

A Comparative Study on Alcohol-Preferring Rat Lines: Effects of Deprivation and Stress Phases on Voluntary Alcohol Intake

Valentina Vengeliene, Sören Siegmund, Manfred V. Singer, John David Sinclair, Ting-Kai Li, and Rainer Spanagel

Background: Voluntary alcohol intake in rats can be influenced by alcohol deprivation phases and stress. We investigated the magnitude of the effects of both deprivation and stress (forced swimming in cold water and foot-shock had been chosen as stressors distinct in their physical and psychological features) on alcohol intake and the influence of these experiences on the time course of alcohol drinking behavior. For the alcohol drinking procedure, a long-term model of alcohol self-administration originally developed for heterogeneous Wistar rats was used and was compared with different alcohol-preferring rat lines.

Methods: Adult male Alko alcohol (AA), alcohol-preferring (P), high-alcohol-drinking (HAD), and unselected Wistar rats were given ad libitum access to water, 5%, and 20% alcohol solutions for 6 months. A deprivation phase of 14 days was performed after 8 weeks of access to alcohol. After 16 weeks and 22 weeks of alcohol access, all animals were subjected to forced swimming and foot-shock, respectively, for 3 consecutive days, while alcohol intake was still being measured.

Results: Alcohol deprivation led to a significant increase in alcohol intake in Wistar rats and P rats. No alcohol deprivation effect was observed in HAD and AA rats; after deprivation, however, their preference for the 20% alcohol solution increased, immediately in the HAD rats and gradually over time in the AA rats. Repeated swim stress caused an increase in alcohol intake in Wistar rats but no changes in the alcohol-preferring rat lines. Foot-shock stress increased alcohol consumption in all lines of rats, but the most pronounced effects were observed in HAD and P rats.

Conclusions: Wistar, HAD, P, and AA rats differentially respond to alcohol deprivation and stress, showing that the genetic background of these different rat lines profoundly affects relapse-like drinking and stress-induced drinking.

Key Words: Long-Term Alcohol Self-Administration, Alcohol Deprivation Effect (ADE), Stress, Relapse, Alcohol-Preferring Rats.

VOLUNTARY ALCOHOL INTAKE and vulnerability to alcohol abuse depends on numerous genetic and environmental factors (Cloninger, 1987). One factor that can affect alcohol intake is alcohol deprivation. The renewed availability of alcohol solutions after a period of deprivation for several days leads to a pronounced but

temporary increase in voluntary alcohol intake and preference (Le Magnen, 1960; Sinclair and Senter, 1967). This robust phenomenon is called the alcohol deprivation effect (ADE) and is observed across several species including rats, mice, monkeys, and humans (Burish et al., 1981; Salimov and Salimova, 1993; Sinclair, 1971). Because the ADE mimics certain aspects of relapse-like drinking, it became a widely used model to examine the efficacy of pharmacological agents to prevent relapse drinking (Heyser et al., 1998; Rodd-Henricks et al., 2000a; Spanagel and Höltner, 2000; Spanagel and Zieglgänsberger, 1997).

Another factor that also can have a pronounced transient effect on voluntary alcohol intake is stress. Animal researchers have developed several protocols to study the effects of different physical and psychological stressors on voluntary alcohol intake in rats (e.g., Bowers et al., 1997; Lynch et al., 1999; van Erp and Miczek, 2001; Volpicelli et al., 1990; for review Pohorecky, 1990). However, the experimental findings have widely varying outcomes: alcohol intake can increase or decrease under stressful conditions or not be affected. It has been suggested that the interaction of alcohol and stress is stressor specific and, in addition,

From the Department of Psychopharmacology (VV, SS, RS), Central Institute of Mental Health, University of Heidelberg, Mannheim, Germany; Department of Medicine IV (SS, MVS), University Hospital of Heidelberg, Mannheim, Germany; Department of Biochemistry (T-KL), Indiana University School of Medicine, Indianapolis, Indiana; and the National Public Health Institute (JDS), Helsinki, Finland.

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Reprint requests: Valentina Vengeliene, Department of Psychopharmacology, Central Institute of Mental Health (CIMH), University of Heidelberg, J5, 68159 Mannheim, Germany; Fax: 49-621-1703-837; E-mail: vengeli@zi-mannheim.de.

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tion, depends on a number of variables that can significantly alter the influence of the stressor on subsequent alcohol intake (e.g., housing conditions, choice of alcohol solutions, duration and timing of stress) (Pohorecky, 1990).

Genetic factors affecting voluntary alcohol intake can be studied in alcohol-preferring rat lines. The introduction of genetic selection for voluntary alcohol intake in the rat yielded animals with a high preference for alcohol and high daily intake of alcohol. The most common used lines are the Finnish Alko alcohol (AA) (Eriksson, 1969), the Indiana University alcohol-preferring (P), the high-alcohol-drinking (HAD) (Li et al., 1993), and the Sardinian preferring (sP) lines (Colombo, 1997).

In the present study, the effects of alcohol deprivation and stress (physical and psychological stress) in three alcohol-preferring rat lines (AA, P, and HAD) were studied. Although alcohol-preferring rat lines are selected for the same phenotype (high alcohol intake and preference), they originate from different genetic backgrounds: The P line originates from an outbred colony of Wistar rats, the HAD line originates from N/Nih rats, which was developed by crossing eight inbred strains, and the AA line also originates from different rat strains (Li et al., 1993). These genetically different alcohol-preferring rat lines can be used to study gene-environment interactions. To this end we have studied the effects of alcohol deprivation and stress on the drinking behavior of alcohol-preferring animals and unselected Wistar rats over a time course of 6 months. For this purpose, we used a long-term model of alcohol self-administration that originally was described for Wistar rats (Spanagel and Höltner, 1999; Spanagel et al., 1996).

METHODS

Animals

Four groups of animals were studied: adult male P rats ($n = 15$; Indiana University, Indianapolis), weighing an average of 433 ± 22 g; male HAD rats ($n = 16$; Indiana University, Indianapolis), weighing an average of 312 ± 16 g; male AA rats ($n = 16$; National Public Health Institute, Helsinki, Finland), weighing an average of 354 ± 32 g at the start of the experiment; and Wistar rats ($n = 24$). The Wistar rats originated from an inbred colony at the Max Planck Institute of Biochemistry (Martinsried, Germany) and were in their 66th generation. These rats weighed an average of 316 ± 20 g at the start of the experiment. All animals were housed individually in standard rat cages under a 12 hr artificial light-dark cycle (lights on at 6:00 AM). Room temperature was kept constant (temperature, $22 \pm 1^\circ\text{C}$; humidity, $55 \pm 5\%$). Standard laboratory rat food and water were provided ad libitum throughout the experimental period. Body weights were measured weekly. The experiments were approved by the Committee on Animal Care and Use of the relevant local governmental body and carried out following the German Law on the Protection of Animals.

Alcohol Self-Administration Procedure

After 2 weeks of habituation to the animal room, rats were given ad libitum access to tap water and to 5% and 20% ethanol solutions (v/v). Alcohol drinking solutions were made up from 96% ethanol diluted with tap water to the different concentrations. Spillage and evaporation were minimized by the use of special bottle caps (TSE, Bad Homburg, Germa-

ny). With this procedure, the ethanol concentration in a given solution stayed constant for at least 1 week (Höltner et al., 1998). The positions of bottles were changed weekly to avoid location preferences. Intakes of 5% ethanol, 20% ethanol, and total ethanol (g/kg of body weight/day) and preference were calculated as the daily average across the 7 measuring days.

Alcohol Deprivation Procedure

All rats underwent a 2 week deprivation cycle after 8 weeks of continuous alcohol availability. After the deprivation period, rats were given access to alcohol again for the rest of the experiment. To measure the alcohol deprivation effect, alcohol consumption was measured daily until a stable baseline was established. After the deprivation phases, alcohol intake and preference were measured daily for 4 days.

Stress-Induced Alcohol Intake

A stable baseline consumption of alcohol was established before the stress procedures were applied. The stress procedures were performed on 3 consecutive days (for 10 min of total duration each day) at approximately 3:00 PM. Alcohol consumption was measured daily before each stress procedure and for 2 days after the stress procedure.

To perform the forced-swim test, rats were placed into a cylindrical plastic tank (55 cm high and 35 cm diameter) filled with tap water (19°C) up to a level of 40 cm. The animals were observed by a video camera, and the latency time until the animals started to float was measured afterward by an observer who was blind to the different rat lines. After the swim stress, animals were dried with a towel and returned to their home cages.

Foot-shock stress was performed in chambers with inside dimensions of $48.5 \times 30 \times 21.5$ cm. The floor was constructed of steel rods 6 mm in diameter and spaced 20 mm apart. Shocks of 0.8 mA intensity were delivered to the grid floor and the walls by a shock generator for a total shock duration of 5 min (in a 10 min session). Current pulses had a phase-duration of 200 msec. The duration of single shocks and intershock times ranged from 5 to 15 sec and was randomized by the software. Chambers, shock generator, and controlling software were obtained from TSE (Bad Homburg, Germany).

Statistics

The statistical package SPSS was used (SPSS, Chicago, IL). Data obtained from alcohol deprivation and stress experiments were analyzed by using two-way analysis of variance (ANOVA) with repeated measures. Whenever significant differences were found, post hoc Student-Newman-Keuls tests were performed. Comparison between groups in the latency to float on swim stress day 1 was done with a one-way ANOVA. The chosen level of significance was $p < 0.05$.

RESULTS

Alcohol Drinking Behavior Over the Whole Time Course of the Experiment

All four lines of rats showed an increase in total alcohol intake during the first 4 week acquisition period, with the increase coming mainly from drinking the 5% solution (Fig. 1). Thereafter, all three alcohol-preferring animal lines maintained a stable level of basal total alcohol intake and preference over the next 4 weeks before deprivation. After alcohol deprivation, all three alcohol-preferring animal lines slightly increased basal total alcohol intake, but total alcohol preference stayed stable over the whole time course of the experiment, whereas unselected Wistar rats reduced their total basal alcohol and preference (Table 1).

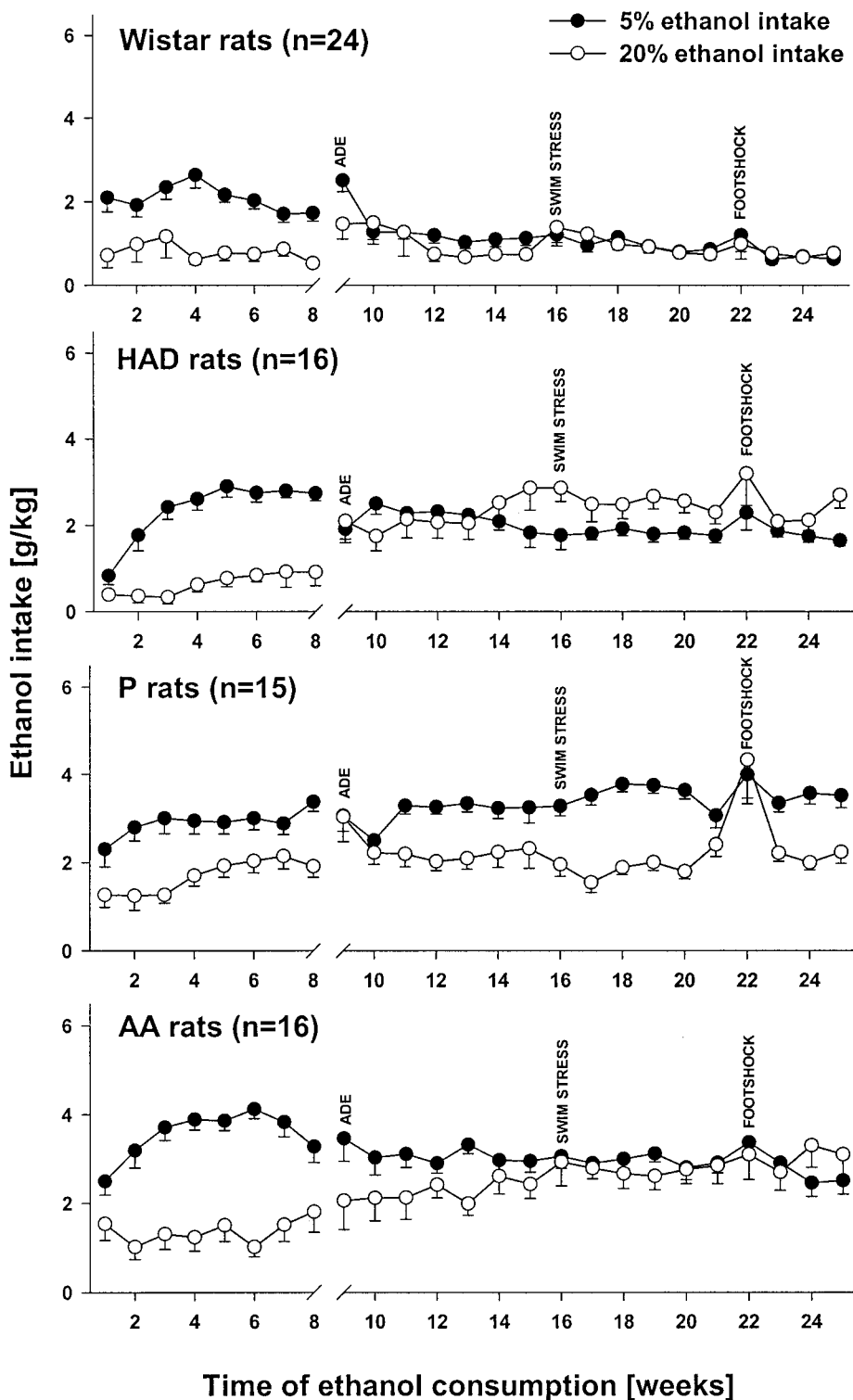


Fig. 1. Time course over 6 months of 5% and 20% ethanol intake (g/kg/day) by control Wistar ($n = 24$), HAD ($n = 16$), P ($n = 15$), and AA ($n = 16$) rats. Ethanol intake was calculated as the average of 7 days of measurements. Data are presented as mean \pm SEM.

In Wistar rats, a temporary increase for the duration of 3 weeks in 20% alcohol intake was observed after alcohol deprivation and swim stress (Fig. 1). In HAD rats, a permanent increase in 20% alcohol intake was observed after alcohol deprivation, persisting over the whole time course of the experiment (Fig. 1, Table 1). In P rats, a temporary 1 week increase in 20% alcohol intake was found after

deprivation, but no marked long-term changes were found (Fig. 1, Table 1). In AA rats, the mean intake of 20% alcohol after deprivation was consistently higher than before deprivation, but it cannot be determined whether this was caused by the deprivation or if it was only part of their general increasing trend throughout the entire experiment (Fig. 1, Table 1). Swim stress and foot-shock did not influ-

Table 1. 5%, 20%, and Total Basal Ethanol Intake (g/kg/day) and Preference Over the Time Course of Ethanol Consumption by Control Wistar ($n = 24$), HAD ($n = 16$), P ($n = 15$), and AA ($n = 16$) Rats

Group	Weeks	Ethanol intake (g/kg/day)			Ethanol preference (%)		
		5%	20%	Total	5%	20%	Total
Wistar rats	4–8	1.9 ± 0.2	0.7 ± 0.1	2.6 ± 0.2	56.2 ± 5.2	6.0 ± 1.2	62.2 ± 5.0
	10–15	1.2 ± 0.2	1.0 ± 0.3	2.1 ± 0.3	44.0 ± 6.6	8.6 ± 1.9	52.6 ± 6.4
	17–21	0.9 ± 0.2	0.9 ± 0.1	1.9 ± 0.2	39.8 ± 5.4	10.8 ± 1.5	50.6 ± 4.9
HAD rats	4–8	2.8 ± 0.2	0.9 ± 0.3	3.7 ± 0.3	89.5 ± 3.6	7.4 ± 3.0	96.9 ± 1.2
	10–15	2.2 ± 0.2	2.2 ± 0.4	4.4 ± 0.3	75.8 ± 4.3	22.3 ± 4.7	98.0 ± 0.5
	17–21	1.8 ± 0.2	2.5 ± 0.3	4.3 ± 0.2	71.3 ± 4.1	26.0 ± 3.6	97.3 ± 1.1
P rats	4–8	3.0 ± 0.2	2.0 ± 0.3	5.1 ± 0.2	79.5 ± 4.0	14.2 ± 2.2	93.7 ± 2.5
	10–15	3.2 ± 0.2	2.2 ± 0.3	5.3 ± 0.3	82.2 ± 2.7	14.1 ± 1.8	96.4 ± 1.3
	17–21	3.6 ± 0.2	2.0 ± 0.2	5.5 ± 0.3	83.5 ± 2.1	12.2 ± 1.6	95.7 ± 1.4
AA rats	4–8	3.8 ± 0.3	1.5 ± 0.4	5.2 ± 0.3	87.0 ± 3.1	10.0 ± 2.8	97.0 ± 1.1
	10–15	3.1 ± 0.3	2.3 ± 0.4	5.3 ± 0.3	78.3 ± 4.5	16.5 ± 3.3	94.8 ± 2.3
	17–21	2.9 ± 0.2	2.7 ± 0.3	5.7 ± 0.3	78.1 ± 3.2	19.4 ± 2.7	97.5 ± 1.0

Ethanol intake and preference were calculated as the average of 7 days of measurements. Excluded weeks: 0–4 (acquisition period), 9th, 16th, and 22nd (experimental weeks). Data are presented as mean ± SEM.

ence the total time course of alcohol intake in either the Wistar rats or in the alcohol-preferring rat lines (Fig. 1).

Alcohol Deprivation Effect

Alcohol deprivation led to a significant difference in alcohol intake and preference between rat groups after the representation of the ethanol solutions [factor group: $F(3,283) = 29.5$, $p < 0.0001$, and $F(3,283) = 14.6$, $p < 0.0001$ for intake and preference, respectively]. Post hoc comparisons revealed that alcohol consumption by Wistar rats differed from all other rat groups. The following analysis showed that alcohol deprivation led to a significant increase in alcohol intake and preference in unselected Wistar rats after deprivation on days 1 through 4 (Fig. 2). The total alcohol preference increased from $49 \pm 5\%$ before deprivation to $79 \pm 4\%$ on the first day after deprivation and was still significantly elevated on the fourth day ($64 \pm 4\%$) but not on the fifth day ($52 \pm 4\%$) or later. The preference values for the selected lines before deprivation were all close to 100%, thus precluding any increases being caused by deprivation. However, there was a significant decrease in total alcohol preference on day 1 after deprivation in HAD rats ($p < 0.003$; Fig. 2) because they switched from drinking mainly 5% solution to consuming similar amounts of 5% and 20% solution (Fig. 1). This change in total alcohol preference did not affect alcohol intake by HAD rats ($p = 0.176$). P rats showed a significant increase in alcohol intake after deprivation ($p < 0.002$; Fig. 2). There were no significant changes in alcohol intake ($p = 0.683$) in AA rats after alcohol deprivation (Fig. 2).

Stress-Induced Alcohol Intake

Changes in alcohol intake caused by forced swim stress for 10 min on 3 consecutive days were significantly different between the four rat groups [factor group: $F(3,283) = 3.6$, $p < 0.014$], but no differences were found in alcohol preference ($p = 0.983$). The preference values for the selected lines before deprivation were all close to 100%, thus pre-

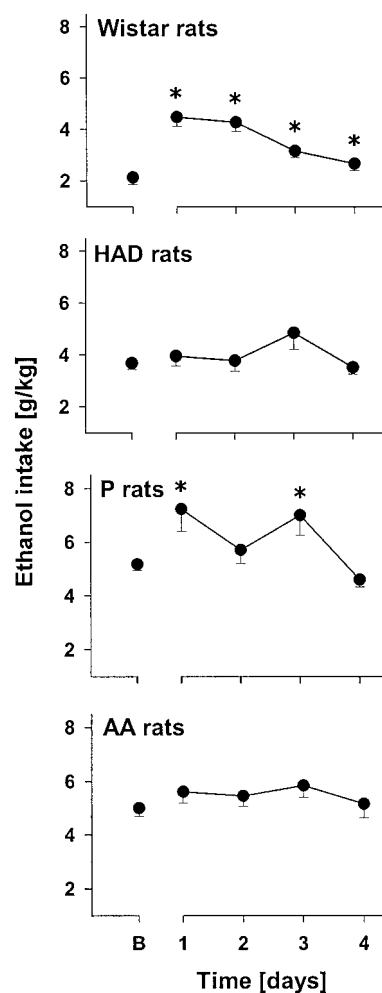


Fig. 2. Total ethanol intake (g/kg/day) by control Wistar ($n = 24$), HAD ($n = 16$), P ($n = 15$), and AA ($n = 16$) rats before and after an alcohol deprivation period of 2 weeks. The average of 4 days of measurements as a baseline drinking is shown. Data are presented as mean ± SEM. *Significant differences to baseline drinking ($p < 0.05$).

cluding any increases being caused by stress. Post hoc comparisons revealed a significant increase in alcohol consumption by unselected Wistar rats after swim stress ($p <$

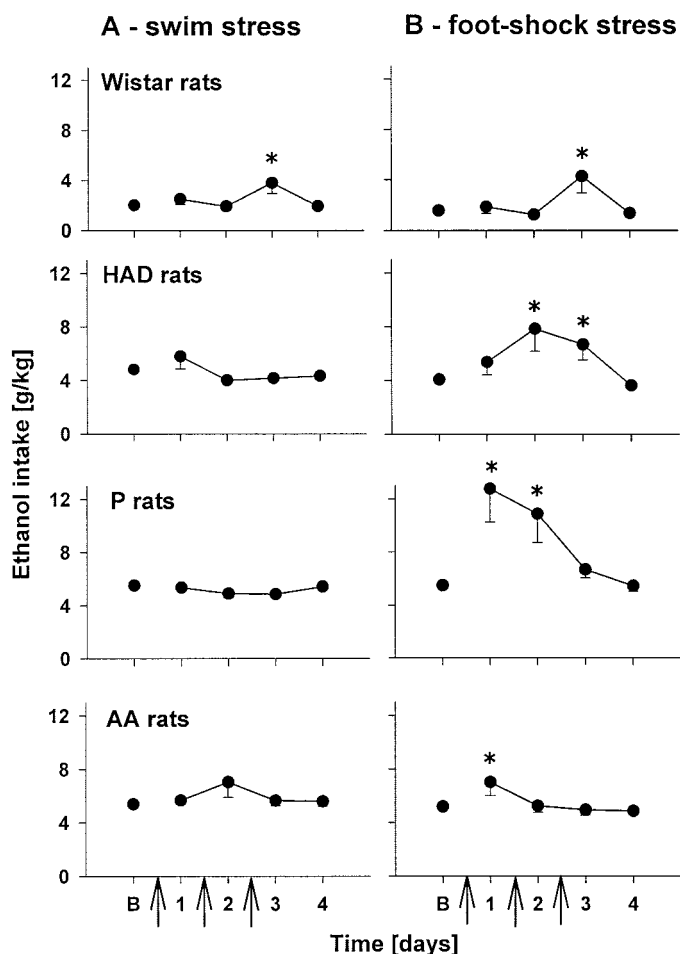


Fig. 3. Total ethanol intake (g/kg/day) by control Wistar ($n = 24$), HAD ($n = 16$), P ($n = 15$), and AA ($n = 16$) rats in response to 3 consecutive days of forced swim stress (A) and 3 consecutive days of foot-shock stress (B). Arrows indicate days of stress. The average of 4 days of measurements as a baseline drinking is shown. Note that the increase in total ethanol intake was produced mainly by the increase of 20% ethanol consumption in all rat groups, and that animals that drank a high amount of alcohol on day 1 were different from those on day 2. Data are presented as mean \pm SEM. *Significant differences to baseline drinking ($p < 0.05$).

0.02) but no significant changes in alcohol intake in HAD, P, and AA rats (Fig. 3A). Latency to float was significantly lower in AA rats compared with other rat lines (AA, 86 ± 6 sec; Wistar, 206 ± 27 sec; HAD, 176 ± 24 sec; P, 156 ± 31 sec; $p < 0.01$).

Foot-shock stress for 10 min on 3 consecutive days led to a significant increase in alcohol consumption in unselected Wistar rats and all alcohol-preferring lines (Fig. 3B). F and p values for the factor day on alcohol intake were as follows: Wistar, $F(4,119) = 3.6$, $p < 0.008$; HAD, $F(4,79) = 3.6$, $p < 0.01$; P, $F(4,74) = 5.6$, $p < 0.001$; and AA, $F(4,79) = 2.7$, $p < 0.035$. In particular, intake from the 20% alcohol solution was increased after foot-shock stress (Fig. 1). Therefore, there were no significant changes in total alcohol preference in any of the four rat groups. Overall, there were significant differences in alcohol intake between groups after foot-shock stress [group \times day interaction

effect on alcohol intake ($F(9,283) = 2.9$, $p < 0.003$], with most pronounced effects observed in HAD and P rats.

DISCUSSION

In the present study, long-term alcohol drinking behavior (up to 6 months) was comparatively studied in unselected Wistar rats and alcohol-preferring rat lines (HAD, P, AA). Furthermore, the effects of alcohol deprivation and stress were examined in all animals. After an alcohol deprivation phase of 2 weeks, a significant transient increase in voluntary alcohol intake and preference (ADE) ensued in the Wistar rats. An ADE also was observed in P rats. In contrast, HAD and AA rats did not exhibit any changes in alcohol intake when alcohol was presented again after deprivation, but both showed increases specifically in the intake of the 20% alcohol solution. The intake of 20% solution after deprivation was similar in HAD and AA rats, with both showing a tendency to increase progressively. Such long-term effects on alcohol drinking behavior were not observed in Wistar and P rats. Repeated swim stress caused a slight increase in alcohol intake in Wistar rats but no changes in the alcohol-preferring rat strains. Foot-shock stress increased alcohol consumption in all lines of rats; however, the most pronounced effects were observed in HAD and P rats.

After alcohol deprivation, unselected Wistar rats showed a typical ADE. Thus, alcohol consumption and preference were significantly enhanced for 4 days after re-presentation of the alcohol solutions. Animals increased their alcohol intake and preference approximately 2-fold on the first day of the ADE. This increased alcohol intake declined to baseline drinking levels by the 5th reexposure day. In agreement with previous findings, a detailed analysis of intake for 5% and 20% alcohol solutions showed a preference shift toward the highly concentrated 20% alcohol solution during the ADE (Hölter et al., 1998; Spanagel et al., 1996). Although P rats also exhibited an ADE, this effect was not as pronounced as in unselected Wistar rats. On the first day after re-presentation of the alcohol solutions, P rats exhibited an approximately 40% increase from baseline alcohol drinking levels, with alcohol intake returning to baseline drinking levels by the 4th reexposure day, which is in agreement with previous data presented by McKinzie et al. (1998). In contrast, HAD and AA rats did not show an ADE, which is in accordance with previous reports (Rodd-Henricks et al., 2000b; Sinclair and Tiihonen, 1988). However, previous studies have found that AA rats do increase alcohol consumption after short (<24 hr) deprivation phases but only for the first hour of renewed access to alcohol (Sinclair and Li, 1989). The failure to observe an enhancement in alcohol intake after deprivation in AA rats had been suggested to be the result of a ceiling effect, and thus these rats do not show further increases with longer periods of deprivation (Sinclair and Tiihonen, 1988). The HAD rats were not limited by a ceiling effect because they

show a very pronounced ADE after repeated deprivation phases (Rodd-Henricks et al., 2000b). Interestingly, rather than the temporary increase after deprivation usually seen with the ADE, alcohol deprivation in HAD rats caused a persisting increase in 20% alcohol intake and a decrease in 5% alcohol drinking. This preference shift toward the 20% alcohol solution persisted throughout the whole time course of the experiment, showing that a single deprivation phase in HAD rats had long-lasting consequences for their drinking behavior. This might be true for the AA rats as well, but the possibility cannot be excluded that the increase in 20% solution intake that they showed after deprivation was only a continuation of the increasing trend starting before deprivation.

Besides alcohol deprivation, stressful life events and maladaptive responses to stress influence alcohol drinking and relapse behavior. Although the relationship between stress and alcohol drinking in humans (Pohorecky, 1991) and laboratory animals (Pohorecky, 1990) is complex, it might be that in some individuals alcohol drinking is an attempt to cope with stress. In the present study, the effect of stress on alcohol drinking was examined in unselected Wistar rats and in different alcohol-preferring lines because it is known that stress-induced alcohol drinking has a significant genetic component (Sillaber et al., 2002; Vogel et al., 1990). Wistar rats after being exposed to swim stress for 3 consecutive days temporarily increased their alcohol intake after the last stress day, whereas alcohol-preferring rats did not alter their ingestion of alcohol either during or after this stress period. Interestingly, AA rats showed lower latency to float on the first swim stress day compared with other rat lines, which points to a possible "behavioral despair" of these animals. In agreement, previous studies suggest the presence of a depressed-like state in AA rats (Kiianmaa et al., 1991). This could be a reason for their "poor" response to swim stress with respect to alcohol ingestion.

Foot-shock stress resulted in a marked increase of 20% alcohol intake in HAD and P rats; however, only a small but significant effect was observed in Wistar and AA rats. These findings show that exposure to stress can influence the ingestion of alcohol, but this effect is stressor specific and has a large interindividual variability. Individual data analysis (note: individual data are not shown in the results) for basal alcohol intake and stress-induced alcohol intake did not reveal any correlation, suggesting that prior basal alcohol intake does not predict the size of stress-induced alcohol drinking. It is known that swim stress and foot-shock stress give rise to different physiologic and hormonal response patterns with more pronounced corticosterone release after foot-shock stress (Abel, 1994; Ermisch et al., 1986; Volpicelli et al., 1990; Wotjak et al., 1998). Thus, if both stressors produce different physiologic and hormonal consequences for a stressed subject, it is not surprising that the effect of stress on ingestion of alcohol is stressor specific.

It should be pointed out that the sequence of alcohol deprivation, swim stress, and foot-shock stress was always the same. Although our pilot studies had shown that prior alcohol deprivation has no influence on the following stress effects, the influence of swim stress on the second foot-shock stress was not tested. Nevertheless, the long time between the two stressors (6 weeks) is likely to reduce any possible carryover effects. Furthermore, foot-shock stress was applied as a second stressor because pain as a component of foot-shock was considered to have a longer lasting effect on animal behavior compared with swim stress.

In the present study, the influence of alcohol deprivation and stress on long-term alcohol drinking behavior was examined in genetically predisposed rat lines and in unselected Wistar rats. Different responses to alcohol deprivation and physical and psychological stress were observed in Wistar, HAD, P, and AA rats, indicating that the genetic background of a particular rat line can profoundly affect relapse-like drinking and stress-induced alcohol drinking.

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