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RAPID COMMUNICATION

Genetics of Alcoholism: Simultaneous Presentation of a Chocolate Drink Diminishes Alcohol Preference in High Drinking HAD Rats

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LANKFORD, M. F. AND R. D. MYERS. *Genetics of alcoholism: Simultaneous presentation of a Chocolate drink diminishes alcohol preference in high drinking HAD rats.* PHARMACOL BIOCHEM BEHAV 49(2) 417–425, 1994.—Through selective crossbreeding of the N/Nih heterogeneous stock of rats, two genetic lines of rats have been developed that are categorized by their preference for ethyl alcohol as high alcohol drinking (HAD) and low alcohol drinking (LAD) animals. Corresponding to other strains of rat bred for alcohol selection or rejection, they were subdivided on the basis of their intake of a solution of 10% alcohol vs. water. The present experiments were designed to determine whether the HAD-1 and LAD-1 lines are similar to the P and NP rats in their profile of alcohol consumption. Five successive three-bottle preference tests for alcohol drinking in the presence of water were undertaken in both HAD (n = 9) and LAD (n = 10) rats as follows: 10% alcohol for 5 days; 3–30% concentrations of alcohol increased over 11 days; the maximally preferred concentration of alcohol for 5 days; this maximally preferred concentration of alcohol plus either chocolate Slender for 5 days, or an aspartame solution for 5 days. The intake of alcohol of the LAD rats during the 10% test was 0.4 g/kg/day, whereas during the 3–30% test, the maximum intake was 1.7 g/kg/day; their maximally preferred concentrations ranged between 7% and 9% alcohol. In contrast, the intake of 10% alcohol of the HAD rats was 6.5 g/kg/day, whereas during the 3–30% test the mean daily intake was 6.6 g/kg/day; the maximally preferred solutions of the HAD rats ranged between 13 to 20%, with the mean maximum intake of 10.57 g/kg/day reached at the 20% concentration. Thus, the use of a single concentration of alcohol such as 10% to ascertain preference for alcohol for these lines of rat is not an optimal procedure. In the presence of both the chocolate drink and aspartame, the intakes of the preferred concentration of alcohol of the HAD rats declined markedly, whereas the limited drinking of the LAD rats was unaffected by either palatable fluid. These results differ with those of the P line of rats which sustained their high preference for alcohol even in the presence of the same palatable solutions. Therefore, gustatory factors associated with the sensory quality of the fluids overrode the characteristic preference of the HAD rats for a pharmacologically efficacious solution of alcohol.

Preference Drinking HAD rats Ethanol Palatability LAD rats Alcohol intake Flavored solutions Alcogene Genetics P Rats

BASED on numerous studies including the development of animal models of drinking, overwhelming evidence now exists for a genetic component in the volitional selection of ethyl alcohol (10,19,32). Historically, different strains of rats and mice, which have been plainly differentiated on the basis of their aversion or preference for 10% alcohol in a free choice situation with water, have been bred over innumerable generations (2,11,22,25). However, methodological criticisms of

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these models have emerged primarily because of the use of a single concentration of alcohol offered to the animal as the test fluid together with water (7,31,32). One of the main reasons for this is the arbitrary nature of a single imposed concentration of alcohol which, when consumed in limited volumes, may not possess pharmacological significance to the animal (32). For example, a rodent may select and drink a solution of 3% alcohol but reject a concentration of 9% (3). In fact, mice of the C57BL and BALB/C strains drink either higher or lower volumes of alcohol in concentrations other than 10%, respectively (41).

Successive generations of Wistar-derived rats have been bred to either prefer (P) or not prefer (NP) 10% alcohol offered simultaneously with water in a free-choice situation (20). The P and NP rats show differences also in their diurnal drinking cycles, tolerance to alcohol, withdrawal patterns, spontaneous movement, EEG activity, and levels of serotonin and 5-hydroxyindoleacetic acid (5-HIAA) in the brain (21). Recently, Lankford and co-workers showed that the mean absolute intake of 10% alcohol of the P rats was 4.3 g/kg/day during a standard three-bottle test of preference (17). However, when the solutions of alcohol were increased over 12 days from 3 to 30%, the intakes of the P rats exceeded 6.7 g/kg/day with a maximum intake of 10.9 g/kg/day at the 25% concentration of alcohol (17). Thus, the viewpoint was upheld that a single concentration of alcohol such as 10% does not optimally identify the true preference for alcohol of an individual animal (35). In the same study, it was found that the P rats consumed their preferred concentration of alcohol offered in the presence of either an artificially sweetened drink or a highly nutritious chocolate drink at an average level of nearly 8.0 g/kg/day (17). These observations demonstrated unquestionably that the P line of rats represents a valid animal model related to an innate basis of alcoholism.

Another genetic line of rats, which has been selectively crossbred from the N/Nih heterogeneous stock (37), also has been categorized on the basis of preference for a 10% concentration of alcohol as high alcohol drinking (HAD) and low alcohol drinking (LAD) animals (18). The present experiments were designed to determine whether a 10% solution of alcohol is an optimal concentration for differentiating phenotypically the HAD-1 and LAD-1 rats. Further, the drinking response to a palatable or highly nutritious drink presented simultaneously with the maximally preferred solution of alcohol was examined in terms of the pattern of preference or avoidance of alcohol of the HAD and LAD animals. In this study, a standard three-bottle choice procedure (34) was used to delineate the fluid preference of each HAD and LAD rat under the following conditions: 10% alcohol vs. water; concentrations of alcohol ranging from 3–30% vs. water; the maximally preferred concentration of alcohol (17) vs. water; a sweetened drink, aspartame, vs. water and the maximally preferred concentration of alcohol; and a nutritious flavored drink, chocolate Slender, vs. water and the maximally preferred concentration of alcohol.

METHOD

Male 30-day-old naive HAD (n = 9) and LAD (n = 10) rats from the original N/Nih heterogeneous strain (18,37) were obtained from the Indiana University Alcohol Research Center. On arrival, the rats were quarantined until treatment with ivermectin for pinworms was completed. At 60 days of age, 10 mg/kg cyanamide was administered subcutaneously twice daily to all rats for 3 days to augment and sustain their preference for alcohol (1,4). At 90 days, the rats were housed in individual wire mesh cages at an ambient temperature of 22 to 24°C and on a 12-h illumination cycle with lights on at 0730 h. Water and Purina NIH rodent chow were provided ad lib, and food and fluid intakes as well as body weights were recorded daily at 0730–0830 h. The experiments began at 100 days.

Alcohol Preference Tests

The pattern of preference for alcohol vs. water was determined individually for each HAD and LAD rat using a standard three bottle procedure (36). One tube contained a v/v solution of alcohol in tap water, a second tube served as a blank, and the third tube was filled with tap water. The drinking tubes were rotated on a semirandom schedule daily to prevent the development of a position habit (32). In the first alcohol preference sequence, a 10% alcohol solution was offered together with water for 5 days. Next, an 11-day preference test was initiated in which the concentration of alcohol was raised daily as follows: 3%, 4%, 5%, 7%, 9%, 11%, 13%, 15%, 20%, 25%, and 30%. Over the next 5 days, each rat was offered water and its maximally preferred concentration of alcohol, based on g/kg and proportional intakes, as determined from the 3–30% test sequence (17).

At the end of this period, the groups were divided randomly following a counterbalanced experimental design, so that one-half was given either 5.0 g/l aspartame solution or chocolate Slender in a 2:1 v/v dilution plus tap water and the maximally preferred alcohol concentration. After 5 days, the procedure was reversed so that each group was tested with the alternative palatable solution. Between each of the four preference tests, an interval of 2–4 days elapsed.

Data Analyses

Means and standard errors of the mean were calculated for both groups in terms of both the g/kg/day intake of alcohol and the proportion of alcohol to water during the three preference test series of water vs. alcohol alone, as well as during the presentation of the two flavored test solutions in the presence of both water and alcohol. Means and standard errors of the mean were calculated for both groups for amounts of food and water consumed as well as body weight under each test condition. Analyses of variance were performed using the Instat software program (GraphPAD) to compare each value obtained under successive test conditions. F-tests with a p value of < 0.05 were considered to be statistically significant.

RESULTS

Using the standard three-bottle test procedure, the difference between the HAD and LAD lines of rat in their preference for 10% alcohol vs. water was significant. Table 1 reveals a tenfold difference between the HAD rats which drank 22.8 ± 2.3 ml of alcohol and LAD animals that consumed 1.8 ± 1.0 ml during the 5-day test, $F(1, 94) = 75.44$, $p < 0.01$. As shown in Fig. 1 (top), the mean daily proportion of 10% alcohol to water of the HAD rats also was significantly higher than the LAD rats, i.e., 0.52 ± .06 vs. 0.04 ± 0.03, respectively, $F(1, 94) = 80.42$, $p < 0.01$. As illustrated in Fig. 1 (bottom), the mean g/kg intake of alcohol of the HAD group of 6.5 ± 0.8 g/kg/day was significantly higher than the mean of 0.64 ± 0.32 g/kg consumed by the LAD rats, $F(1, 94) = 52.21$, $p < 0.01$. The rising intake of 10% alcohol during the initial exposure of the rats to the fluid (Fig. 2) was due likely to the earlier administration of cyanamide (1,4).

TABLE 1

MEAN ± SE DAILY BODY WEIGHT (gm), INTAKES OF FOOD (gm), WATER (ml), ALCOHOL SOLUTION (ml), AND TOTAL FLUID (ml) OF HAD-1 (n = 9) AND LAD-1 (n = 10) RATS DURING SUCCESSIVE PREFERENCE TESTS FOR ALCOHOL VS. WATER

	Body Weight	Food Intake	Water Intake	Alcohol Intake	Total Fluid
HAD (10%)	308.0 ± 4.0	22.2 ± 0.6	22.2 ± 1.8*	22.8 ± 2.3	22.5 ± 2.1
LAD (10%)	331.5 ± 5.0	23.7 ± 0.4	36.9 ± 1.1	1.8 ± 1.0	35.7 ± 1.5
HAD (3-30%)	304.2 ± 2.3	21.4 ± 0.4	23.6 ± 1.5*	23.4 ± 1.7	46.2 ± 3.1
LAD (3-30%)	323.0 ± 3.9	22.9 ± 0.3	34.6 ± 0.7	1.4 ± 0.2	36.1 ± 0.7
HAD (PREF)	329.0 ± 3.1	20.0 ± 0.6	18.9 ± 1.4*	28.7 ± 1.7	47.6 ± 3.1
LAD (PREF)	352.5 ± 5.6	23.0 ± 0.5	33.9 ± 1.1	1.4 ± 0.5	17.7 ± 0.8

*$p < 0.01$: HAD vs. LAD water intakes during successive test conditions.

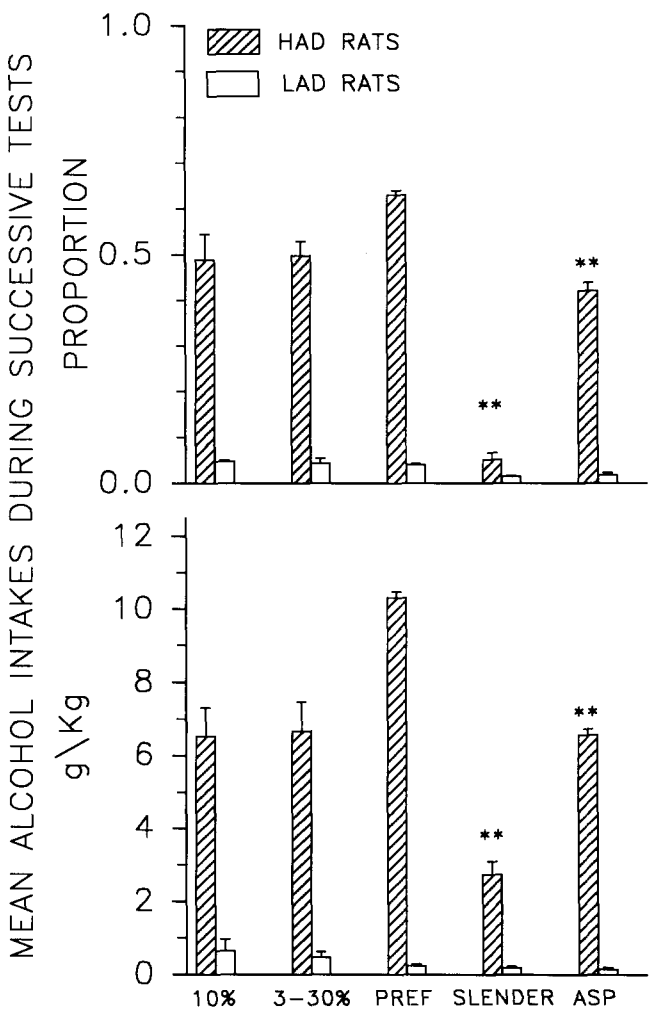

FIG. 1. Composite mean ± SE intakes of alcohol of HAD and LAD rats in terms of proportion of alcohol to total fluid (top) and g/kg intakes (bottom) during successive preference tests with water and: 10% alcohol for 5 days; 3-30% solutions for 11 days; maximally preferred solution of alcohol alone (PREF) for 5 days; maximally preferred solution of alcohol and chocolate Slender for 5 days; and aspartame (ASP) solution and maximally preferred solution of alcohol for 5 days.

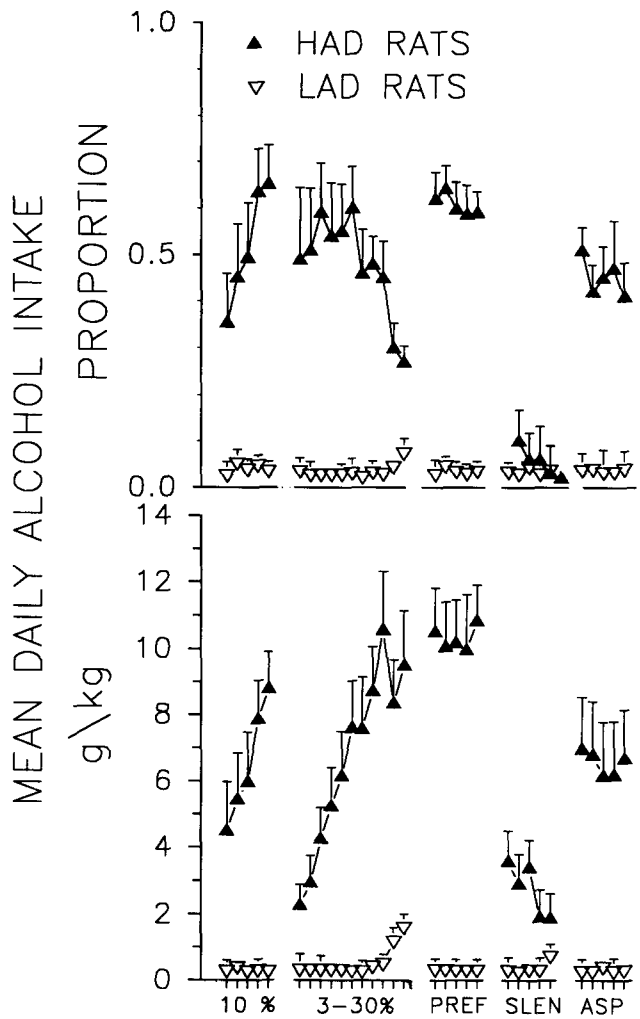

FIG. 2. Mean daily ± SE intakes of alcohol of HAD and LAD rats in terms of proportion of alcohol to total fluid (top) and g/kg intake (bottom) during successive preference tests with water and: 10% alcohol for 5 days; a concentration of alcohol raised daily, i.e., 3%, 4%, 5%, 7%, 9%, 11%, 13%, 15%, 20%, 25%, and 30% over 11 days; maximally preferred solution of alcohol alone (PREF) for 5 days; maximally preferred solution of alcohol and chocolate Slender (SLEN) for 5 days; and aspartame (ASP) solution and maximally preferred solution of alcohol for 5 days.

When presented with concentrations ranging from 3 to 30% over 11 days, the HAD animals drank a consistently higher amount of alcohol at each percent concentration. As shown in Fig. 1 (top), the mean proportion of alcohol to total fluid intake of 0.47 ± 0.03 of the HAD group was 10 times greater than the proportional intake of 0.04 ± 0.01 of the LAD animals, $F(1, 208) = 180.08$, $p < 0.01$. The mean g/kg/day intake of alcohol of the HAD animals was 6.6 ± 0.8 g/kg/day, which differed significantly from 0.5 ± 0.1 g/kg/day of the LAD group, $F(1, 208) = 61.45$, $p < 0.01$. Likewise, the LAD rats drank little or no alcohol at percent concentrations ranging from 3–11%, as illustrated in Fig. 2. However, as the percent concentration was increased, the LAD rats consumed slightly more alcohol with a peak of 1.7 ± 0.4 g/kg/day at 30% (Fig. 2, bottom). As presented in Table 1, neither the intakes of food and fluid nor body weight of the HAD and LAD animals were reduced during the 10% or 3–30% preference tests.

During the test period in which the preferred concentration of alcohol was offered, the solutions consumed by the HAD rats ranged between 13 and 20%, with a mean concentration of 14.2 ± 1.1%, whereas the preferred concentration of the LAD rats was 8.4 ± 0.6%. The 10.3 ± 1.7 g/kg/day intake of alcohol of the HAD animals (Fig. 1, bottom) was sharply higher than the 0.3 ± 0.2 g/kg/day alcohol consumed by the LAD rats, $F(1, 94) = 37.84$, $p < 0.01$. The mean daily proportional intake of alcohol to water (Fig. 1, top) of 0.61 ± 0.17 of the HAD rats was significantly higher than 0.04 ± 0.1 of the LAD rats, $F(1, 94) = 12.45$, $p < 0.01$.

The substitution of either aspartame or chocolate Slender in the third drinking tube served to dissociate further the drinking patterns of the two genetically derived groups. As presented in Table 2, the drinking of both water and individually preferred concentration of alcohol declined while the mean ingestion of total fluid increased. The mean daily intake of alcohol of the HAD rats, recorded during the 5-day test on the preferred concentration of alcohol, of 28.7 ± 1.7 ml per day (Table 1), thus, was reduced significantly to 7.7 ± 1.0 ml per day (Table 2), $F(1, 89) = 113.4$, $p < 0.01$. In contrast, the mean intake of alcohol of the LAD rats was not significantly elevated above the baseline level of 1.4 ± 0.5 ml (Table 1) to 1.7 ± 0.5 ml (Table 2).

As denoted in Fig. 1 (bottom), the mean intake of 2.7 ± 0.4 g/kg/day of alcohol by the HAD animals in the presence of the chocolate drink was significantly lower than the 10.3 ± 1.7 g/kg/day consumed of the preferred solution of alcohol, $F(1, 89) = 18.93$, $p < 0.01$. This decrease in mean intake of alcohol of the HAD rats, nevertheless, was significantly higher than the level of 0.2 ± 0.05 g/kg/day of the LAD group, $F(1, 94) = 55.47$, $p < 0.01$. The mean proportional intake of the HAD rats was also reduced significantly by chocolate Slender (Fig. 1, top) to a level that was less than that observed under any prior test condition, $F(1, 89) = 116.5$, $p < 0.01$. Nevertheless, the proportion of alcohol to water intake of the HAD rats also was significantly greater than that of the LAD group of animals, $F(1, 94) = 51.58$, $p < 0.01$.

As illustrated in Fig. 1 (bottom), the mean intake of 6.6 ± 0.16 g/kg/day of alcohol by the HAD rats in the presence of aspartame was significantly higher than the 0.14 ± 0.04 g/kg of the LAD group, $F(1, 94) = 1683.25$, $p < 0.01$. In spite of the fact that the proportional intakes of the HAD rats fell to a level below that during their 3–30% alcohol preference test (Fig. 1, top), this value remained significantly higher than the proportion of alcohol intake of the LAD rats, $F(1, 94) = 591.43$, $p < 0.01$.

As presented in Table 2, the presence of the chocolate drink in the third drinking tube served to augment fourfold the total amount of fluid ingested. During the same interval, the consumption of food of the HAD rats declined from 20.0 g per day to 16.5 g per day, because of the caloric value of chocolate Slender. When the third drinking tube contained aspartame, neither the total fluid ingested increased nor the total amount of food eaten changed significantly (Table 2).

Individual Responses to Flavored Solutions

Animals in both HAD and LAD groups exhibited somewhat variable drinking responses during each of the successive test situations. As presented in Fig. 3, proportional intakes of 10% alcohol and the g/kg/day consumed of HAD rat 1, HAD 2, and HAD 12 reached a peak by either the fourth or fifth days. When the concentration of alcohol was increased from 3 to 30% during the second test sequence, the intake of alcohol rose sharply to above 15 g/kg/day and, as reported previously (17), in a manner similar to that of the P-line of rats.

When the chocolate and aspartame solutions were presented along with water and the maximally preferred concentration of alcohol, the preference patterns of individual HAD and LAD rats also were distinctive. As illustrated in Fig. 3, the intake of 15% alcohol by HAD 1 of 11 to 17 g/kg/day persisted in the presence of aspartame but declined to below 4.0 g/kg/day in the presence of the chocolate drink (Fig. 3). The consumption of the 13% concentration of alcohol of HAD 2 declined by one half in the presence of aspartame but fell below 4.0 g/kg/day when chocolate Slender was offered. However, the drinking of 13% alcohol of HAD 12 was suppressed only moderately, but equally, by both flavored solutions (Fig. 3).

Although the LAD rats typically drank less than 1.0 g/kg/day concomitant with a negligible proportional consumption

TABLE 2

MEAN ± SE DAILY BODY WEIGHT (gm), INTAKES OF FOOD (gm), WATER (ml), PREFERRED ALCOHOL SOLUTION (ml), FLAVORED FLUID (ml), AND TOTAL FLUID (ml) OF HAD AND LAD RATS DURING 5 SUCCESSIVE DAYS OF PREFERENCE TESTING FOR CHOCOLATE SLENDER OR ASPARTAME VS. ALCOHOL

	Body Weight	Food Intake	Water Intake	Alcohol Intake	Flavored Fluid	Total Fluid
HAD (chocolate)	341.6 ± 3.1	16.5 ± 0.9	10.2 ± 1.3	7.7 ± 1.0	158.4 ± 7.9	177.9 ± 7.7
LAD (chocolate)	365.0 ± 6.6	18.8 ± 0.8	9.9 ± 1.2	1.7 ± 0.5	104.3 ± 5.4	115.9 ± 5.7
HAD (aspartame)	342.1 ± 3.1	21.3 ± 0.7	5.1 ± 0.6	18.8 ± 1.8	21.6 ± 2.0	46.2 ± 2.1
LAD (aspartame)	365.6 ± 6.4	23.1 ± 0.4	16.9 ± 2.1	0.7 ± 0.2	21.4 ± 2.4	38.9 ± 1.0

$p < 0.01$: HAD food intakes—10% and PREF vs. chocolate Slender; LAD food intakes—10% and PREF vs. chocolate Slender.

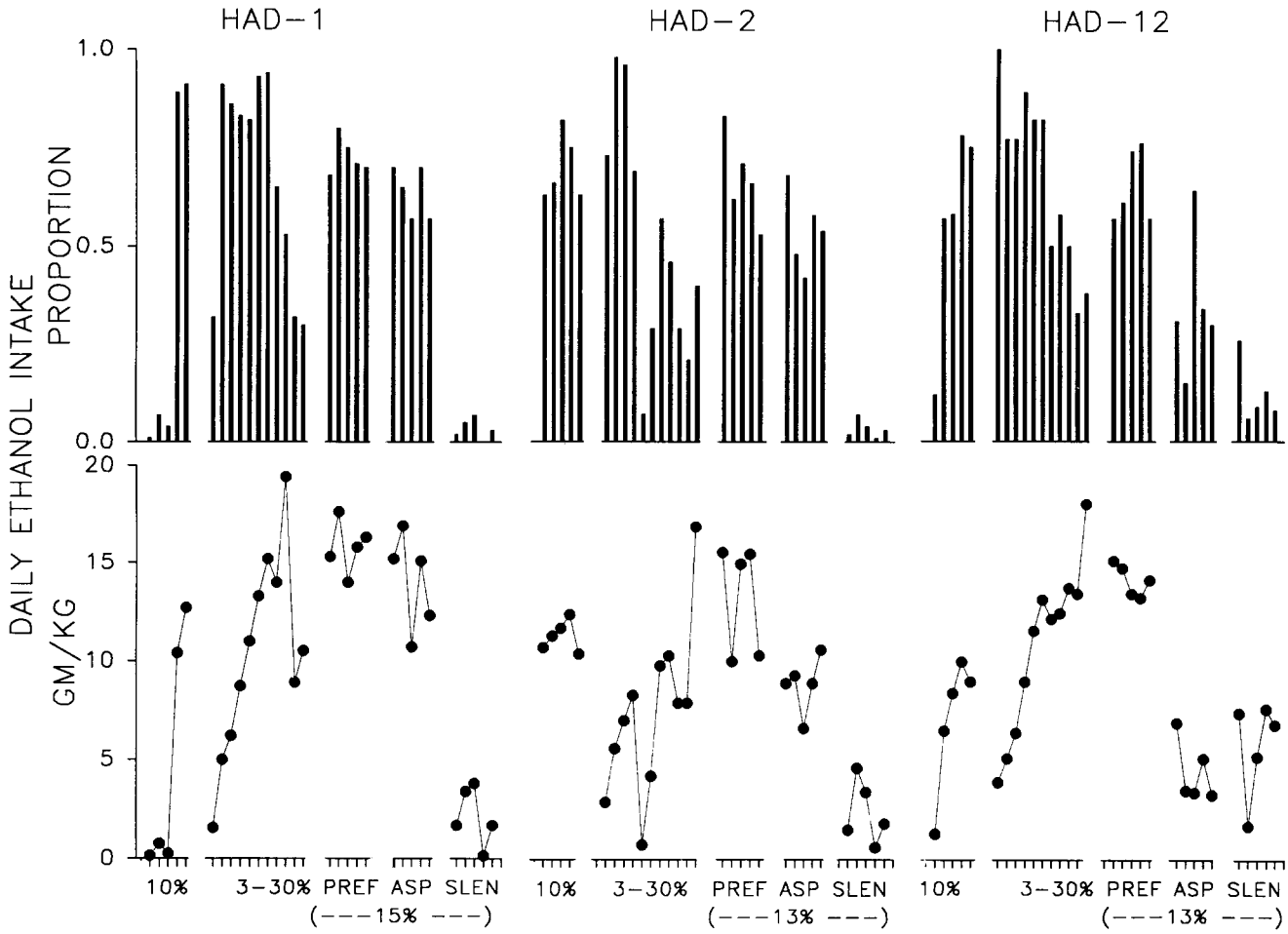

FIG. 3. Daily intakes of alcohol of three representative HAD rats in terms of proportion of alcohol to total fluid (top) and absolute g/kg intake (bottom) during successive sequences in which water was offered together with: 10% solution; a concentration of alcohol raised daily from 3% to 30%; the maximally preferred solution of alcohol alone (PREF); the maximally preferred solution of alcohol and chocolate Slender (SLEN); and aspartame (ASP) solution and maximally preferred solution of alcohol for 5 days.

during all test sequences (Fig. 4), the intake of LAD 5 showed a rising pattern as the alcohol concentration increased to 30%. In fact, LAD 5 consumed 1.0 to 3.0 g/kg/day of 9% alcohol in the presence of chocolate Slender. Although LAD 9 and LAD 12 also increased their intakes slightly as the solutions of alcohol were increased in concentration, the levels never exceeded 2.0 g/kg/day (Fig. 4, bottom).

DISCUSSION

Previously, it was shown that the HAD line of rats consumes 10% alcohol in an amount of 5.5 g/kg/day (16). The present results show that the HAD rats drank almost 1.0 g/kg/day more of the 10% alcohol solution than previously reported, possibly because of the action of cyanamide that augments and sustains drinking of rat strains for which alcohol is not generally preferred (1,4). Further, during the 3-30% preference test, the drinking of alcohol of the HAD rats climbed significantly to reach a peak consumption of 10.6 g/kg/day at the 20% concentration. During the test in which the HAD rats were offered their maximally preferred concentration of alcohol, this level of drinking persisted; however, their intake of alcohol declined precipitously in terms of both absolute g/kg and proportion in the presence of chocolate Slender, and in some rats, aspartame. The decline in the proportional intakes of alcohol of the HAD group during the presentation of chocolate Slender was due to the large amount of the fluid consumed (Table 2) and corresponds to that observed in an earlier study with the high alcohol preferring P rat (17).

A comparison of the drinking patterns of the HAD rats with those of the genetic P line of rat, wherein a similar experimental paradigm was used (17), shows that the HAD rats consume significantly more g/kg/day of 10% alcohol than the P animals. However, as presented in Fig. 5, during the 3-30% preference sequence, the proportional intake of the P rat is greater than that of the HAD line. Moreover, the markedly suppressed intake of alcohol of the HAD rats during the interval of chocolate Slender (Fig. 5) is in sharp contrast to the sustained consumption of alcohol of the P rats (17). This switch in preference to the flavored fluid could have been due to the palatability of chocolate drink, its nutritional content, or a combination of both factors. In interpreting the disparity between the HAD and P rats, it is possible that the duration of exposure to 10% alcohol, the 3 to 30% concentrations, and

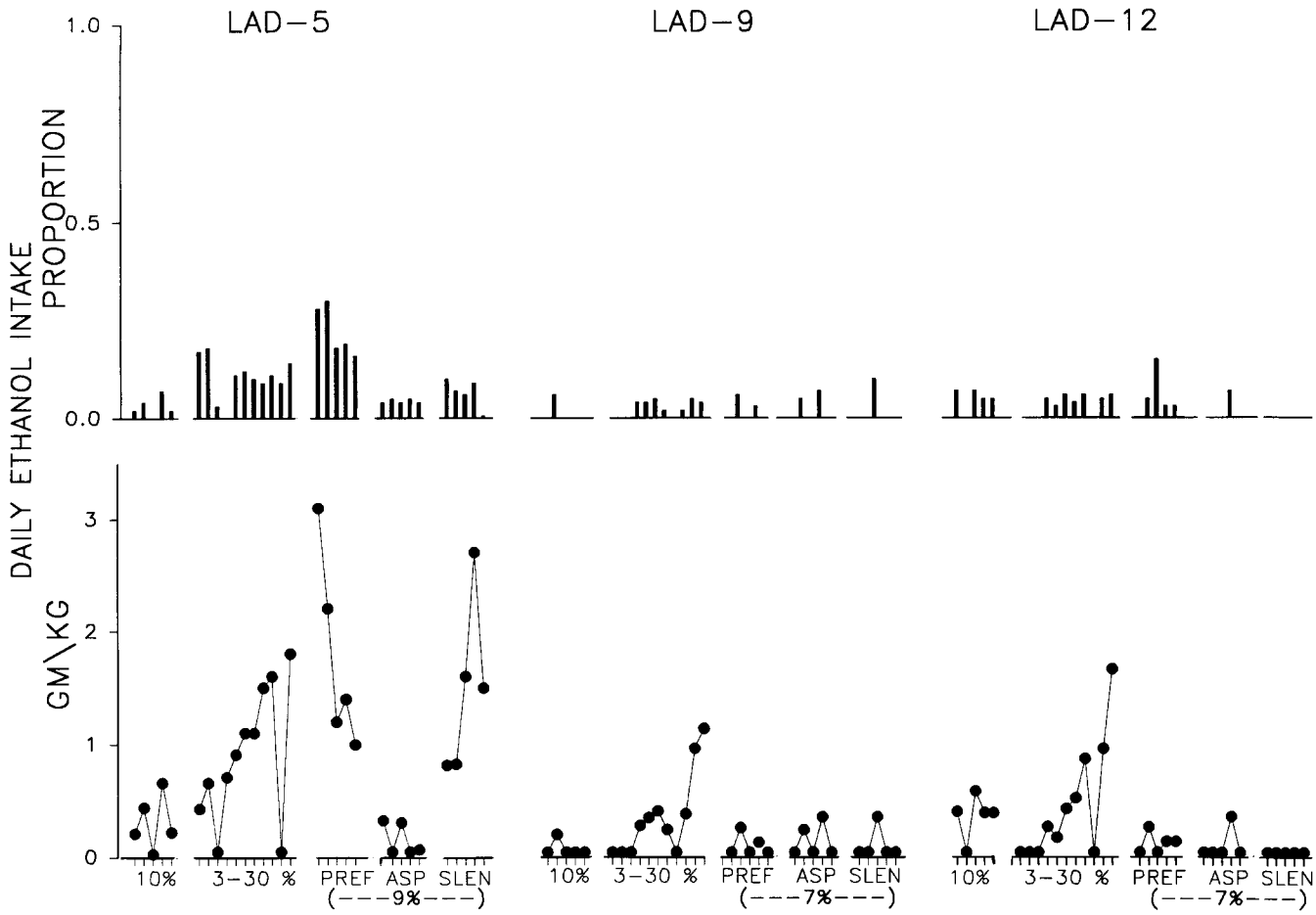

FIG. 4. Daily intakes of alcohol of three representative LAD rats in terms of proportion of alcohol to total fluid (top) and absolute g/kg intake (bottom) during successive sequences in which water was offered together with: 10% solution; a concentration of alcohol raised daily from 3% to 30%; the maximally preferred solution of alcohol alone (PREF); this maximally preferred solution of alcohol and chocolate Slender (SLEN); and aspartame (ASP) solution and maximally preferred solution of alcohol for 5 days.

the maximally preferred solution affected differentially the HAD rats in an unknown but unique manner. Alternatively, the chocolate-flavored fluid could have affected the response of the HAD rats to a far greater degree than the P animals. Nevertheless, the overall intakes of the chocolate drink and in some cases, aspartame, by the P rat generally were of equal magnitude as that of the HAD rat.

In spite of the disparity in the drinking of alcohol of the HAD and P rats in the presence of the chocolate drink, a comparison of neurochemical measures between these lines of rat reveal similarities that have been correlated with the preference or rejection of alcohol (9,42). For example, in both the HAD and the P rat, agonists or antagonists of the dopamine receptor, administered peripherally in appropriate doses, can suppress alcohol drinking substantially (6,38). In addition, both lines of rat possess lower levels of dopamine, 5-HT and their respective metabolites than the alcohol nonpreferring LAD and NP lines within specific regions of the brain (12,28,29). Rats of the P, NP, and HAD lines also exhibit differential densities of 5-HT_{1A} and 5-HT_2 receptors and of GABAergic nerve terminals in different cerebral structures (13,23,24,39,40). Conversely, the extracellular levels of dopamine and 5-HT are enhanced in both HAD and LAD rats by alcohol (42), which reflects little difference in their sensitivity to the fluid, and suggests that a dissociation may exist between the preference for alcohol and the functional activity of the mesolimbic pathways that contain dopaminergic and serotonergic neurons. Although the P and HAD rats exhibit similar EEG theta activity in the hippocampus (27), the HAD rat is more reactive to the stimulating effect of a low dose of alcohol than the LAD (16) even though both lines react similarly to the discriminative effects of alcohol (15).

Taken together, the present findings raise the issue of validity pertaining to other well-known genetic models of experimental alcoholism, which include the Fawn Hooded rat (5) and those classified as UChA (alcohol drinking) (22), AA (alcohol addicted) (7), and AT (alcohol tolerant) (14). That is, if an animal drinks a large volume of a high concentration of alcohol in preference to water, just as the HAD and P rats do, one would surmise that the ingestion of alcohol is unusually reinforcing to the animal (19,34), particularly if the solution of alcohol offered to the animal is in the gustatorily noxious range (26). Further, the physiological significance of alcohol to the rat is evident if drinking of an ordinarily aversive concentration of alcohol persists in the presence of a sweetened, palatable solution (8). Should such a preference for alcohol

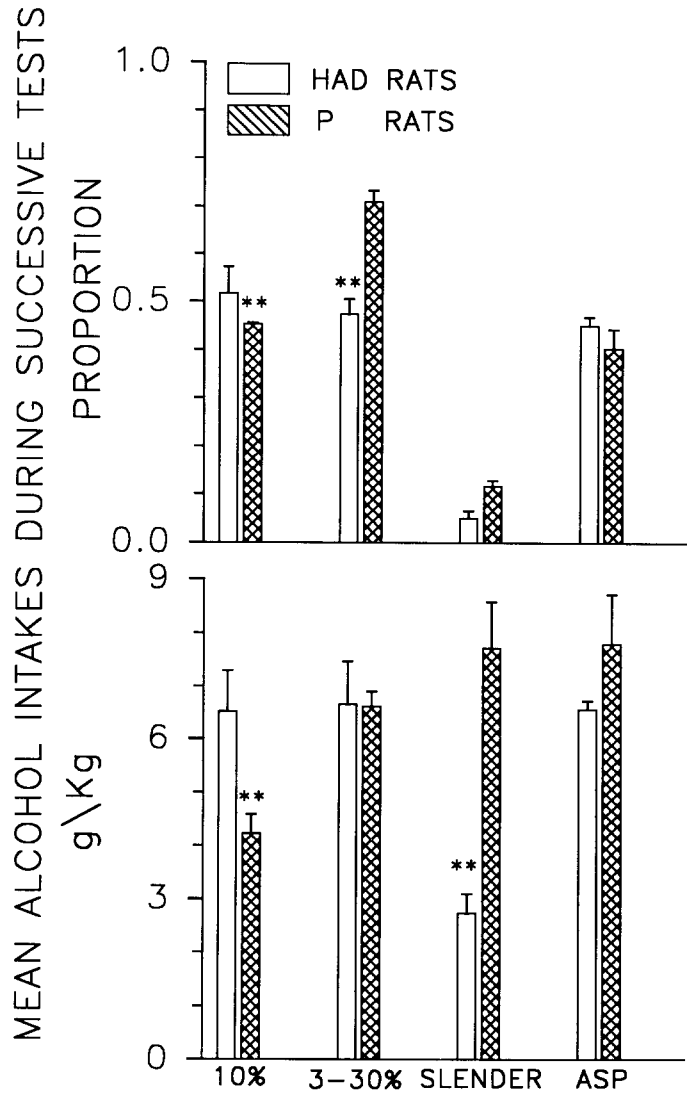

FIG. 5. Comparison of mean ± SE daily intakes of alcohol of HAD rats and P rats in terms of proportion of alcohol to total fluid intake (top) and absolute g/kg intake (bottom) during: 5-day preference test with 10% solution vs. water; 11 day test with 3-30% solutions of alcohol vs. water; maximally preferred solution of alcohol vs. water and chocolate Slender (SLEN); and maximally preferred solution of alcohol vs. water and aspartame (ASP) solution. Differences were significant between proportional values during 3-30% test, $F(1, 94) = 35.37, p < 0.01$, whereas g/kg values were significant during the preference tests for 10% alcohol, $F(1, 94) = 7.65, p < 0.01$, and SLEN, $F(1, 94) = 25.95, p < 0.01$.

continue to the same degree in the presence of a nutritious, flavorful drink such as chocolate Slender, then both the reinforcing property of alcohol and the pharmacological consequence of ingestion of alcohol supervene the factor of palatability or nutrient value of alternative fluids (32). In fact, a preference for alcohol in the face of a chocolate-laced drink would ostensibly rule out the gustatory element of novelty of alcohol as contributing to its sustained intake (26,33). Clearly, each of these factors should be considered before a strain or line of genetically bred rats can be classified as a model of alcohol drinking.

Recently, it has been demonstrated that the P rat fulfills the criterion of such a pattern of preference, and it has been concluded that the P rat is, indeed, a valid animal model of alcoholism (17). Apparently, the gene pool of the P rat is expressed in the form of a mechanism, which is coded for alcohol preference regardless of the presence of a highly preferred fluid, as well as in the absence of any environmental or psychosocial input. However, the present results show that the HAD line of rat may not fulfill such a preference criterion for an experimental model of alcoholism in the same way as the P line of rat (17) because its drinking of alcohol declines when a highly palatable drink is offered in the choice situation (Fig. 3). In a sense, the response of the HAD animal may be analogous to the alcoholic individual who can modify or even control immoderate drinking behavior in the face of an alternative, rewarding set of circumstances. Nevertheless, further research will be required to delineate the factors that are responsible for the reversal in preference of alcohol, which include the variables of duration of exposure, inclusion of alcohol in the flavored solution, and the element of appetitive processes in general.

In conclusion, three critical questions remain. What does it mean when a rat or other animal of a genetically high drinking line or strain continues to prefer alcohol if a nutritious palatable fluid is available? What does it mean when the genetically high-drinking animal rejects alcohol in the presence of a sweetened drink? Does a decline in the self-selection of alcohol caused by taste, a nutritional, or dietary factor serve to reduce the utility of the animal as a model for experimental alcoholism? Finally, the present results would seem to demonstrate that the taste of a palatable alternative to alcohol will have to be considered in the elucidation of the mechanisms responsible for both the reinforcing effects of alcohol as well as its other pharmacological actions.

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