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Gender Differences in Learned Helplessness Behavior Are Influenced by Genetic Background

BARBARA J. CALDARONE, TONY P. GEORGE, VENETIA ZACHARIOU AND MARINA R. PICCIOTTO

Department of Psychiatry, Yale University School of Medicine, 34 Park Street, 3rd Floor Research, New Haven, CT 06508

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CALDARONE, B. J., T. P. GEORGE, V. ZACHARIOU AND M. R. PICCIOTTO. *Gender differences in learned helplessness behavior are influenced by genetic background.* PHARMACOL BIOCHEM BEHAV **66**(4) 811–817, 2000.— Learned helplessness behavior was examined in female and male C57BL/6J (B6), 129/J (129) and (B6 × 129)F1 mice, common genetic backgrounds for the generation of knockout models, as well as in mice of a mixed genetic background (outbred mice). Both genotype and gender differences were observed in learned helplessness. Outbred males showed increased shuttle escape latencies following 60, 120, or 360 inescapable shocks compared to nonshocked controls, but outbred females showed no increase in escape latencies following inescapable shock pretreatment. B6 females showed increased escape latencies following 60, 120, or 360 inescapable shocks, whereas B6 males showed increased latencies only after 360 shocks. Female and male 129 and B6129F1 mice did not show an increase in escape latencies following inescapable shock, but this was most likely due to poor escape performance in nonshocked control mice. Differences in escape performance could not be explained by differences in pain thresholds between genotypes. These results support the idea that genetic background and gender are important to consider when using the learned helplessness model in genetically manipulated mice. © 2000 Elsevier Science Inc.

Learned helplessness Stress Animal model Depression C57BL/6J 129/J Genetics Strain differences Genetic background Knockout mice

FOLLOWING exposure to uncontrollable shock, rats and mice exhibit a variety of behavioral deficits, including a profound disruption of escape performance (1,16,26–28). This phenomenon, known as learned helplessness, has been proposed as an animal model of depression because some of the behavioral changes observed in animals exposed to inescapable shock share similarities with clinical depression in humans (15). The strongest evidence for learned helplessness as a model of depression comes from neurochemical and pharmacological studies. Stress parameters that induce learned helplessness have been shown to influence levels of norepinephrine (NE), dopamine (DA), and serotonin (5-HT) (29,30), neurotransmitters that have been implicated in clinical depression in humans (5). Furthermore, monoamine oxidase (MAO) inhibitors, tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and electroconvlusive shock (ECS), which are effective in treating depression in humans, can block learned helplessness in animals (27,32).

Only a proportion of rodents exposed to inescapable shock develop the learned helplessness syndrome, with estimates ranging from 10–80% (1,7). Although some of this variability can be accounted for by the stress parameters used to induce helplessness, the difficulty and type of escape response, or the criterion used to define learned helplessness (16), a proportion of the variability is likely due to genetic

Requests for reprints should be addressed to M. R. Picciotto, Department of Psychiatry, Yale University School of Medicine, 34 Park Street, 3rd Floor Research, New Haven, CT 06508.

variation. For example, some inbred mouse strains show a profound escape deficit following inescapable shock, whereas other strains are not affected (28). In addition, rat lines have been selectively bred for susceptibility to develop learned helplessness. In the LH line, more than 95% of the animals exhibit the escape deficit, and some rats exhibit helplessness even in the absence of training. The non-LH line is relatively resistant to developing helplessness, and fewer than 5% of the rats show the escape deficit following training (11).

One approach to determining which genes may be involved in susceptibility to developing learned helplessness would be to examine specific candidate genes thought to be involved in depression in knockout mouse models. A number of knockout mice have been developed that have targeted genes that influence neurotransmitter systems, such as the DA (2,9,25,39), 5-HT (21,35), NE (12,14), and ACh (19,22,31) systems, which are thought to be involved in depression.

One issue that has recently been raised with interpreting the behavioral effects of genetic manipulations is the influence of genetic background on mutant phenotypes (8). It seems clear that behavioral changes in mice with a targeted mutation depend not only on the disrupted gene, but also on the background genotype (8). Most knockout mice are generated from targeted mutations in embryonic stem (ES) cells derived from a number of substrains of the mouse strain 129. The 129 ES cells that carry the induced mutation are introduced into a blastocyst-stage embryo, and the resulting chimeras are usually mated to C57BL/6 (B6) mice. As a consequence of this mating, in addition to the targeted gene, mice will carry alleles of both the B6 and 129 mouse strains. The B6 and some 129 mouse strains have been found to differ substantially on several behaviors, including locomotor activity and spatial learning (13,18,20).

In addition to strain differences, gender differences have been characterized in learned helplessness (33,34), which is intriguing given the higher prevalence of depression in women (38). However, no systematic study of genetic influences on gender differences in learned helplessness has yet been performed. It is, therefore, of interest to determine whether male and female animals of inbred mouse strains show strain-specific differences in performance in the learned helplessness paradigm. Although learned helplessness has previously been characterized in C57BL6 mice (26–28), no studies have examined helplessness in the 129 strains or in B6129F1 hybrids. In the present study, we compared learned helplessness in males and females from the C57BL/6J and 129/J inbred strains, their F1 hybrid, and in mice of a mixed genetic background.

METHOD

Animals

Experimentally naive male and female C57BL/6J (B6), 129/J (129) or (B6x129)F1 (B6129F1) mice were obtained from Jackson Laboratory (Bar Harbor, ME). Mice of a mixed genetic background (outbred mice) were obtained by breeding C57BL/6 and SJL mice to get an F1 generation. These mice were crossed to ICR animals. Next, several mice of this generation were crossed to mice backcrossed in house for eight generations to C57BL/6J (of origin 129/SvJ×C57BL/6J×DBA/2J). Finally, several individuals of this mixed population were crossed to C57SJLF1 mice. These mice were originally generated as the product of matings to generate transgenic and knockout animals, and because of the large variability in genetic backgrounds, were used as a mixed background control for the current set of experiments. Mice, ranging in age from 8–20 weeks, were group housed in cages with a maximum of five mice per cage. Mice were kept in a colony room maintained at 22°C on a 12 L:12 D cycle, with lights on at 0700 h. Food and water were available at all times. All animal procedures used in these studies were approved by the Yale Animal Care and Use Committee.

Apparatus

Learned helplessness training was administered in a shuttle box (Med Associates) (43 × 17 × 25.5 cm) in which the front, back, and ceiling were clear Plexiglas, and the sides were aluminum. Scrambled shock (0.30 mA intensity) was delivered by a shock source to a grid floor, which was made of stainless steel bars 2 mm in diameter, spaced 0.50 cm apart. During learned helplessness training, a gray Plexiglas panel was inserted into the shock chamber, dividing it in half. Mice were placed on either side of the chamber so that two mice were administered shock simultaneously. Mice of the same

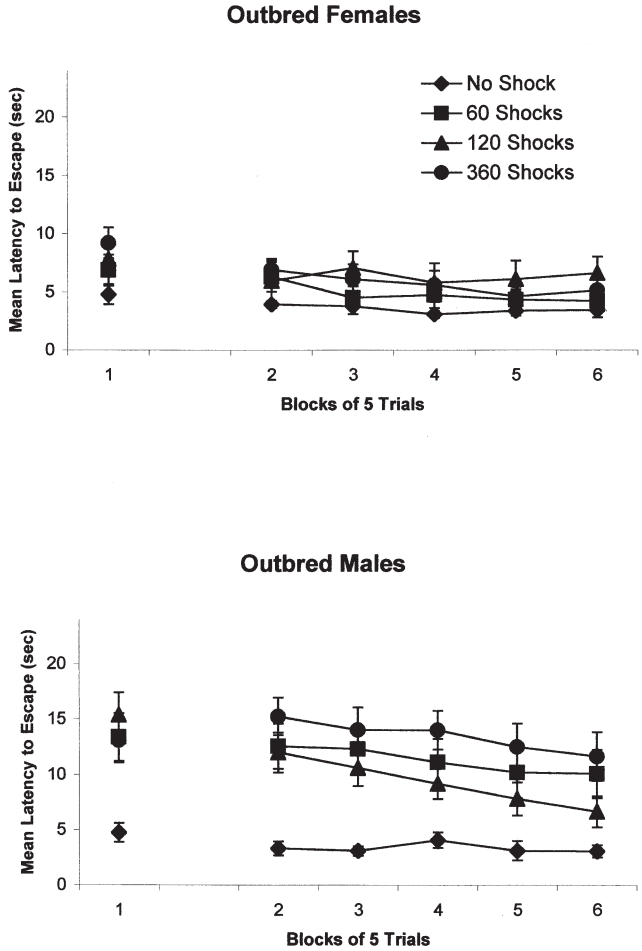

FIG. 1. Mean (±SEM) latency to escape over blocks of five trials as a function of number of inescapable shocks in female and male outbred mice (n = 12–16 per group). Block 1 is the average of five trials with no gate delay, and blocks 2–6 are the average of five trials with a 2-s gate delay. Trials were terminated after 24 s.

strain were always shocked together, although gender sometimes varied. No difference was seen if mice were shocked either individually or two at a time in pilot experiments. Escape testing was administered in the same chamber, except that a white Plexiglas gate was inserted that divided the chamber into two equal compartments. The gate was equipped with a door that opened manually into a 9 × 11.5-cm archway with a 1-cm hurdle.

Learned Helplessness Training

Learned helplessness was assessed in outbred, B6, 129, and B6129F1 mice. Training and testing procedures were based on published methods (28). Learned helplessness was induced by administering inescapable footshock which consisted of either 60 (6-s duration, administered once every 54 s), 120 (4-s duration, administered once every 26 s), or 360 (2-s duration administered once every 10 s) shocks. A nonshocked control group was exposed to the apparatus for an equivalent period of time but did not receive shock. For outbred mice, 12–16 mice of each gender were used for each group. For B6, 129, and B6129F1 mice, 12 mice of each genotype and gender were used for each group.

Shuttle Escape Testing

Approximately 24 h after learned helplessness training, mice were tested on the shuttle escape task. The side of the chamber on which each mouse was placed at the start of the trial was alternated. Mice were given 30 shuttle escape trials with 30-s intervals between the start of each trial. On the first five trials, the gate opened at the same time that the shock was turned on. For the remaining trials, the gate opened 2 s after shock onset. Each trial was terminated when the mouse

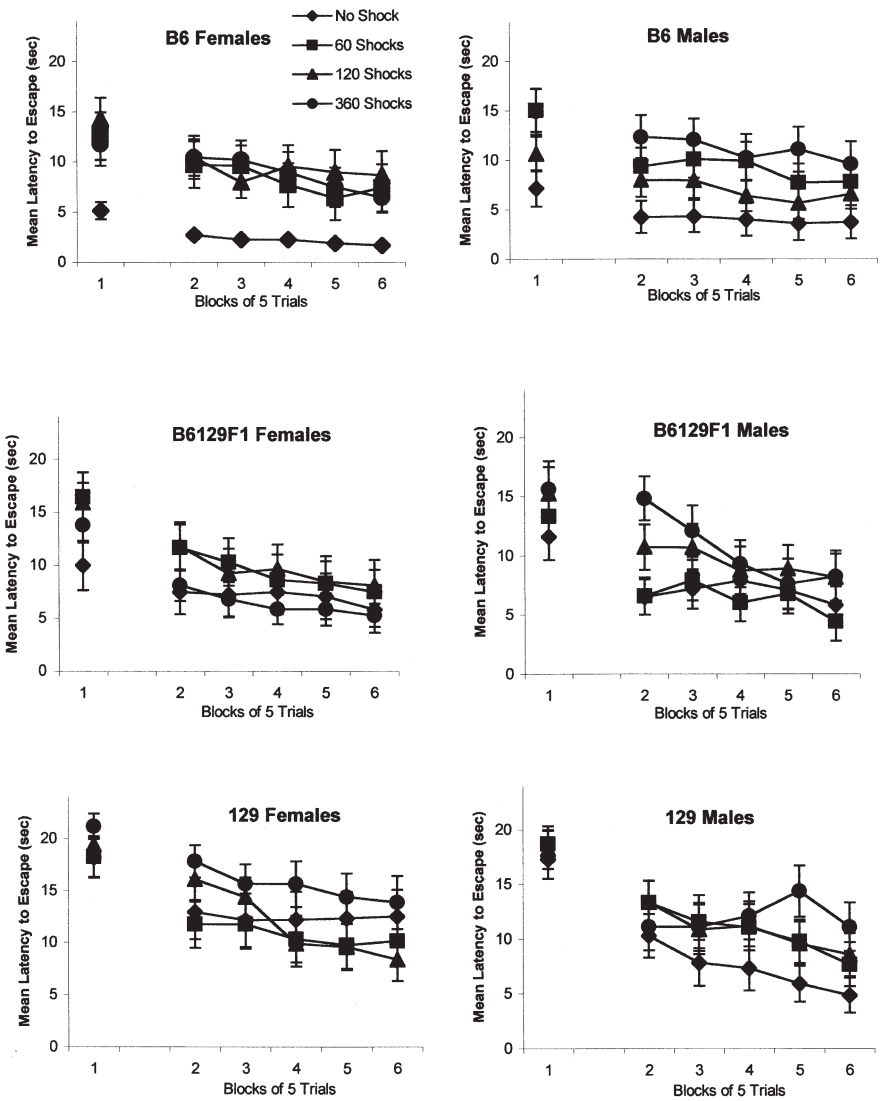

FIG. 2. Mean (±SEM) latency to escape over blocks of five trials as a function of number of inescapable shocks in female and male B6, 129, and B6129F1 mice (n = 12 per group). Block 1 is the average of five trials with no gate delay, and blocks 2–6 are the average of five trials with a 2-s gate delay. Trials were terminated after 24 s.

crossed over the hurdle into the adjacent compartment. If an escape response was not made, the trial was terminated 24 s after shock onset. If mice escaped the shock by jumping onto the hurdle on two consecutive trials, the hurdle was removed for the remainder of the escape test.

Shock Reactivity Test

Current thresholds for reactivity to shock were determined for B6, 129, and B6129F1 mice. Five mice of each genotype and gender were used. Procedures were based on published methods (6,10). Mice were placed in the shock apparatus and allowed to habituate for 3 min. Mice were given a series of 1-s shocks, starting at 0.05 mA and increasing to 1.0 mA in increments of 0.05 mA. Shocks were delivered 30 s apart. Mice were scored for flinch (any observable reaction to the shock), run, vocalization, or jump reactions. The test was terminated once the mouse jumped or an intensity of 1.0 mA was reached. Mean current thresholds to evoke flinch, run, vocalization, and jump were calculated. The test was scored by an observer who was unaware of results of the learned helplessness testing.

Data Analyses

Escape latencies were averaged over five trials. Block 1 (trials 1–5 without a gate delay) was analyzed using analysis of variance (ANOVA) with genotype (outbred, B6, 129, B6129F1), gender, and number of shocks (0, 60, 120, and 360) as the between-group variables. Blocks 2–6 (trials 6–30 with a 2-s gate delay) were assessed by a mixed-factor ANOVA with genotype (outbred, B6, 129, B6129 F1), gender, and number of shocks (0, 60, 120, and 360) as the between group variables and block (blocks 2–6) as the within-group variable. Overall escape latencies were computed by averaging escape latencies over 30 trials. ANOVA on overall escape latencies was computed with genotype (outbred, B6, 129, B6129F1), gender, and number of shocks (0, 60, 120, and 360) as the between-group variables. Shock reactivity data were analyzed by ANOVA with genotype (B6, 129, B6129F1) and gender as the between-subjects variables. Significant main effects and interactions were followed up by the posthoc Tukey Honestly Significant Difference (HSD) test ($\alpha = 0.05$).

RESULTS

Genotype Comparison

Significant differences were seen in shuttle escape latencies across genotype and gender. For the block of trials without a gate delay (block 1), escape latencies showed a significant genotype $\times$ gender interaction, $F(3, 361) = 3.54$, $p < 0.05$ (Figs. 1 and 2). For the block of trials with the 2-s gate delay, escape latencies showed a significant number of shocks

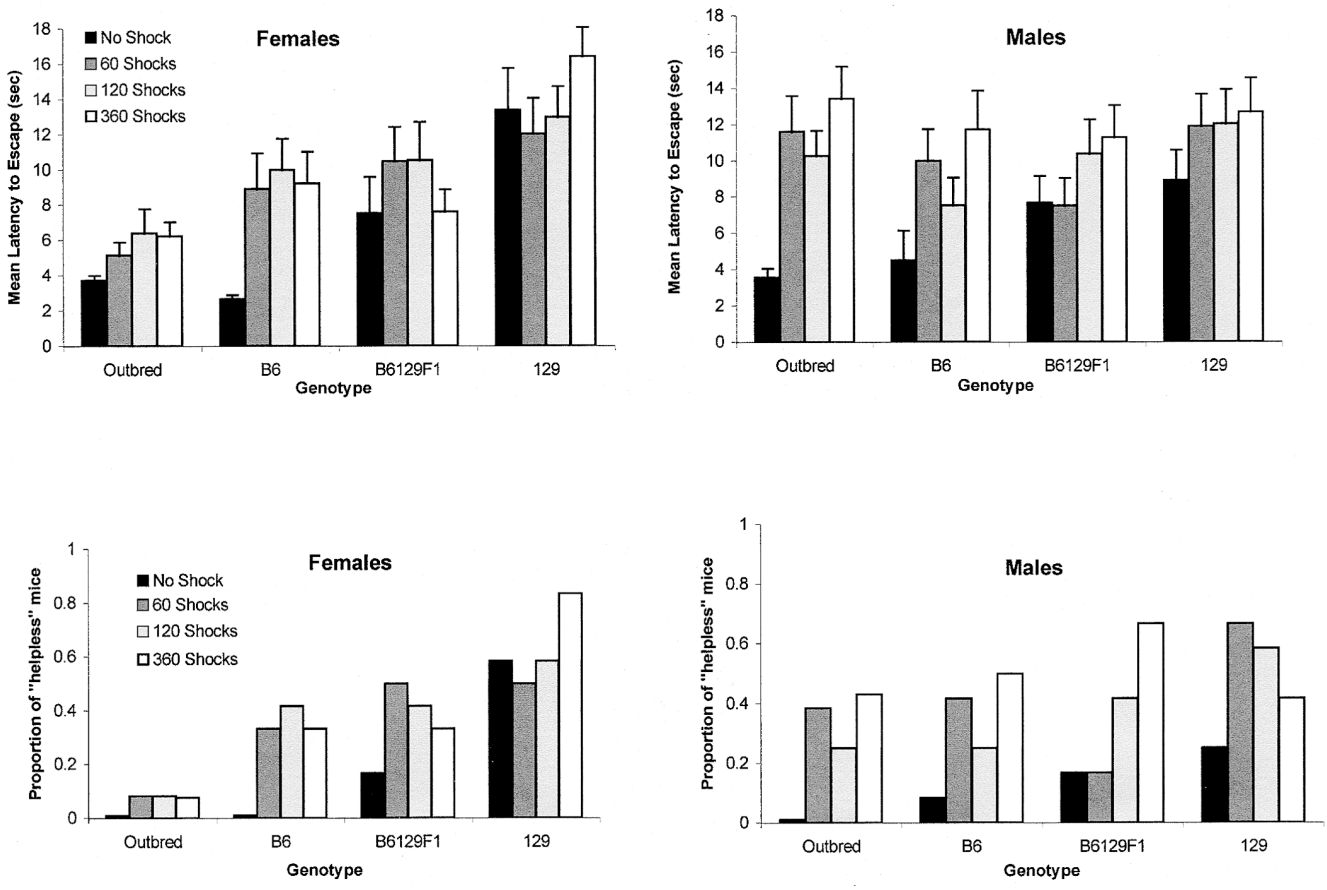

FIG. 3. The top panel shows the mean (±SEM) overall latency to escape across trials 1–30 as a function of number of inescapable shocks, genotype, and gender (top panel). The bottom panel shows the proportion of mice exhibiting learned helplessness. An arbitrary criterion was established such that mice with an average overall escape latency greater than or equal to 10 s were termed "helpless" mice.

× genotype × gender × block interaction, $F(36, 1444) = 2.10$, $p < 0.001$. Overall latencies showed a genotype × gender interaction, $F(3, 361) = 5.50$, $p < 0.01$ (Fig. 3, top panel). Post hoc tests revealed that outbred mice showed a profound gender difference in overall escape latency following exposure to inescapable shock. In overall escape latency, outbred males that received inescapable shock during training showed increased escape latencies compared to nonshocked controls, whereas females that received inescapable shock during training showed escape performance equivalent to nonshocked controls. Females and males of the B6 strain both showed longer overall escape latencies following training with inescapable shock, although gender differences were observed. In B6 females, overall escape latencies were disrupted following 60, 120, and 360 shocks. However, B6 males that received 60 and 120 shocks failed to show a significant disruption in escape behavior, whereas B6 males that received 360 shocks had significantly longer escape latencies compared to control mice that were not shocked during training. Female and male 129 and B6129F1 mice showed no increase in overall escape latencies following inescapable shock. This lack of difference was most likely due to the poor escape behavior of the nonshocked control mice. Analysis of overall escape latency of nonshocked control outbred, B6, 129, and B6129F1 mice revealed a main effect of genotype, $F(3,93) = 11.79$, $p < 0.001$. Post hoc tests on overall latencies of nonshocked mice showed that 129 and B6129F1 mice had longer escape latencies than B6 and outbred mice ($ps < 0.05$).

We established an arbitrary criterion such that mice with overall escape latencies greater than or equal to 10 s were considered "helpless." Figure 3 (bottom panel) shows the proportion of helpless mice of each genotype and gender. Consistent with earlier reports, estimates of mice exhibiting learned helplessness ranged from approximately 10–80% (1,7).

Shock Reactivity

Reactivity to shock, as measured by flinch and vocalization thresholds, did not vary as a function of genotype or gender ($ps > 0.05$) (Fig. 4). A main effect of genotype was found for both running, $F(2, 24) = 4.85$, $p = 0.017$, and jumping, $F(2, 24) = 4.89$, $p = 0.017$, but no main effect of gender or interaction of genotype with gender was observed for these variables. Post hoc tests revealed that B6129F1 females showed less running in response to shock than B6 females ($p = 0.008$) and 129 and B6129F1 females showed less jumping in response to shock than B6 females ($ps < 0.05$). No differences in run or jump thresholds were observed for males.

DISCUSSION

As has been seen in earlier studies, we found genotype and gender differences in the degree of disruption in shuttle escape behavior following inescapable shock (28,33,34). Specifically, B6 mice showed a moderate disruption in escape performance following 360 shocks, with no significant differences between male and female mice. This finding replicates previous studies that found an escape deficit following inescapable shock in B6 mice following 360 inescapable shocks (28) and no differences between genders in C57BL/6ByJ mice (26). In the current study, although female B6 mice showed an escape deficit following 60 and 120 shocks, these shock parameters were less effective in producing a deficit in escape behavior in B6 males. In outbred mice, males exhibited a robust escape deficit following 60, 120, and 360 shocks, but females showed no escape deficit following any of these shock pretreatments. This gender difference in learned helplessness in outbred mice is similar to reports in Sprague–Dawley rats, which demonstrated that female rats were less disrupted by the effects of inescapable shock than male rats (33,34). We have extended findings on B6 and outbred mice to include the 129 inbred strain and B6129F1 hybrid. The 129 and B6129F1 mice that received inescapable shock did not show an increase in shuttle escape latencies compared to nonshocked controls. However, the nonshocked control 129 and B6129F1 mice tended to show poor escape performance, with approximately 20–60% of the mice reaching the criterion for learned helplessness.

Although differences in pain sensitivities have been described between inbred mouse strains (36) as well as between male and female rats (3), it is unlikely that variation in pain sensitivity influenced escape performance in the present study. First, the genotype differences in jump thresholds in females could not explain differences in escape performance, because the average jump threshold was well above the shock intensity used in the present study. B6 and B6129F1 females differed in run thresholds, which were within the range of shock intensity used in the current study. However, it is unlikely that these differences could account for differences in

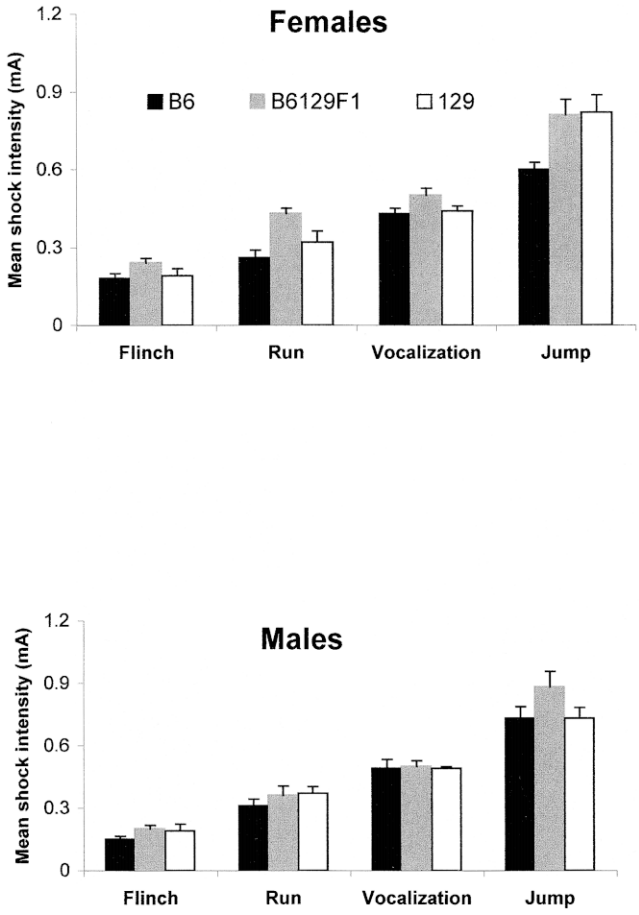

FIG. 4. Mean (±SEM) shock intensity (mA) to evoke flinch, run, vocalization and jump responses in B6, 129, and B6129F1 male and females mice ($n = 5$ per group).

escape performance because the pattern of shock reactivity does not follow the same patterns of escape behavior in nonshocked control mice. In nonshocked control females, 129 mice exhibited the longest escape latencies, B6 the shortest, with B6129F1 mice intermediate between the two parental strains.

Several possible mechanisms could be responsible for the genotype and gender differences in escape performance following inescapable shock. The 129 mice were slower to acquire the escape response when compared to B6 mice. Mice of some 129 strains have been shown to be less active than B6 mice (13,17), and as a result of this decreased activity, 129 mice may be less likely than B6 to initiate active motor responses. Differences in locomotor activity could account for the gender difference observed in outbred mice, because outbred female swiss mice have been shown to be more active than males (4). Strain and gender differences in learning ability could have an effect on learned helplessness. Strain differences have been demonstrated for active avoidance learning, with 129/J mice showing poor avoidance conditioning (23,24). In rats, females have been shown to be better at active avoidance learning than males (3). This might contribute to the absence of the shuttle escape deficit observed following inescapable shock in outbred female mice. However, it is possible that general locomotor activity and avoidance conditioning is independent of the motor factors that are associated with escape performance. An alternate explanation for the differences in escape performance between mouse strains could be related to differential neurochemical response to foot shock stress. Mouse strains have been shown to differ in alterations in brain dopamine, norepinepherine, and serotonin levels in response to foot shock stress (30), and it has been suggested that alterations in these neurotransmitters are responsible for inducing learned helplessness (37).

In the present study, genotype and gender differences were demonstrated in learned helplessness. Some strains, such as the B6 strain, which shows moderate learned helplessness, would be an appropriate genetic background for studying the effects of single gene mutations in mouse models of depression. However, other genetic backgrounds, such as the 129 and B6129F1 would be inappropriate because the nonshocked control mice show poor escape performance. These results emphasize the importance of considering genetic background as well as gender when studying single gene mutation effects on learned helplessness in knockout mice.

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