayed increased activation after a challenge dose of ethanol.

Middaugh et al. (24) suggested that development of chronic tolerance in C57BL mice is mediated by unmasking excitation via developing tolerance to depressant effects of ethanol. Likewise, results presented in Fig. 3 show that chronic ethanol intake in LS mice produced tolerance to the inhibitory effects of 2.5 and 3.0 g/kg ethanol but had no major effect on locomotor activation produced by doses less than 1.5 g/kg ethanol. If locomotor activation is caused by disinhibition, that is, inhibition of inhibitory processes, it is clear that tolerance does not develop to such inhibitory action but does develop to the locomotor-inhibitory effects of ethanol. An equally valid hypothesis is that locomotor activation is caused by ethanol enhancement of excitatory pathways, for example, mesocorticolimbic dopaminergic neurons as suggested by others (16). The results are consistent with two different mechanisms mediating the activating and inhibitory effects of subhypnotic doses of ethanol and indicate that the processes respond differentially to chronic ethanol intake.

Experiments were performed to determine whether SS and LS mice differed in the rates of acquisition and decay of tolerance. The results in Fig. 7 were obtained with 2.5 g/kg ethanol and indicate that chronic ethanol-induced activation (unmasked inhibition) in SS and tolerance in LS mice have similar rates of acquisition and decay. These results support the conclusion that the same mechanisms mediate tolerance to ethanol-induced locomotor inhibition in LS and SS mice, even though these lines differ markedly in initial sensitivity to this effect of ethanol.

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