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# Preabsorptive vs. Postabsorptive Control of Ethanol Intake in C57BL/6J and DBA/2J Mice

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*Experimentally naive male mice of both strains were exposed to a two-bottle choice situation (ethanol vs. water) and their drinking behavior was observed during the first hour. DBA/2J mice developed a significant avoidance of 2% or 10% ethanol during the first 10 min. At 15 and 60 min following introduction of the bottles, no DBA mouse exhibited more than a 6 mg % blood ethanol level while all of the C57BL mice exceeded this concentration. Significant postabsorptive effects in the DBA mice seem unlikely at these very low blood ethanol values. Animals of both strains were examined for their ability to form lithium-induced conditioned taste aversions to 2% ethanol or 15% sucrose solutions. DBA mice readily formed conditioned aversions to both solutions, but the C57BL strain significantly avoided only the sucrose. C57BL mice appear to have difficulty in discriminating the 2% ethanol from distilled water. The neural sensitivity to ethanol was examined in both strains using the sleep time test and the grid test. C57BL mice were significantly more sensitive than DBA mice in both tests.*

**KEY WORDS:** alcohol (ethanol) preference; sleep time test; lithium-induced conditioned aversion; C57BL and DBA mice.

## INTRODUCTION

Inbred mice differ markedly in their alcohol consumption when presented with a two-bottle choice situation (ethanol vs. water) for several days. The largest differences reported are between mice of the DBA/2 strain, which exhibit a strong avoidance of ethanol, and C57BL mice, which usually show

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a preference for a 10% (v/v) ethanol solution over water. Five- to fifteenfold differences in daily ethanol consumption have been reported between C57BL and DBA/2 mice (McClearn, 1968; Fuller, 1964; Rodgers, 1972).

Since mice do not become grossly intoxicated in the ethanol vs. water choice situation, it is evident that some type of ethanol intake control mechanism(s) operates to prevent the ingestion of toxic quantities of ethanol. Considerable effort has been made to elucidate the biochemical or physiological mechanisms responsible for the control of ethanol intake, largely in the hope of discovering the mediating biochemical events between gene action at the cellular level and at the level of the organism (e.g., behavior). Some of the mechanisms which have been proposed and investigated are the rate of ethanol metabolism (Rodgers *et al.*, 1963; Thiessen *et al.*, 1966, 1967; Schlesinger, 1966), neural sensitivity to the intoxicating effects of ethanol (Kakihana *et al.*, 1966; Schneider *et al.*, 1973), nutritional factors (Mirone, 1957), and toxic acetaldehyde accumulation following ethanol ingestion (Schlesinger *et al.*, 1966; Sheppard *et al.*, 1968, 1970; Horowitz and Whitney, 1975). All of these proposed mechanisms assume that pharmacologically significant amounts of ethanol must be, at some point, absorbed into the bloodstream from the gastrointestinal tract. Therefore, these mechanisms can operate only postabsorptively (following absorption into the blood). In contrast, possible preabsorptive mechanisms (those operating prior to the absorption of ethanol into the blood) such as taste, odor, and mucosal irritation have been relatively little studied experimentally, even though the suggestion has often been made that they may be important (Rodgers, 1972; Rodgers and McClearn, 1962; Fuller, 1967; Nachman *et al.*, 1971; LeMagnen, 1972; Wilson, 1972). In addition, preabsorptive and postabsorptive mechanisms could interact, as would be the case if preabsorptive cues (e.g., taste) became a conditioned stimulus through pairing with aversive postabsorptive consequences (e.g., intoxication).

## EXPERIMENT 1

The purpose of this experiment was to observe the development of ethanol avoidance by DBA/2J mice (and the associated blood ethanol levels) at the earliest time an avoidance could be demonstrated.

### Method

Twenty-two DBA/2J and 15 C57BL/6J males were presented with 10% (v/v) ethanol vs. water for a 60-min test period beginning 1–2 hr after light offset on an automatic (12L:12D) light cycle. In like manner, a group of 17 DBA/2J males were presented with 2% (v/v) ethanol vs. water. The subjects

were 14–18 weeks old and were without any prior exposure to alcohol or other experimental treatments. Two to four hours prior to preference testing, the mice were housed singly and deprived of food and water until the time of testing. This was done to ensure that some drinking would occur in most of the animals during the test period without producing so much thirst that the animals would drink indiscriminantly from the first bottle encountered. In spite of these measures, some of the mice failed to drink at least three times during the 60-min test period and were therefore eliminated from the study. The animals which surpassed the three drink or more criterion were 16 DBA/2J and ten C57BL/6J mice given 10% ethanol vs. water and 13 DBA/2J given 2% ethanol vs. water. For these animals, the mean total fluid consumption during the test period was about 0.3 ml for both strains given 10% ethanol vs. water and 0.4 ml for the 2% ethanol vs. water group. Since the volume of fluid consumed was so low and thus was difficult to quantify, the preference ratios were based on the number of drinks taken from the ethanol bottle divided by the total from both bottles. A drink was defined as an episode where an animal's tongue was clearly seen to make contact with the fluid in the sipper tube by an observer who was blind as to the bottle contents. A drink involved from one to several licks in quick succession. The ethanol bottle was presented equally often on the left or right side of the cage. Graduated 25-ml cylinders served as bottles which were placed 8 cm apart near the middle of the cage, with the drinking tips about 5 cm above the floor. Food was available, which typically allowed a series of alternations between eating and drinking throughout the test period.

Throughout this paper, two-tailed $t$ tests were employed except where noted. Fluids were freshly prepared each day using distilled water and 95% ethanol.

At the end of the 60-min preference test period, 10-$\mu$l blood samples were taken from the suborbital sinus of eight DBA and eight C57BL mice presented with 10% ethanol vs. water. The samples were promptly diluted tenfold in 0.9% saline and centrifuged at 3000$g$ for 5 min to remove blood cells. Four microliters of the diluted plasma was then injected onto a ¼-inch by 5-ft. Porapak Q column (130°C) in a Carle model 211 gas chromatograph (FID) at an amplifier attenuation of 20. Retention time was 7 min at a flow rate (He) of 80 ml/min. Blood samples taken from mice not exposed to ethanol were used as blanks. Mice assayed for blood ethanol did not differ in ethanol preference or consumption from those not assayed.

Eight additional DBA/2J mice were subjected to the same procedure outlined above except that they were sacrificed by decapitation 15 min after introduction of the 10% ethanol vs. water choice situation. All blood ethanol concentrations (BEC) are expressed as milligram percent.

## Results

The alcohol preference scores for each 10-min interval during the 60-min test period are shown in Fig. 1. The avoidance of ethanol by the DBA/2J mice was statistically significant in the first 10 min of exposure to the two-bottle choice situation for either the 10% ethanol ($\chi^2$, $p < 0.01$) or 2% ethanol ($\chi^2$, $p < 0.01$) groups. The ethanol avoidance persisted throughout the test period ($\chi^2$, $p < 0.001$ for either group). In contrast, the C57BL mice did not differ from a 50% ethanol preference ratio at any 10-min interval during the test period, although there is an overall trend toward a slight preference. No significant departure from a 50% ratio was evident for the very first drink taken by the animals in any of the three groups ($\chi^2$, $p$'s $> 0.2$).

These data were also analyzed as blocks of three successive drinks instead of time intervals. A statistically significant avoidance of ethanol by the DBA mice was evident by the end of the first block of three drinks for the 10% ethanol group and by the second block for the 2% group ($\chi^2$, $p$'s $< 0.01$). For the 10% group, a statistically significant avoidance of ethanol was demonstrable at a time when the animals had averaged only one drink from the 10% ethanol bottle. Completion of the first block required an average of 14 min following presentation of the bottles.

Table I summarizes the data over the entire test period for the DBA and C57BL mice exposed to 10% ethanol vs. water. Also shown are the blood ethanol concentrations (BEC) at the end of the 60-min period. The

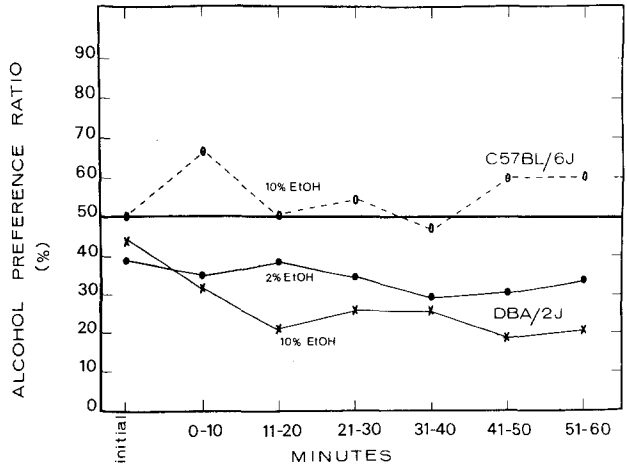


**Fig. 1.** Alcohol preference ratios for each 10-min interval and the very first drink taken ("initial"). These ratios are based on the number of drinks taken from the ethanol bottle divided by the total number taken from both bottles.

**Table I.** Consumption and Blood Ethanol Data for the 60-min Choice Period for 10% Ethanol vs. Water (means ± SD)

| | *N* | Mean preference ratio | EtOH drinks | 10% EtOH consumed (ml) | Mean blood EtOH (mg %)[a] |
|---|---|---|---|---|---|
| C57BL/6J | 10 | 55% | 7.2 ± 4.6 | 0.19 ± 0.12 | 13.6 ± 8.6 |
| DBA/2J | 16 | 26% | 3.3 ± 2.0 | 0.04 ± 0.05 | 1.0 ± 2.1 |

[a] Based on eight animals per strain.

C57BL mice took over twice as many drinks (and consumed a much larger volume) from the 10% ethanol bottle than did the DBA mice ($p$'s $< 0.01$), while the total number of drinks from both bottles and total fluid volume consumed did not differ between strains. It should be noted that the volume consumed is subject to considerable error since the graduated cylinders employed were accurate only to the nearest 0.1 ml.

The mean BEC for the C57BL mice at the end of the test period was significantly greater than that of the DBA mice ($p < 0.005$), largely because five of the eight DBA mice sampled did not attain measurable levels of blood ethanol. The GC assay employed has a detection limit of about 0.2 mg %. The acetaldehyde levels were too small to be reliably detected. The small amounts of ingested ethanol must first pass through the hepatic portal system where most of the ethanol is apparently metabolized before it can enter the systemic circulation.

The eight DBA mice sacrificed 15 min after introduction of the 10% ethanol and water bottles showed a mean BEC (±SD) of 1.2 ± 1.9 mg %, a value very similar to the 1.0 mg % found in the DBA mice sampled after 60 min. At the time of sacrifice, the mean ethanol preference ratio was 0.33. Four of these animals did not attain a measurable BEC. For both groups of DBA mice sampled for BEC, there was essentially no correlation between the ethanol preference ratio and the BEC when the groups were considered separately or when they were pooled ($r$'s $\leq 0.24$, n.s.). The BECs found in the DBA mice are so low that significant postabsorptive effects seem unlikely.

## EXPERIMENT 2

The purpose of this experiment was to determine strain differences in the capacity to develop a lithium-induced conditioned aversion to the taste of ethanol. The stimulus saliency of ethanol ingestion for DBA and C57BL mice could then be estimated using an experimental design patterned after that of Nachman *et al.* (1971).

## METHOD

Twenty-seven 14-week-old male mice from each strain were placed on a restricted water access schedule (90 min each day) for 4 days. Fluid consumption for the first 10 min was recorded daily. Food was freely available throughout the experiment except for this 10-min period. Four days were allowed to ensure that the animals would drink readily during the 10-min test period. On the fifth day, nine mice of each strain were given 10 min access to a 2% (v/v) ethanol solution (pretest), followed 3 min later by an i.p. 3 mEq/kg injection of isotonic (0.15 M) LiCl. On days 6–8, the animals were restabilized on the 90-min daily water access schedule followed, on day 9, by a 10-min reexposure to the 2% ethanol solution (posttest). Another group of nine animals per strain was treated identically except that 15% sucrose was given as the test solution on days 5 and 9 instead of ethanol. A 2% ethanol concentration was chosen in order to ensure approximately equal consumption for both strains upon first exposure on day 5. At higher ethanol concentrations (e.g., 10%), DBA mice consume much less than C57BL mice (unpublished observation). A control group ($N$ = 9 for each strain) was treated identically to the 2% ethanol groups except that no lithium was given.

### Results

The LiCl-induced taste aversion data are shown in Fig. 2. The DBA mice showed a highly significant ($p < 0.01$) reduction in ethanol intake following lithium treatment (posttest) relative to the first exposure (pretest). In contrast, the C57BL mice showed little indication of a conditioned aversion to the 2% ethanol solution. Both strains, however, showed a highly significant ($p < 0.01$) conditioned aversion to the 15% sucrose solution, indicating that both strains are fully capable of forming conditioned aversions under these conditions. The control groups of both strains (not shown) exhibited a small (about 11%) increase in ethanol consumption in the posttest vs. the pretest. Exposure to only the 2% ethanol on day 5 (1.07 ml, C57BL; 1.02 ml, DBA) in an amount equivalent to a dose of 0.7 g/kg produced no conditioned aversion to 2% ethanol for either strain. The amount of water consumed in 10 min on days 4 and 8 (1 day prior to the alcohol or sucrose presentations) did not differ between strains for either the lithium-injected or control groups ($p$'s > 0.2).

## EXPERIMENT 3

The purpose of this experiment was to assess the nervous system sensitivity to ethanol in both strains by means of the sleep time test and the grid test.

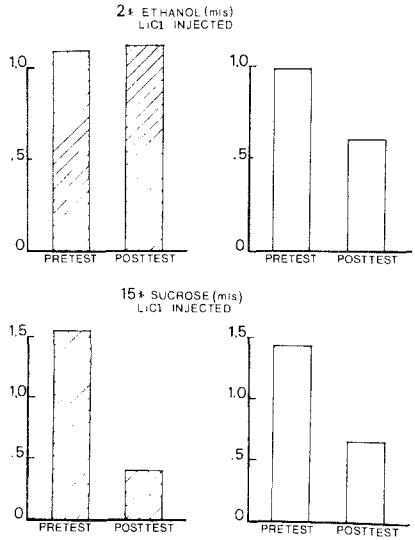


**Fig. 2.** Ten-minute fluid consumption (ml) before and after an injection of LiCl for animals exposed to 2% ethanol (top row) or 15% sucrose. The C57 mice are represented by the cross-hatched bars, the DBA mice by the open bars.

## Method

The duration of loss of the righting reflex was determined in four groups of five male mice of each strain given a single dose of 2.5, 2.7, 3.0, or 3.4 g/kg, respectively, of ethanol given i.p. as a 25% (v/v) solution in 0.9% saline. The details of this procedure have been described elsewhere (Belknap *et al.*, 1972). Animals were 14–16 weeks of age and were tested 3–4 hr after light onset.

The grid test was administered to four additional groups of five male mice of each strain given a single dose of 1.2, 1.7, 2.2, or 2.5 g/kg, respectively, of ethanol given i.p. as a 25% (v/v) solution in 0.9% saline. The injections were given 10 min before testing at about 3 hr after light onset. The grid test is a measure of neuromuscular impairment, which is sensitive to drug-induced stumbling or staggering at low to moderate dose ranges. A mouse is required to walk along a 3-cm-wide alley laid out in the form of a square with a ½-inch wire mesh floor (grid) and bounded by 15-cm-high walls. Intoxicated mice stumble frequently, with one or more feet passing through the grid and contacting an underlying plate suspended below the grid. An error is scored whenever contact is made with the plate, which is resting on the pan of a top-loading balance. This arrangement prevents the plate from supporting the animal's body weight. The grid test score is the number of errors per unit distance traversed (12 cm) during a 2-min test period. Since mice are highly thigmotaxic, the enclosed alley arrangement

elicits a high level of ambulation without freezing or crouching. The details of the apparatus and procedure have been described elsewhere (Belknap, 1975).

## Results

The duration of loss of the righting reflex (sleep time) was significantly longer in the DBA (vs. C57BL) mice at the two highest doses employed (3.0 and 3.4 g/kg, $p$'s $< 0.05$). However, the strain differences were reversed at the two lowest doses employed ($p < 0.05$, 2.5 and 2.7 g/kg groups pooled), with the DBA mice sleeping less than half as long as the C57BL mice. These data are shown in Fig. 3. The dose–response plots are essentially linear except for the lowest dose given to the DBA mice. This is probably due to a "floor effect" since three of the five animals failed to lose the righting reflex and were thus assigned a score of zero. This situation did not arise with any of the other groups. If the $X$ intercepts of the linear regression lines are used as estimates of the minimum dose necessary to produce loss of the righting reflex (Damjanovich and MacInnes, 1973), then the C57BL mice exhibited a greater neural sensitivity to ethanol than did the DBA mice. The greater DBA (vs. C57BL) sleep times at the higher doses are probably due to differences in the rate of ethanol metabolism (Damjanovich and MacInnes, 1973). At the lower doses, which produce very short sleep times, any differences in rate of metabolism would probably not have suffi-

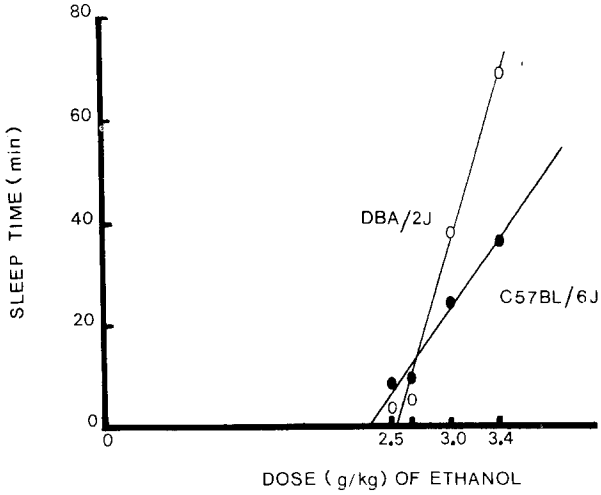


**Fig. 3.** Sleep times as a function of ethanol dose. The linear regression lines are also shown. Each point represents five mice which were injected only once.

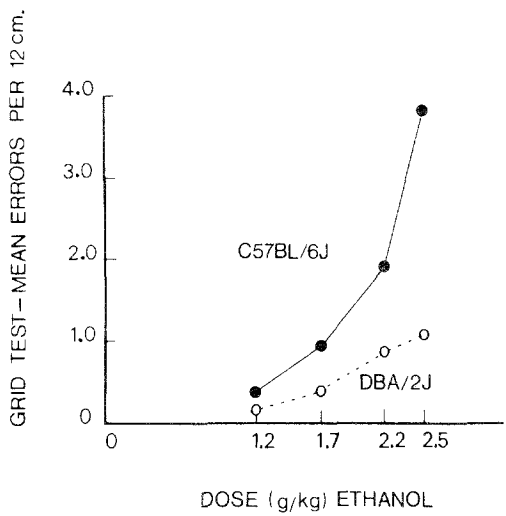


**Fig. 4.** Grid test scores as a function of ethanol dose. Each point represents five mice which were injected only once. Animals of both strains injected with saline (not shown) score at essentially zero (0.05 errors per 12 cm).

cient time to operate in order to produce an appreciable effect. The time interval between injection and loss of the righting reflex (induction time) for all doses was not significantly different between strains, although there was a trend toward shorter induction times for the C57BL mice.

In the grid test also (shown in Fig. 4), the C57BL mice proved to be significantly more sensitive to the intoxicating effects of ethanol than were the DBA mice at the three highest doses employed ($p$'s $< 0.05$). The grid test scores were roughly twice as great at all four doses in the C57BL (vs. DBA) mice.

## DISCUSSION

The avoidance of ethanol by DBA mice develops quickly at a time when the BECs are so low as to be barely detectable (Experiment 1). Two possibilities follow from this: either (1) DBA mice are so exquisitely sensitive to ethanol, or its metabolites, that even these low BECs are sufficient to produce aversive postabsorptive effects, or (2) postabsorptive effects are insignificant as a cause of ethanol avoidance development. The latter possibility seems more likely in view of the very low BECs observed and the essentially zero correlation between BEC and ethanol avoidance.

Over a period of several days, most of the 23 DBA/2 mice studied by Thomas (1969) avoided ethanol (vs. water) when the ethanol concentration

in the bottles was as low as 0.01% (v/v), and all of them avoided a 0.1% solution. This is equivalent to a daily intake, per mouse, of less than 0.3 $\mu$l of absolute ethanol for the 0.01% concentration. Significant postabsorptive effects seem unlikely with such small amounts, especially if the ethanol ingestion is distributed throughout a large part of the dark hours.

The observation that C57BL mice are deficient in their ability to form lithium-induced aversions to 2% ethanol (Experiment 2) suggests that the ethanol solution lacks stimulus saliency for the C57BL mice relative to DBA mice. Apparently, C57BL mice have difficulty in discriminating the 2% ethanol solution from the distilled water. A similar deficiency in C57BL mice was noted by Nachman *et al.* (1971) with respect to 6.7% ethanol, but not 0.1% saccharin or 15% sucrose. Under the same conditions, BALB/c mice (an ethanol-avoiding strain) readily formed lithium-induced aversions to all three fluids. In contrast to the ethanol-avoiding strains, preabsorptive factors appear to be relatively unimportant in C57BL mice. Bilateral removal of the olfactory bulbs abolished the avoidance of 10% ethanol normally shown in BALB/c mice, while having no effect on the ethanol preference usually seen in C57BL mice (Nachman *et al.*, 1971). Removal of the anterior third of the cerebrum, including the olfactory bulbs, increased the ethanol preference ratio in A and BALB/c mice (Rodgers and McClearn, 1962). When C57BL mice were injected with ethanol, a reduction in voluntary 10% ethanol consumption occurred in the ensuing 24 hr which approximated the amount injected (McClearn and Nichols, 1970). Thus elimination of preabsorptive stimuli by injection had little or no effect on the self-regulation of daily ethanol exposure. Thiessen *et al.* (1967) reported that ethanol consumption in lactating C57BL females increased roughly in proportion to increases in liver size and rate of ethanol metabolism, suggesting that ethanol intake is a function of metabolic capacity in this strain. The amount of ethanol consumed daily by C57BL mice roughly approximates their metabolic capacity (Thiessen *et al.*, 1967; Rodgers, 1967), while DBA mice consume only a small fraction of their metabolic capacity.

An important consideration is whether the experience of being intoxicated is more aversive for one strain than for the other. Fuller (1967) adapted C57BL and DBA/2 mice to a 15-min-per-day water access schedule for 1 week, followed by 5 days of 5 min daily access to an 8% ethanol vs. water choice situation. Overt intoxication was produced, yet the reduction (about $\frac{1}{3}$) in the ethanol preference ratio was about the same in both strains over the five daily test sessions. It would appear that the conditioned aversion to ethanol induced by ethanol intoxication is about the same in both strains. Horowitz and Whitney (1975) tested the conditioned aversion to a 0.7% saccharin test solution induced by 5, 10, or 20% ethanol i.p.

injections. The DBA/2 strain displayed a markedly greater conditioned aversion to saccharin than did C57BL mice, suggesting that the ethanol injection was more aversive for the DBA mice. These results suggest the reverse rank order than the Fuller (1967) report, which is probably attributable to the different routes of ethanol administration and the experimental designs employed.

The sleep time and grid test results (Experiment 3) suggest that C57BL mice are more sensitive to the effects of ethanol relative to DBA mice in the range of doses studied. The sleep time results are in agreement with those reported by Damjanovich and MacInnes (1973). In addition, these authors found that C57BL mice were more sensitive than DBA mice (and less sensitive than BALB/c mice) to the effects of ethanol as determined by the BECs at the time of "waking" from the sleep time test and the fall time (time interval between ethanol injection and loss of ability to cling to a vertically placed wire mesh). Whitney and Whitney (1968) found that C57BL mice were more likely than AKR, BALB, and DBA/8 mice to suffer lethal effects from a large i.p. dose of ethanol; however, only the C57 vs. AKR comparison was significant. Differing results were reported by Schneider *et al.* (1973), who found that DBA mice were more susceptible than C57BL mice to ethanol-induced suppression of the jaw jerk reflex in barbital-anesthetized animals. However, the authors report no data on possible strain differences in the sensitivity of the jaw jerk reflex to the barbital anesthesia alone. Lin (1975) reported that blood and brain ethanol levels were higher upon regaining the righting reflex in starved (16-hr food deprived) C57BL/6J mice compared with starved DBA/2J mice. The dose was 4.2 g/kg, which produced a 30% mortality in this sample. The DBA mice had a median sleep time of 4½ hr, which was almost four times greater than that observed in the C57 mice. It is possible that the findings of this study pertaining to neural sensitivity are confounded by the greater physical weakness induced in the DBA mice by several hours of near lethal respiratory depression and body temperature loss. Overall, it would appear that the matter of neural sensitivity differences between DBA and C57BL mice must remain somewhat inconclusive. However, it seems likely that the strain differences involved are small relative to the differences in alcohol preference or voluntary alcohol consumption. Of course, it must be borne in mind that the doses used in these studies (and the resulting BEC) are far greater than those found in alcohol preference experiments. Neural sensitivity at very small doses may present a very different picture from that seen at anesthetic doses.

The data reviewed here suggest that the ethanol intake control mechanisms are, to a large extent, qualitatively different in these two strains. Preabsorptive mechanisms seem to predominate in DBA mice,

while postabsorptive mechanisms probably predominate in the control of ethanol intake by C57BL mice.

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