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DBA/2J mice develop stronger lithium chloride-induced conditioned taste and place aversions than C57BL/6J mice

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Abstract

Genetic differences in lithium-induced conditioned aversion were examined using both place- and taste-conditioning procedures. In the place-conditioning procedure, adult male C57BL/6J (B6) and DBA/2J (D2) mice were exposed to a differential conditioning procedure in which each mouse received four 30-min pairings of a distinctive floor cue immediately after IP injections of either 0.75, 1.5, or 3.0 mEq/kg LiCl. A different floor cue was paired with saline injections. A separate group of control mice received saline injections paired with both floor types. Subsequent floor preference testing revealed greater conditioned aversion in D2 mice compared to B6 mice in groups receiving 3.0 mEq/kg LiCl. Lower LiCl doses did not produce conditioning in either strain. In a conditioned taste-aversion procedure, fluid-restricted mice received four trials in which access to 0.2 M NaCl solution was followed by IP injection of either 0.75, 1.5, 3.0, or 6.0 mEq/kg LiCl. D2 mice showed stronger conditioned taste aversion than B6 mice at all doses, suggesting that taste conditioning may be a more sensitive index of aversive drug sensitivity than place conditioning. These findings are not well explained by strain differences in general learning ability or by strain differences in stimulus salience or innate preference. Rather, these data appear more consistent with previous studies showing strain differences in lithium pharmacokinetics and in general sensitivity to aversive events.

Keywords: Lithium chloride; Conditioned place aversion; Conditioned taste aversion; Inbred mice; C57BL/6J; DBA/2J

1. Introduction

Studies aimed at characterizing genetic differences in effects of alcohol and other abused drugs have frequently used the C57BL/6J (B6) and DBA/2J (D2) inbred mouse strains because of their marked difference in various drug responses [9]. Interest in these two strains has also been encouraged by an increasing number of gene-mapping studies that use the BXD recombinant inbred strains, which were originally derived from an F2 cross of the B6 and D2 strains (see review: Ref. [10]). Recently, B6 and D2 mice have been found to differ in two learning tasks commonly used to study motivational effects of abused drugs, i.e., place and taste conditioning. For example, B6 and D2 mice differ in conditioned place preference produced by morphine [15,37], ethanol [15], cocaine [13,36], amphetamine, etonitazine, and GBR 12909 [36]. These strains have also been shown to differ in conditioned taste aversion produced by ethanol [6,22,29–31] and nicotine [28].

Based on studies showing stronger conditioned place preference in B6 mice than in D2 mice with several different drugs (cocaine, amphetamine, etonitazine, GBR 12909), Seale and Carney [36] concluded that D2 mice display a "generalized abnormality in appetitive/hedonic responsiveness." However, this conclusion was not supported by subsequent data showing stronger conditioned place preference in D2 mice when morphine [15,37] or ethanol [15] was used. Thus, the direction of the strain difference in sensitivity to rewarding drug effects depends on the type of drug. Other findings also suggest that differences between B6 and D2 mice in ethanol- or cocaine-induced conditioned place preference may disappear when temporal parameters of the conditioning paradigm are varied [12,13].

Because only a few drugs producing aversive effects have been studied in these strains, conclusions about strain

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differences in sensitivity to such effects are limited. In general, D2 mice appear to be more sensitive than B6 mice to aversive effects of ethanol [6,22,29–31] and nicotine [28] in the taste-conditioning task. D2 mice are also more sensitive to aversive effects of the alcohol metabolite acetaldehyde in this task [16]. In the place-conditioning paradigm, there appears to be only one comparison of these strains in which an abused drug produced an aversive effect. Specifically, Seale and Carney [36] reported that amphetamine produced a conditioned aversion in D2 mice but a conditioned preference in B6 mice (doses not specified).

Based on the aforementioned data, one might speculate that D2 mice are generally "hyperresponsive" to aversive drug effects. However, the literature on relative sensitivity of B6 and D2 mice to a commonly used aversive drug, lithium chloride (LiCl), is rather equivocal at present. In several studies, a single pairing of a sweet tasting solution (saccharin or sucrose) with LiCl (1.5–3.0 mEq/kg) produced similar conditioned taste aversion in both strains [2,3,16]. When a low concentration of ethanol (e.g., 2% v/v) was used as the taste stimulus, B6 mice developed weaker conditioned aversions than D2 mice [2,3]. However, this outcome was attributed to strain differences in salience of the ethanol taste stimulus, not to strain differences in sensitivity to LiCl's aversive effects. In another study involving a very wide range of LiCl doses (1.5 to 12 mEq), a single sucrose–lithium pairing also failed to produce strain differences in taste aversion, although a follow-up study found greater resistance to extinction in D2 mice at a high LiCl dose (6 mEq/kg; [23]). Overall, published LiCl studies provide relatively weak support for a greater sensitivity to aversive drug effects in D2 mice.

The present experiments extended previous research on genetic differences in LiCl-induced conditioned aversions in two ways. First, we compared aversions produced in B6 and D2 mice using a place-conditioning task found to distinguish these strains in response to ethanol [12,15], morphine [15], and cocaine [13]. This task has not previously been used to study inbred strain differences in LiCl's aversive effects. Further, the present procedure allowed for the determination of locomotor activity during conditioning and testing. Strain differences in locomotor activity levels have the potential to influence performance in this task [12]. Activity is also useful as an independent measure of LiCl's behavioral effects. Second, we examined development of conditioned taste aversion using a multiple-trial taste-conditioning protocol. This protocol utilized a saline solution as the taste stimulus, with a 60-min access period during conditioning and test trials. A similar procedure has been used to determine B6/D2 differences in development of ethanol- and nicotine-induced conditioned taste aversion [28–30]. Although sweet solutions (e.g., saccharin) are often used in taste-conditioning procedures, saline is more effective in conditioning taste aversion with these strains [30]. In addition, long duration conditioning and test trials offer greater opportunity for extinction. As indicated above, previous studies of LiCl-induced taste conditioning in these strains have used one conditioning trial, sweet tastes, and short (10 min) conditioning and test trials. If D2 mice are generally more sensitive to aversive drug effects, one ought to see aversive conditioning at lower LiCl doses in D2 mice or after a fewer number of conditioning trials.

2. Materials and methods

2.1. Subjects

Adult male inbred B6 and D2 mice were obtained from the Jackson Laboratory (Bar Harbor, ME) at 6 weeks of age and allowed to acclimate to the animal colony for 2 weeks before training. In the place-conditioning experiment, groups of four mice were housed in polycarbonate cages ($27.9 \times 9.5 \times 12.7$ cm) with cob bedding in a Thoren rack. In the taste-conditioning study, mice were housed individually in hanging stainless steel cages ($24 \times 18 \times 18$ cm) with wire mesh fronts and bottoms. The colony room was maintained on a normal 12 L:12 D cycle (lights on at 0700 h) at an ambient temperature of $21 \pm 1°C$. All procedures were conducted during the light phase. Lab chow was available continuously in the home cages. Daily access to fluids was restricted in the taste-conditioning study as described below.

2.2. Apparatus

The place-conditioning apparatus consisted of 24 identical acrylic and aluminum boxes ($30 \times 15 \times 15$ cm) contained in separate ventilated, light- and sound-attenuating enclosures (Coulbourn Instruments Model E10-20). Six sets of infrared light sources and photodetectors were mounted 2.2 cm above the floor at 5-cm intervals on the long walls of each box. Occlusion of the infrared light beams was used both as a measure of general activity and to detect the animal's position (left vs. right side). Total activity counts and amount of time spent on each side of the chamber were recorded every minute by computer (10-ms resolution).

The floor of each box consisted of interchangeable halves made of one of two textures. The "grid" floor was composed of 2.3-mm stainless-steel rods mounted 6.4 mm apart in acrylic rails. The "hole" floor was made from perforated stainless steel (16 ga) with 6.4-mm round holes on 9.5-mm staggered centers. This combination of floor textures was chosen on the basis of previous studies showing that drug-naive control groups from each strain spend about half their time on each floor type during preference

tests [12,15]. The floors and inside of the box were wiped with a damp sponge and the litter paper beneath the floors was changed after each animal.

The taste-conditioning experiment was conducted in the home cages. Fluids were presented at room temperature in 25-ml graduated glass cylinders with curved stainless steel drinking spouts inserted through the fronts of the cages. Consumption was measured to the nearest 0.1 ml, and was corrected for spillage and evaporation by subtracting the mean fluid loss measured in two drinking tubes placed on an empty cage for an equal period of time.

2.3. Place-conditioning procedure

The experiment involved three phases: habituation (one session), conditioning (eight sessions), and testing (one session). Sessions were conducted 5 days a week with a 2-day break between the first four and second four conditioning sessions. Each mouse was weighed and injected (IP) immediately before being placed in the center of the apparatus for each session.

2.3.1. Habituation

The habituation session was intended to reduce the novelty and stress associated with handling, injection, and exposure to the apparatus. All mice were injected with saline and placed in the conditioning box on a smooth floor covered with paper for 5 min.

2.3.2. Conditioning

During the conditioning phase, mice from each strain were randomly assigned to a saline control group ($n=10–11$) or to one of three LiCl dose groups: 0.75, 1.5, or 3.0 mEq/kg. LiCl dose was manipulated by varying the volume of a 0.15-M solution of LiCl in sterile distilled water. Conditioning was conducted using a between-group discrimination design [7]. Within each LiCl dose group, mice were randomly assigned to one of two conditioning subgroups ($n=12–14$/subgroup) and exposed to a Pavlovian differential conditioning procedure. On all conditioning trials, subjects had access to both sides of the apparatus, and floor texture was homogeneous. On alternate days, mice in the GRID+ subgroups received LiCl prior to placement on the grid floor (CS+ trial), and saline prior to placement on the hole floor (CS − trial). In contrast, mice in the GRID − subgroups received saline before placement on the grid floor (CS − trial) and LiCl before placement on the hole floor (CS+ trial). Mice in the saline control groups received saline injections on both types of trial. Four 30-min conditioning trials of each type were given over an 8-day period; order of exposure to CS+ and CS − was counterbalanced within each subgroup. Because the two conditioning subgroups within each treatment condition were matched for overall exposure to each floor type, LiCl and saline, and differed only in the floor–LiCl contingency, any differences between the subgroups during preference testing should be attributed learning produced by the CS–drug contingency [11].

2.3.3. Place preference test

The floor preference test was given 24 h after the last conditioning trial. All subjects received a saline injection just before placement in the apparatus with half grid floor and half hole floor. Relative position of the floors (i.e., left vs. right) was counterbalanced within each subgroup. The primary dependent variable was the amount of time spent on the grid floor during the 60-min test session.

2.4. Taste-conditioning procedure

Subjects were adapted to a water restriction schedule (2 h water per day) over a 6-day period. At 48-h intervals over the next 10 days, all mice received 1-h access to a solution of NaCl (0.2 M in tap water) between 0900 and 1000 h. After all but the last exposure to NaCl, all mice received an injection of LiCl (0.75, 1.5, 3.0, 6.0 mEq/kg) immediately after access to NaCl ($n=6–10$ mice per group in each strain). All mice also received 30-min access to tap water 5 h after each NaCl access period to prevent dehydration. A 2-h access to tap water was given during intervening days.

2.5. Statistical analysis

Data were analyzed by factorial analysis of variance (ANOVA) using strain and LiCl dose as between-group factors. Conditioning subgroup was also included as a between-groups factor in the analysis of the floor preference test. Conditioning trial (trial 1 vs. trial 4) was included as a within-group factor in the analysis of activity data from the place-conditioning experiment. The alpha level for all analyses was set at 0.05.

3. Results

3.1. Place conditioning

Due to equipment malfunction, data from two subjects were lost from conditioning trial 4, and data from one subject were lost on the preference test.

3.1.1. Conditioning trials

Table 1 lists mean activity rate on the first and last CS − (saline) and CS+ (LiCl) conditioning trials for each strain × dose group (data are collapsed over conditioning subgroup). B6 mice were generally more active than D2 mice on the first trial, but not on the fourth trial. Furthermore, LiCl produced a similar dose-dependent reduction in activity in both strains, but repeated exposure to LiCl did not appear to produce tolerance to the drug's activity suppressing effect. Three-way ANOVA (strain × dose × trial) of the CS+ (LiCl) data yielded significant main effects of strain,

Table 1
Mean activity counts per minute (±SEM) on first and last conditioning trials for each group

Strain	LiCl dose (mEq/kg)	Conditioning trial 1		Conditioning trial 4	
		CS − (saline)	CS + (LiCl)	CS − (saline)	CS + (LiCl)
B6	0[a]	39.5 ± 1.7		33.9 ± 2.1	
	0.75	41.8 ± 2.1	40.7 ± 2.8	31.9 ± 2.2	30.4 ± 1.7
	1.5	41.0 ± 2.0	36.3 ± 1.9	36.4 ± 1.9	28.0 ± 1.5
	3.0	43.6 ± 1.9	25.7 ± 1.6	35.5 ± 2.0	15.5 ± 0.8
D2	0[a]	39.7 ± 2.3		33.4 ± 2.1	
	0.75	38.2 ± 1.5	34.9 ± 2.2	35.4 ± 1.7	34.7 ± 1.6
	1.5	36.1 ± 2.0	34.5 ± 1.7	33.0 ± 1.8	24.0 ± 1.8
	3.0	35.2 ± 1.2	20.5 ± 1.6	31.1 ± 1.8	13.8 ± 1.2

[a] Activity data of saline-only control groups were averaged over the two saline exposures given on the same days that LiCl-treated mice received their CS+ and CS − conditioning trials.

$[F(1,155)=5.1,\ p<0.05]$, dose $[F(2,155)=668.9,\ p<0.001]$, and trial $[F(1,155)=70.2,\ p<0.001]$, and significant strain × trial $[F(1,155)=5.7,\ p<0.05]$, and strain × dose × trial $[F(2,155)=4.3,\ p<0.05]$ interactions. Separate follow-up analyses (strain × dose) for each conditioning trial indicated that the three-way interaction in the overall analysis could be attributed to a significant strain × dose interaction on trial 4 $[F(2,155)=4.1,\ p<0.05]$, but not on trial 1 $[F(2,157)=0.4]$. Post hoc pairwise comparisons (Tukey's) on trial 4 indicated that there was no difference between strains at any of the LiCl doses.

Three-way ANOVA (strain × dose × trial) of the CS − (saline) data in Table 1 revealed significant main effects of strain $[F(1,155)=7.5,\ p<0.01]$, and trial $[F(1,155)=43.1,\ p<0.001]$, and a significant strain × trial interaction $[F(1,155)=6.8,\ p<0.01]$. Separate follow-up analyses for each conditioning trial showed that the two-way interaction in the overall analysis was due to a significant strain effect on trial 1 $[F(1,157)=14.7,\ p<0.001]$, but not on trial 4 $[F(1,155)=0.7]$.

Activity of the saline-only control groups decreased slightly over trials, but did not differ between strains (see Table 1). Two-way ANOVA (strain × trial) showed only a significant main effect of trial $[F(1,19)=10.5,\ p<0.01]$.

3.1.2. Place preference test

Fig. 1 shows mean time spent on the grid floor by each conditioning subgroup during the preference test. In this experimental design, evidence of place conditioning is provided by comparing the GRID+ and GRID − subgroups within each dose group, that is, whether or not the grid floor was paired with LiCl using between-group comparisons. This comparison showed little evidence of place conditioning in either strain at the two lower doses. At the highest dose, however, GRID+ groups generally spent less time on the grid floor than GRID − groups, indicating development of a conditioned place aversion to the floor paired with LiCl. Moreover, the magnitude of conditioned aversion was greater in D2 mice than in B6 mice. These observations were supported by a three-way ANOVA (strain × dose × conditioning subgroup) that yielded significant main effects of strain $[F(1,151)=4.2,\ p<0.05]$, and conditioning subgroup $[F(1,151)=13.2,\ p<0.001]$, and significant interactions of strain × dose $[F(2,151)=3.2,\ p<0.05]$, dose × conditioning subgroup $[F(2,151)=14.8,\ p<0.001]$, and strain × dose × conditioning subgroup $[F(2,151)=3.8,\ p<0.03]$. To facilitate interpretation of the three-way interaction, separate two-way ANOVAs (strain × conditioning subgroup) were conducted at each dose. These analyses showed no effect of conditioning subgroup or interaction at either of the two lower doses. However, analysis of the 3-mEq/kg groups yielded a significant conditioning subgroup effect $[F(1,50)=40.4,\ p<0.001]$, and a significant strain × conditioning subgroup interaction $[F(1,50)=7.9,\ p<0.01]$. Follow-up comparisons (Tukey's) revealed a significant conditioning subgroup difference in D2 mice

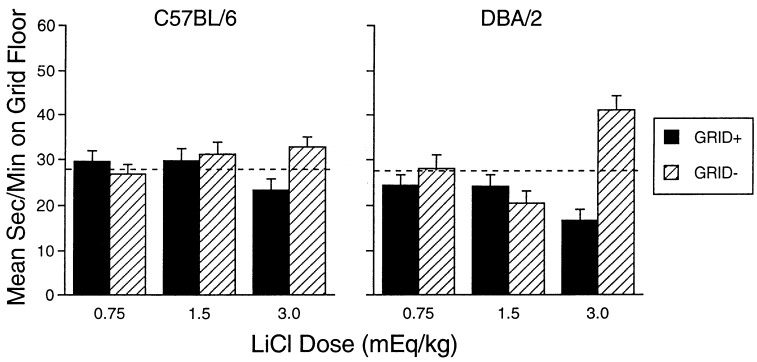

Fig. 1. Mean seconds per minute (+SEM) spent on the grid floor during floor choice testing in B6 and D2 mice. GRID+ groups had previously received pairings of the grid floor with LiCl (and hole floor with saline), whereas GRID − groups had previously received pairings of the grid floor with saline (and hole floor with LiCl). Conditioned place aversion is shown when time spent on the grid floor by the GRID+ group (dark bars) is less than time spent on the grid floor by the GRID − group (cross-hatched bars). Dashed lines indicate time spent on the grid floor by saline-treated control mice. Each subgroup contained 10–14 mice from each strain.

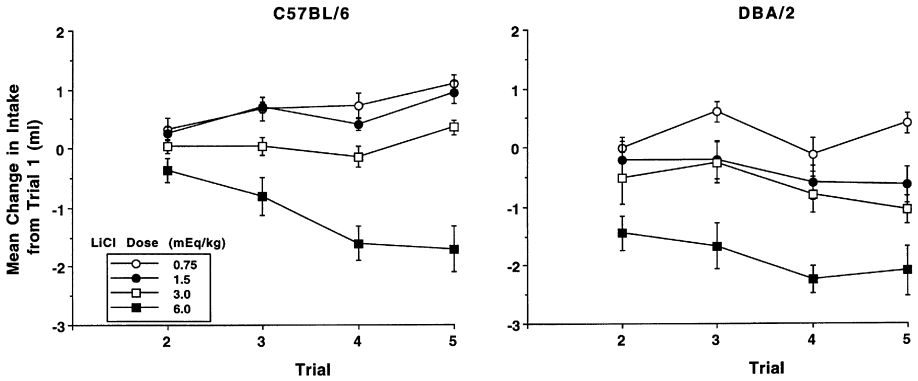

Fig. 2. Mean change in intake of NaCl (ml ± SEM) in B6 mice (left panel) and D2 mice (right panel) for each LiCl dose after each taste–drug pairing. Change scores were computed by subtracting each subject's intake on trial 1 from its intake on each subsequent trial. Each dose group contained 6–10 mice from each strain.

($p < 0.001$), indicating conditioned aversion, but only a nonsignificant trend for conditioned aversion in B6 mice ($0.05 < p < 0.10$).

The dashed lines in Fig. 1 represent performance of the saline control groups. As reported previously [8,11], saline-treated mice from both strains spent about 50% of the session on each floor type, suggesting that performance of the experimental groups was not biased by a strong unconditioned preference for either floor type. One-way ANOVA indicated that the control groups from each strain did not differ [$F(1,19)=0.4$].

Activity during the preference test (after saline injection) was slightly higher in B6 mice (34.2 ± 1.1) than in D2 mice (30.6 ± 0.9), but there were no differences among groups previously treated with different doses of LiCl. These observations were supported by a two-way ANOVA (strain × dose) that yielded only a significant main effect of strain [$F(1,176)=6.4$, $p < 0.01$].

3.1.3. Taste conditioning

Mean intakes of NaCl were similar across strains prior to injection of LiCl on the first conditioning. B6 and D2 mice drank an average of 2.5 ± 0.1 and 2.3 ± 0.1 ml, respectively. Two-way ANOVA (strain × dose) yielded no significant main effects or interaction. Although untreated groups were not included in this study, a previous report using a similar procedure indicates no change in NaCl intakes over trials in vehicle-treated B6 and D2 mice [6].

To correct for minor differences in initial intake of the flavor CS, intake measured on trial 1 was subtracted from each subject's intake on subsequent trials. The effects of taste–drug pairing are shown in Fig. 2, which plots the mean change in NaCl intake as a function of dose for both strains on the trial after each successive taste–drug pairing. As can be seen, both strains showed a dose-dependent effect that became more pronounced over trials. However, D2 mice consistently showed lower intake than B6 mice. On the final trial, D2 mice showed reductions in NaCl intake (i.e., negative change scores) at all but the lowest LiCl dose. In contrast, B6 mice showed reductions in NaCl intake only at the highest LiCl dose. Overall, these findings are consistent with LiCl dose-dependent development of conditioned taste aversion. Moreover, these data indicate that D2 mice develop taste conditioning at lower doses and after a fewer number of conditioning trials than B6 mice.

These conclusions were supported by strain × dose ANOVAs conducted separately on intake difference scores for each trial shown in Fig. 2. These analyses yielded significant main effects of strain [all Fs(1,50)>7.7, $p < 0.01$] and dose [all Fs(3,50)>6.6, $p < 0.001$] on all trials. The interaction was not significant on any trial, although it approached significance on trial 5 [$F(3,50)=2.4$,.05 < $p < 0.01$].

4. Discussion

Both experiments were consistent in suggesting that D2 mice are more sensitive to aversive effects of LiCl than B6 mice. At a dose that produced similar suppression of activity in both strains (3 mEq/kg), D2 mice expressed a robust conditioned place aversion, whereas B6 mice showed only a nonsignificant trend toward aversion (Fig. 1). At the two lower doses, neither strain showed evidence of place conditioning. The taste-conditioning study (Fig. 2) also revealed strain and dose-dependent differences in LiCl-induced suppression of a paired flavor solution. The strain difference in conditioned taste aversion was apparent after only one taste–drug pairing, and was maintained over the next three conditioning trials. Because reliable strain effects were observed at lower doses and after a smaller number of conditioning trials, the taste-conditioning task appeared to provide a more sensitive index of aversive drug sensitivity than the place-conditioning task. For example, the 0.75-mEq/kg lithium dose produced lower NaCl intakes in D2 mice compared to B6 mice after four taste-conditioning trials, whereas this same dose did not produce changes in floor preference after four place-conditioning trials.

The finding of a significant strain difference in taste aversion after only one conditioning trial contrasts with several previous failures to show differences between these strains in LiCl-induced taste conditioning [2,3,16,23]. There are at least two possible reasons for this discrepancy. First, all of the preceding studies used a highly preferred sweet taste solution, whereas the present study used a salient, but generally less well-preferred salty solution. Previous studies from this lab suggest that conditioned taste aversion produced by a given drug dose develops more rapidly to a salty taste than to a sweet taste in D2 mice [30]. It is possible that the greater innate preference for sweet over salty tastes interfered with development of LiCl-induced conditioned taste aversion in previous studies. A second difference between the present study and most of the earlier ones is the use of relatively long duration taste-conditioning/test trials, i.e., 60 min in the present study vs. only 10 min in three previous studies [2,3,23]. Although the progress of NaCl intakes within each 60-min session was not determined in this study, longer test trials provide an opportunity for extinction because sampling of the flavor could occur throughout the session. For example, B6 and D2 mice may have had equally low intakes early in each session, with B6 mice consuming greater amounts of the flavor only later in the sessions. Therefore, the stronger conditioned taste aversion in D2 mice reported here may actually be another example of their greater resistance to extinction [23].

Although the present findings are consistent with a strain difference in sensitivity to LiCl's aversive effects, consideration must be given to two alternative interpretations. First, given that both tasks rely on associative learning, it is possible that D2 mice simply develop conditioned motivational responses more rapidly than B6 mice. However, this suggestion is not supported by previous studies showing stronger place preference induced by several abused drugs in B6 mice than in D2 mice [36]. Moreover, the literature does not offer evidence of a consistent difference between these strains in general learning ability. For example, B6 mice perform better in a Morris water maze task [39,40], a radial maze task [1,35] and a spatially discriminated operant task [24], whereas D2 mice show better performance in shock avoidance learning [4,5] and in appetitive maze tasks [5,26]. Thus, it does not appear that the present findings can be explained by strain differences in learning ability.

Another issue for consideration is whether the B6 and D2 strains differ in terms of salience or innate preference for the tactile or taste stimuli used in these conditioning procedures. In the case of place conditioning, data from saline-treated control animals tested here and in previous studies (e.g., Refs. [12,15]) show no strain difference in innate preference for the tactile CSs used in place conditioning. Moreover, because the direction of the strain difference in place conditioning varies as a function of drug [13,15] when the same stimuli are used, it does not appear that strain differences in place conditioning can be attributed to systematic strain differences in the salience of these tactile stimuli. In the case of taste conditioning, the similarity in initial intake of the NaCl-flavored solution argues against the suggestion of a strain difference in innate preference. Furthermore, although the literature suggests that B6 and D2 mice differ in their preference for or ability to detect intermediate concentrations of NaCl (30–150 mM), the direction of the strain difference is opposite what one would expect on the basis of the present findings. That is, B6 mice reject NaCl at lower concentrations than D2 mice [25], a difference that should facilitate rather than retard development of conditioned taste aversion in B6 mice.

The mechanism underlying the strain difference in sensitivity to LiCl's aversive effects in these tasks is currently unknown. Previous studies of lithium chloride toxicity have shown a lower LD_{50} [38] and more rapid death following lethal injection [15] in D2 mice than in B6 mice. Also, D2 mice show higher lithium concentrations than B6 mice in various tissues 1 h after injection of a non-lethal dose [18], suggesting slower elimination of lithium in D2 mice. Such findings raise the possibility that strain differences in lithium-induced conditioned aversions may be caused, in part, by strain differences in lithium pharmacokinetics. That is, D2 mice may develop stronger conditioned aversions after injection of a lithium dose because drug concentrations are higher or persist longer in critical tissues.

It is also possible that these strains differ more generally in terms of their sensitivity to aversive events. This suggestion is consistent with previous studies showing stronger conditioned taste aversions induced by ethanol (e.g., Refs. [22,29]), acetaldehyde [16] and nicotine [28] in D2 mice than in B6 mice. This hypothesis is also supported by studies showing greater sensitivity to electric shock [20] and better shock avoidance behavior [4,5] in D2 mice. One potential mechanism underlying the aforementioned sensitivity of D2 mice compared to B6 mice may be a general reaction to stress. Although these strains do not differ in corticosterone levels after restraint stress [34], D2 mice show higher corticosterone and ACTH levels after an acute injection of ethanol [33].

In conclusion, the present results are consistent with the notion that genotype is important for place- and taste-aversion learning with lithium. B6 and D2 mice also differ in sensitivity to ethanol-, morphine- and cocaine-induced conditioned place preference [13,15,36,37], as well as taste aversion conditioned by ethanol and nicotine [22,28,29]. It may also be noted that a number of different mouse genotypes differ in sensitivity to ethanol-, and nicotine-induced conditioned taste aversion [14,28,31,32], and in sensitivity to ethanol-induced conditioned place preference [12,14,32]. A variety of rat genotypes have also been shown to differ in the development of conditioned taste

aversion produced by ethanol [7,8], nicotine [17], cocaine [21], THC [27], and lithium [19]. Although additional research is needed to more fully characterize the mechanisms underlying the strain differences in sensitivity to the motivational effects of lithium chloride and various abused drugs, the present findings offer strong evidence against the earlier conclusion that D2 mice are "hyporesponsive" to such effects [36].

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