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Ethanol, Nicotine, Amphetamine, and Aspartame Consumption and Preferences in C57BL/6 and DBA/2 Mice

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MELISKA, C. J., A. BARTKE, G. McGLACKEN AND R. A. JENSEN. *Ethanol, nicotine, amphetamine, and aspartame consumption and preferences in C57BL/6 and DBA/2 mice.* PHARMACOL BIOCHEM BEHAV **50**(4) 619–626, 1995.—Using a two-bottle choice paradigm, adult C57BL/6 and DBA/2 mice (11 males and 10 females per strain) were given access to tapwater and an ascending series of concentrations of ethanol, nicotine, amphetamine, and the artificial sweetener, aspartame. The C57 mice consumed more ethanol, nicotine, and amphetamine, and showed greater preferences for these substances, than did the DBA/2 mice. In contrast, DBAs consumed more and showed greater preference for aspartame than C57s. However, measures of drug and aspartame consumption and preference were moderately intercorrelated when the effects of gender and strain were controlled for. This pattern of results suggests that factors modulating differences between C57BL/6 and DBA/2 mice in ethanol consumption and preference also modulate differences in consumption of nicotine and amphetamine.

Alcohol Genes Reward Reinforcement Drug self-administration Two-bottle choice Vulnerability

THE IDENTIFICATION of neurobiologic factors influencing vulnerability to substance abuse is commanding increasing research attention. Since the original demonstration of differences among inbred mouse strains in preferences for ethanol consumption (24), differences among rodent strains in self-administration of ethanol (1,2) and a wide variety of other substances have been well documented (12,15,27). For example, C57BL/6 mice, which consume ethanol far more readily than do DBA/2 and BALB/c mice, also self-administer morphine, pentobarbital, and psychomotor stimulants far more readily than do DBA/2 or BALB/c mice (3,14,30). Similarly, inbred rat strains such as Lewis and Fischer 344 also differ from each other in self-administration of ethanol, stimulants, and opiates (11,33). Recent work indicates that behavioral and physiologic responses to ethanol and nicotine, as well as consumption of these substances, may be regulated by common genetic mechanisms (5,6). Taken together, these findings suggest that genetic factors may modulate individual differences in susceptibility to the reinforcing effects of ethanol and other drugs, and that differences in vulnerability to self-administration of several different drugs may be mediated by the same biologic mechanisms (4,13,15).

Strains of rats and mice exhibiting a preference for ethanol consumption in a two-bottle choice situation also appear to prefer sweet-tasting substances more than ethanol-nonpreferring strains. For example, lines of rats selectively bred for high ethanol consumption also consume more and show greater preferences for saccharin than lines bred for low ethanol consumption (32). Similarly, C57BL mice consume more saccharin than do DBA mice, and moderately high correlations between ethanol and saccharin consumption have been found when multiple strains are compared (1,9). These observations may indicate that ethanol and saccharin taste similarly sweet to rodents (1). Alternately, ingestion of ethanol and saccharin may activate common neural mechanisms that mediate the effects of reinforcement from a variety of sources (17,26). Whether preference for sweets, including substances other than saccharin, is related to consumption of drugs of abuse besides ethanol has not been systematically studied.

In the present experiment, consumption of and preference

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for ethanol, L-nicotine, D-amphetamine, and the nonnutritive sweetener, aspartame, were measured in the same groups of C57BL/6 and DBA/2 mice, using the two-bottle choice paradigm. The experiment was designed to compare oral self-administration of these substances across a broad ranges of concentrations, and to assess the degree to which ethanol consumption was related to consumption of the other substances. To the extent that common mechanisms regulate consumption of these substances, consistent strain differences, as well as significant correlations between measures of consumption of the different substances, were expected.

METHODS

Animals

A total of 21 C57BL/6 (C57) and 21 DBA/2 (DBA) mice, 11 males and 10 females each, obtained from Harlan/Sprague Dawley, were tested with ethanol (ETH), L-nicotine (NIC), D-amphetamine (AMP), and aspartame (ASP). To minimize carryover effects from one drug to the next, while providing the opportunity to measure consumption of different drugs by the same animals, a minimum of 21 days was allowed to elapse between tests with different drugs. Animals were approximately 110 days old at the start of ETH testing, 180 days old at the start of NIC testing, 280 days old at the start of AMP testing, and 350 days old at the start of ASP testing. One female DBA died before the tests with NIC. Mice were housed individually in 17.5 × 30.0 × 12.0-cm-deep plastic cages in a room with a 12 L : 12 D photoperiod (lights on at 0600 h) and temperature of 22 ± 1°C, with free access to food (Purina Formula 5008, Richmond, IN) throughout the study.

Apparatus

Standard wire cage tops were modified to accommodate two water bottles, one on the left and one on the right of each cage. To minimize fluid leakage, the standard sipper tube of each 250-cc water bottle was replaced with a 16-ga, 19-mm special blunted tube (model E8B; Electrocap International, Columbus, OH), which was polished to smoothness at the tip. Mice drank readily from these tubes, and fluid leakage was typically < 1.0 g/day.

Preparation of Solutions

Logarithmic progressions of concentrations of solutions of the substances tested were prepared as follows: Solutions of ETH were prepared by diluting 95% ETH with tapwater to concentrations of 1.0, 2.2, 4.6, 10.0, and 22.0% v/v. NIC solutions were prepared by diluting L-nicotine hemisulfate (400 mg/ml; Sigma) to concentrations of 1.0, 1.6, 2.5, 4.0, 6.3, 10.0, 16.0, 25.0, 40.0, 63.0, and 100.0 μg/ml, w/v). AMP solutions were prepared by dissolving D-amphetamine sulfate (Sigma) in tapwater to produce concentrations of 1.0, 2.2, 4.6, and 10.0 μg/ml AMP as base. ASP solutions were prepared by diluting Asp-Phe Methyl Ester (Sigma, St Louis, MO) to concentrations of 0.056, 0.10, 0.18, 0.32, 0.56, and 1.00 mg/ml.

Procedure

After habituating mice to the two-bottle choice drinking conditions for 8 days, bottles containing either tapwater or drug solution were presented, one on the left and one on the right side of each mouse's home cage. Every 24 h the positions of the two bottles were reversed. Every 48–96 h, bottles were weighed to the nearest 0.1 g, and the change in weight of each bottle was recorded. A "blank," calculated by determining weight lost due to leakage and evaporation from four identical pairs of bottles placed on empty cages, was subtracted from the change in bottle weights to determine weight of fluid(s) actually consumed. Drug concentrations were increased, usually every 4–12 days, to produce each ascending series of concentrations, and consumption and preference data were averaged across days for each concentration tested. The schedule of presentation of each solution was as follows: ETH 1.0% (8 days), 2.2%, and 4.6% (12 days each), 10.0% (14 days), 22.0% (6 days); NIC 1.0, 1.6, and 2.5 μg/ml (2 days each), 4.0 μg/ml (4 days), 6.3 μg/ml (6 days), 10.0, 16.0, 25.0, 40.0, 63.0 and 100.0 μg/ml (8 days each); AMP 1.0, 2.2, and 4.6 μg/ml (6 days each); 10.0 μg/ml (12 days); ASP 0.056 and 0.10 mg/ml (4 days each), 0.18 mg/ml (6 days), 0.32 mg/ml (8 days), 0.56 and 1.0 mg/ml (4 days each).

RESULTS

Table 1 shows mean body weights, total fluid consumed (gram per kilogram per day of drug solution plus water), and maximum quantities of drug consumed (weight of drug per kilogram per day) across test concentrations of each drug. Separate gender × genes analyses of variance (ANOVAs) showed that females tended to consume larger total quantities of fluids than males, whereas DBAs ingested more total fluids than C57s. As Table 1 shows, C57s displayed greater maximum consumptions of ETH than DBAs [$F(1, 38) = 9.78$ and 28.70, respectively, for males and females (both $p < 0.001$)]. The C57 females, but not males, also consumed more amphetamine than did DBA females [$F(1, 37) = 37.4$, $p < 0.001$]; in contrast, C57s ingested significantly less ASP than did DBAs [$F(1, 37) = 10.87$, $p < 0.01$ for males and $F(1, 37) = 21.10$, $p < 0.001$ for females]. Differences between strains in NIC consumption were not statistically significant (both $p > 0.05$).

To explore the concentration dependency of these effects adequately, it was deemed important to take into account the gender and strain differences in quantities of fluid consumed, because the quantity of drug consumed in a two-bottle choice test depends on the volume of fluid consumed per day. For example, if mice drink without preference half their fluids from each bottle, mice that habitually ingest more total fluid per day will consume more drug (grams per kilogram per day) than those that also drink without preference from both bottles, but that consume less fluid per day. Thus, two groups exhibiting no preference [preference ratio (PR) = 0.50] for a particular substance could differ in quantity of drug consumed simply because they differ in daily fluid consumption.

To remove potential bias due to these differences in fluid consumption, drug consumption was adjusted by calculating the quantity of each drug expected to be consumed, based on the null assumption that each animal drank half of its total fluid from the drug bottle and half from the water bottle. Adjusted consumption was then calculated by subtracting expected consumption from the actual amount of drug (grams per kilogram per day) consumed: adjusted consumption = (actual consumption − expected consumption). A second measure, the PR, was defined as the ratio of (unadjusted) drug solution consumed to total fluid consumed (PR = Drug/Drug + Water) per day. Both measures were analyzed with separate, 2-between, 1-within (gender × genes × drug concentration) analyses of variance (ANOVAs) with Geisser-Greenhouse correction for sphericity of repeated measures on the drug concentration factor. Analyses of simple main effects

TABLE 1

MEAN (±SEM) BODY WEIGHTS, FLUID CONSUMPTION (GRAMS PER KILOGRAM PER DAY OF DRUG + WATER) AND MAXIMUM DRUG CONSUMPTION BY MALE AND FEMALE DBA/2 AND C57BL/6 MICE

	Body Weight (g)		Total Fluid Consumed (g/kg/day)		Maximum Amount of Drug Consumed (per kg/day)	
	DBA/2	C57BL/6	DBA/2	C57BL/6	DBA/2	C57BL/6
Males						
ETH	28.2 (0.5)	27.7 (0.4)	0.16 (0.01)	0.14 (0.01)^{a}	2.0 (0.3)^{b}	9.1 (1.0)^{b,***}
NIC	30.7 (0.7)	32.3 (0.8)	0.14 (0.01)^{c}	0.11 (0.01)^{c,**}	3.0 (0.3)^{b}	3.0 (0.4)^{c}
AMP	32.6 (0.7)	36.6 (1.0)	0.12 (0.01)^{c}	0.09 (0.01)^{c,***}	0.45 (0.05)^{c}	0.40 (0.03)^{b}
ASP	33.5 (0.8)	37.3 (1.8)	0.14 (0.01)^{b}	0.09 (0.01)^{c,***}	80.2 (7.4)^{c}	50.4 (6.0)^{**,a}
Females						
ETH	22.5 (0.7)	23.3 (0.7)	0.17 (0.01)	0.17 (0.01)	3.9 (0.4)	13.3 (1.6)***
NIC	22.6 (0.6)	25.6 (0.9)	0.20 (0.01)	0.16 (0.01)***	4.8 (0.5)	5.3 (0.4)
AMP	24.0 (0.7)	26.6 (0.8)	0.16 (0.01)	0.13 (0.01)***	0.23 (0.03)	0.56 (0.03)***
ASP	24.1 (0.6)	29.0 (1.5)	0.22 (0.04)	0.13 (0.01)**	116.5 (8.5)	71.7 (3.8)***

Mice were tested with ethanol (ETH), nicotine (NIC), d-amphetamine (AMP), and aspartame (ASP) in a two-bottle choice test. Quantities consumed are grams per kilogram per day for ETH and milligrams per kilograms per day for NIC, AMP, and ASP. Asterisks denote significant differences between same-sexed DBAs and C57s: $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$. Letters denote significant differences between males and females of the same strain: $^{a}p < 0.05$; $^{b}p < 0.01$; $^{c}p < 0.001$.)

were performed on significant gender × genes × drug concentration interactions ($p < 0.05$). To test whether PRs exceeded chance expectation, 0.50 was subtracted from individual PR values at each drug concentration, and ANOVAs were performed to determine whether the mean remainder differed significantly from 0.00 for each drug tested.

Ethanol

Consistent with the analysis of raw consumption reported in Table 1, C57BL/6 mice consumed far more ETH (adjusted grams per kilograms per day) across concentrations [$F(1, 38) = 55.9$, $p < 0.001$] (Fig. 1A), and exhibited greater preferences for ETH [$F(1, 38) = 59.2$, $p < 0.001$] than did DBA/2 mice (Fig. 2A) Males and females of both strains did not differ significantly in adjusted consumption or preference (all $p > 0.05$). In both males and females, PRs were significantly greater than chance expectation (PR = 0.50) with the 4.6 and 10.0% ETH concentrations (all $p < 0.05$). DBAs showed only a concentration-dependent aversion to ETH at all concentrations tested.

Nicotine

Data on consumption of NIC with concentrations < 16.0 μg/ml were excluded because effects of these lower doses were negligible. In contrast to the raw data nicotine consumptions, analyses of adjusted nicotine consumptions indicated that, overall, C57s exceeded DBAs in NIC consumption (adjusted milligrams per kilograms per day) [$F(1, 37) = 29.1$, $p < 0.001$] (Fig. 1B). Analysis of a significant genes × gender × concentration interaction for PRs showed that C57 females displayed a greater preference for NIC across doses than did DBAs [$F(1, 37) = 6.35$, $p < 0.05$]; C57 and DBA males differed in preference with only the two highest concentrations, 63 and 100 μg/ml (Fig. 2B). Adjusted NIC consumption exceeded chance expectation [$F(1, 37) = 4.28$, $p < 0.05$], and the PR exceeded 0.50 [$F(1, 37) = 4.03$, $p < 0.05$] when C57 females consumed the 40 μg/ml NIC solution.

Amphetamine

Overall, mice consumed only modest amounts of AMP and exhibited no reliable preference for any AMP concentration (all $p > 0.05$). Male C57s showed neither preference nor aversion to AMP across concentrations (Figs. 1C and 2C) while consuming more (adjusted milligrams per kilogram per day) of the 10.0 μg/ml concentration than did DBAs [$F(1, 37) = 8.90$, $p < 0.01$]. As with the analysis of raw AMP consumption, adjusted consumption by female C57s was greater than that of DBA females at the 2.2 μg/ml [$F(1, 37) = 9.67$, $p < 0.01$] and higher concentrations (all $p < 0.001$). Although male DBAs consumed far more AMP than did female DBAs [$F(1, 37) = 61.43$, $p < 0.001$], male C57s did not differ significantly from female C57s.

Aspartame

As expected, mice consumed ASP avidly, especially with concentrations above 0.10 mg/ml (Figs. 1D and 2D). Across strains, females consumed more ASP (adjusted milligrams per kilograms per day) than did males [$F(1, 35) = 11.87$, $p < 0.001$]. Contrary to expectation, DBAs consumed more ASP, overall, than did C57s [$F(1, 35) = 10.26$, $p < 0.01$]. DBAs also displayed greater preferences for ASP overall than did C57s, with the exception that male C57s preferred 0.10 mg/ml ASP more than did male DBAs [$F(1, 35) = 5.30$, $p < 0.05$]; female DBAs preferred ASP concentrations of 0.18 and 0.32 mg/ml more than did C57s.

Intercorrelations Among Consumption Measures

To assess the degree to which measures of ETH, NIC, AMP, and ASP consumption covaried, partial correlation coefficients, controlling for strain and gender of subjects, were calculated on consumption and preference measures averaged across all test concentrations. Across strains and genders, adjusted ETH and NIC consumptions, and preference ratios, tended to be modestly but significantly intercorrelated, as

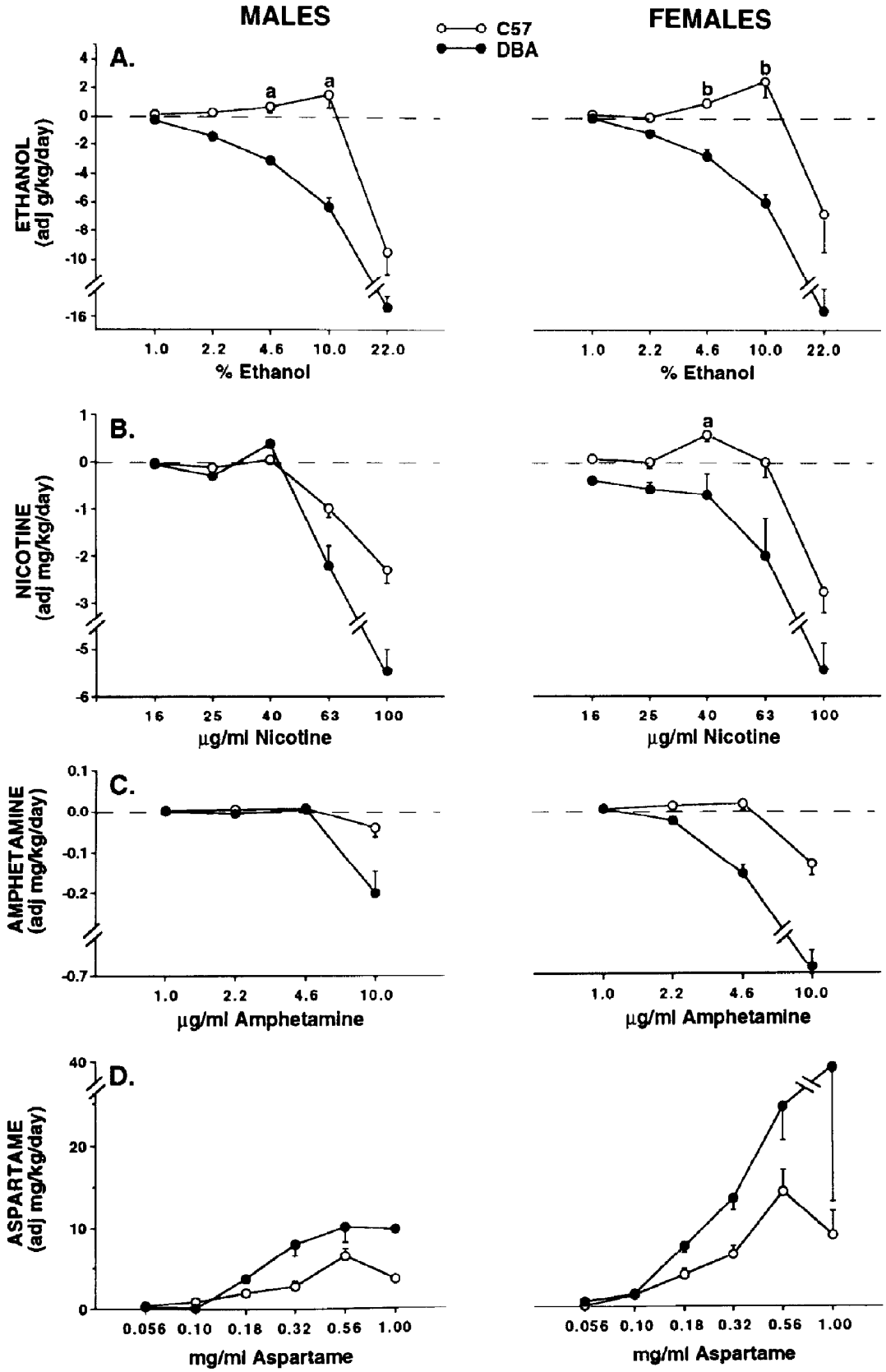

FIG. 1. Two-bottle choice consumption, adjusted for individual differences in total fluid ingestion, of (A) ethanol, (B) nicotine, (C) amphetamine, and (D) aspartame in male and female C57BL/6 and DBA/2 mice (N = 9 to 11/group). Vertical bars represent standard errors. Lower-case letters denote adjusted consumption means that are significantly greater than chance expectation (i.e., 0.0): a = $p < 0.05$; b = $p < 0.01$.

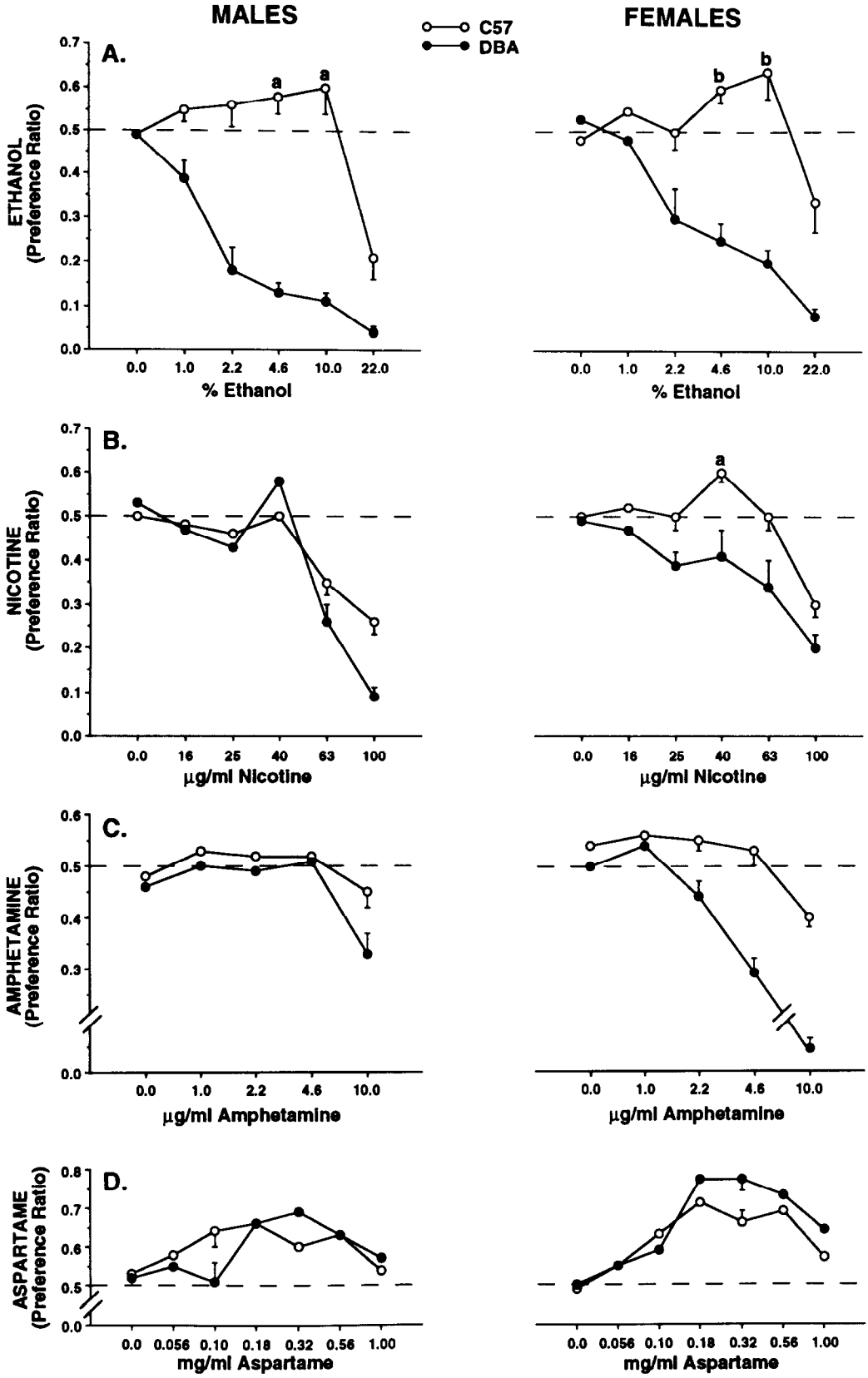

FIG. 2. Two-bottle choice preference ratios for (A) ethanol, (B) nicotine, (C) amphetamine, and (D) aspartame in male and female C57BL/6 and DBA/2 mice (N = 9 to 11/group). Vertical bars represent standard errors. Lowercase letters denote preference ratio means that are significantly greater than chance expectation (PR = 0.50): a = $p < 0.05$; b = $p < 0.01$: a = $p < 0.05$; b = $p < 0.01$.

TABLE 2

PARTIAL CORRELATIONS, CONTROLLING FOR GENDER AND STRAIN, FOR ETHANOL, NICOTINE, AMPHETAMINE, AND ASPARTAME CONSUMPTION AND PREFERENCE

	Ethanol	Nicotine	Amphetamine	Aspartame
A. Adjusted consumption				
Ethanol		.545*	.235	.426†
Nicotine			.499*	.160
Amphetamine				.198
B. Preference ratios				
Ethanol		.389†	−.019	.304‡
Nicotine			.383†	.324‡
Amphetamine				.272‡

Analyses were performed on means across all concentrations tested. Significance levels (one-tailed): *$p < 0.001$; †$p < 0.01$; ‡$p < 0.05$.

were NIC and AMP consumption and preference (Table 2). Thus, high-ethanol-consuming mice tended to ingest more NIC than did low-ethanol-consuming mice, within both strains (Fig. 3). Furthermore, even though DBAs consumed more ASP than C57s, ASP consumption was positively correlated with ETH consumption within strains (Fig. 4). As Table 2B indicates, preference for ASP was also modestly but significantly correlated with preferences for ETH, as well as for NIC and AMP.

Summary

Consumption and preference for ETH, NIC, AMP, and ASP was dependent on gender, strain, and concentration of the substances presented. Overall, C57s consumed more and showed greater preferences for ETH, NIC, and AMP than did DBAs. In contrast, DBAs consumed and preferred ASP more than did C57s. Overall, consumption and preference measures for the different substances were modestly but significantly intercorrelated when contributions of strain and gender were controlled for statistically.

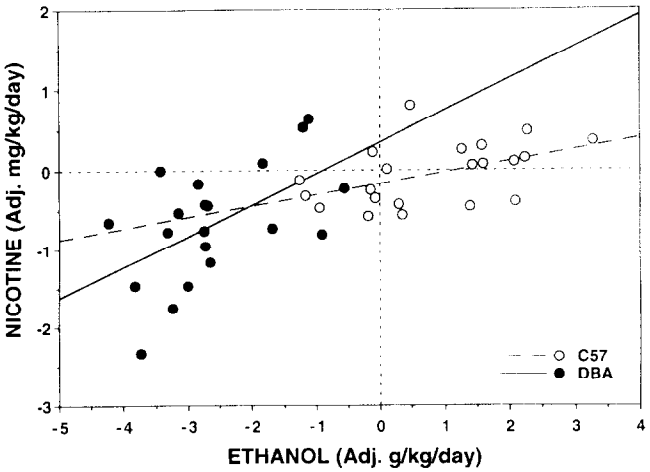

FIG. 3. Relationship between (adjusted) ethanol and nicotine consumption in C57 and DBA mice. Separate regression lines for C57s and for DBAs were fitted by the least-squares method.

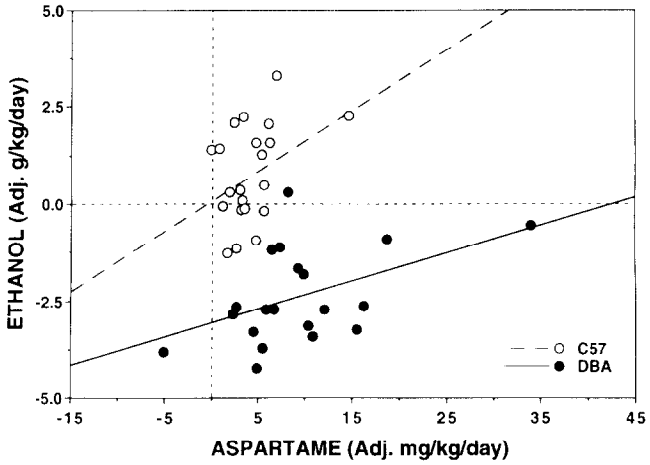

FIG. 4. Relationship between (adjusted) aspartame and ethanol consumption in C57 and DBA mice. Separate regression lines for C57s and for DBAs were fitted by the least-squares method.

DISCUSSION

Differences between C57BL/6 and DBA/2 mice in two-bottle choice consumption and preference for ETH comparable to those observed here are widely reported (1,20,24). The present study is the first to compare the C57BL/6 and DBA/2 strains with respect to oral self-administration of NIC, AMP, and ASP, and to determine intercorrelations between measures of consumption of these substances in the same animals. Our results reveal a high degree of concordance in the measures of consumption of some of these substances.

For example, ETH and NIC consumption and preferences were positively correlated when gender and strain differences were controlled for statistically. After adjusting for differences in total fluid ingestion, consumption of NIC was also greater in C57s than in DBAs, particularly among females, which also exhibited a significant preference (PR > 0.50) for the 40 μg/ml concentration. Although robust oral NIC consumption by laboratory rodents is not widely reported, Collins and Marks (5) found that C57BL/6 mice (gender unspecified) consumed in excess of 12 mg/kg per day of NIC (unadjusted) when presented with nicotine in concentrations of 100 μg/ml or more. In that study, C57s also showed greater preferences for NIC solutions than mice from the A/J strain. Collins and Marks interpreted their findings as evidence of strain differences in sensitivity to the rewarding effects of NIC. A plausible alternative interpretation is that increased NIC consumption reflects reduced aversive effects of NIC in the C57BL/6, relative to the DBA/2 strain. Together with the present results, these findings suggest that inbred mouse strains may be valuable in studies of nicotine self-administration.

D-Amphetamine administered by injection is reinforcing in rodents (34,35), but an outright preference for oral consumption of AMP using the two-bottle choice paradigm has not been reported. Although C57s consumed more AMP than did DBAs in the present study, quantities consumed were small, and a significant preference (PR > 0.5) for AMP was not exhibited at any concentration tested. This suggests that unlike oral cocaine (14,25; unpublished results, this laboratory), AMP does not sustain oral consumption in mice. That oral AMP is actually aversive to rodents (18) is suggested by the fact that taste aversions to saccharin have been conditioned in rodents when concentrations as low as 10 μg/ml AMP are

presented in highly palatable solutions of saccharin (29) or ASP (unpublished results, this laboratory). The present findings suggest that aversive taste may limit oral AMP ingestion, but C57s may be somewhat more tolerant to these aversive effects than DBAs. A similar tolerance to the aversive taste of nicotine could have contributed to the positive correlation between measures of AMP and NIC self-administration we observed.

Because high-ethanol-consuming lines of rats and mice consume and prefer saccharin solutions more than low-ethanol-consuming lines (1,9,26,32), we expected C57s to ingest more of the nonnutritive sweetener aspartame than DBAs. In fact, C57s consumed less and exhibited lower preferences for ASP than did DBAs. Thus, the group data fail to confirm the expected relationship between consumption of a sweet substance and consumption of ETH, NIC, and AMP in mice. Although an explanation for the disparity between our results and those reported previously with ETH and saccharin is not readily apparent, it is possible that ASP and saccharin are discriminably different to mice, with ASP being relatively more palatable to DBAs than to C57s. Saccharin's taste is complex, and includes an aversive component (7) that may cause C57s and DBAs to react differently to it than they do to ASP. It is also possible that the particular sequence of drug tests used in the present study—i.e., presentation of ETH, NIC, and AMP solutions before presenting ASP—modified preferences of the two strains for sweet-tasting substances. Thus, prior exposure to unpalatable solutions may have conditioned DBAs to prefer the sweet-tasting ASP more than C57s. Confounding effects of sequence of drug testing could have been reduced or eliminated had the present study incorporated a random order of drug presentation, or a systematic crossover design. Furthermore, testing animals' consumption of saccharin at the conclusion of the ASP trials may have clarified whether the observed results were unique to ASP, and may have revealed whether prior exposure to the other substances had changed the animals' preferences for sweet-tasting substances.

Nevertheless, ASP consumption and preference correlated positively with ETH consumption and preference within strains (i.e., when gender and strain differences were controlled for statistically). Notably, ASP preference (but not consumption) also correlated modestly positively with preferences for NIC and AMP. Thus, the present results confirm an association between preference for sweet-tasting substances and preference for ETH within C57 and DBA strains, while suggesting that sweet consumption may also be predictive of consumption of other abused substances.

Strain differences in oral drug consumption are likely to reflect both "preingestional" (peripheral/taste) as well as "postingestional" (central/pharmacologic) factors (15,27). For example, enhancing palatability by sweetening solutions with saccharin increases ETH consumption in ethanol-preferring C57BL/6 mice; but ethanol-avoiding DBA/2 mice, which consume saccharin solutions in preference to tapwater, avoid even sweetened ETH solutions (1), which suggests that postingestional effects of ETH are aversive to DBAs. Similarly, whereas C57s consume solutions of morphine plus quinine in preference to comparably bitter solutions of quinine alone, DBAs show no such preference for morphine plus quinine (9). This suggests that postingestional/pharmacologic effects modulate morphine-quinine consumption in C57s, but not in DBAs. Thus, whereas peripheral/taste factors influence oral ingestion of ethanol and other drugs, postingestional factors may account for at least some of the observed differences between strains in ethanol and drug consumption.

Rodent strains that ingest larger quantities of ETH also tend to self-administer larger quantities of opiates and psychomotor stimulants than do strains that consume less ETH. For example, a concordance between operant self-administration of ethanol, cocaine, and opiates has been noted in C57 and DBA mice (3,14,30). In humans, higher levels of alcohol use tend to be associated with higher levels of tobacco use (10,23). Together with the positive correlations between NIC and ETH consumption we observed, these findings support the notion that common reward mechanisms mediate reinforcement from ethanol and other abused substances (4,15). Various lines of evidence suggest that many psychoactive drugs share the capacity to enhance dopaminergic transmission within mesolimbic reward circuits (19,36). Thus, individual differences in mesolimbic dopaminergic function may mediate some of the observed strain differences in self-administration of ethanol and other drugs (16,28).

Finally, it would be valuable to determine whether the quantities of drugs ingested in studies such as the present one produce intoxication or other pharmacologically relevant effects in test animals. Rats display motor incoordination when ETH is administered in a single oral bolus in doses as low as 0.5–1.0 g/kg (21). Rats will also ingest comparable quantities of ETH within an hour when it is available in a limited access paradigm (22,31). With access limited to an hour, mice of the C57BL/6 strain have been reported to consume in excess of 1.6 g/kg, achieving blood alcohol levels of 60 mg% (20). Consumption of 5.6 g/kg of ETH in 30 min of operant responding was reported to induce intoxication to the point of loss of righting reflex in C57BL/6 mice (8). Whether signs of intoxication or other behavioral manifestations reliably accompany oral ingestion of quantities of ETH, NIC, and AMP like those consumed in the present study remains to be established.

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