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Acute mild footshock alters ethanol drinking and plasma corticosterone levels in C57BL/6J male mice, but not DBA/2J or A/J male mice

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Abstract

Stress is an often-reported cause for alcohol consumption in humans. Acute intermittent footshock is a frequently used paradigm to produce stress in laboratory animals including mice. The effect produced by intermittent footshock stress on ethanol self-administration has been inconsistent: both increases and decreases in ethanol consumption have been reported. The current set of studies further investigates, in three commonly studied mouse strains, the effect of footshock stress on ethanol self-administration. Furthermore, the effect of footshock on plasma corticosterone levels was determined to investigate potential biochemical correlates. Adult male C57BL/6J, DBA/2J, and A/J mice were allowed to self-administer 10% (wt/vol) ethanol for 12 days in a standard 23-h two-bottle paradigm before receiving either 15 min of mild inescapable footshock or no footshock. Shock intensity was equal to the mean intensity at which each strain vocalized as previously determined. Following footshock, animals had the opportunity to self-administer ethanol for an additional 23 h. Separate animals were subjected to either footshock or no shock prior to collection of plasma for corticosterone. Mild footshock stress altered ethanol self-administration and increased plasma corticosterone levels in C57BL/6J mice. Footshock stress did not alter ethanol self-administration or plasma corticosterone levels in DBA/2J or A/J mice. These data demonstrate that mild footshock stress is a suboptimal method of modeling the stress-induced increases in ethanol consumption often reported by humans.

Keywords

Ethanol self-administration; Mice; Footshock stress; Corticosterone

Introduction

The interaction of stress and alcohol self-administration is important, but not well understood. Acute stress, such as footshock, has been shown to increase plasma corticosterone in rodents (Anisman et al., 2001; Hajos-Korcsok et al., 2003). Furthermore, acute administration of corticosterone (Fahlke & Eriksson, 2000; Fahlke & Hansen, 1999; Fahlke et al., 1996) increases

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ethanol self-administration in rodents. Therefore, it might be expected that footshock stress would increase ethanol self-administration.

Acute intermittent footshock is frequently used to investigate the interaction of stress and drug seeking (for review see Shaham et al., 2000). For example, acute footshock stress will reinstate alcohol-seeking behavior in rats and mice (Liu & Weiss, 2003; Martin-Fardon et al., 2000; for review see Le & Shaham, 2002). In addition to alcohol, footshock stress will also reliably reinstate cocaine-seeking (Erb et al., 1996; McFarland et al., 2004), nicotine-seeking (Buczek et al., 1999), and heroin-seeking behavior in rodents (Shaham et al., 1997; Shalev et al., 2001). Although it has frequently been demonstrated that acute footshock stress can reinstate drug-seeking behavior under extinction conditions, studies investigating the relationship of foot-shock stress to ongoing drug self-administration, particularly ongoing ethanol self-administration, have been mixed.

The reduction of stress following ethanol consumption is an often-reported cause for alcohol drinking in humans (Brown et al., 1995; Cooper et al., 1992; Dawson et al., 2005, 2007). Indeed, the belief that alcohol consumption is stress reducing is a long-established hypothesis (Conger, 1956; Goeders & Goeders, 2004; Volpicelli, 1987). Attempts to determine the relationship between stress and alcohol intake in animals have led to conflicting results. It has been reported that footshock stress can increase ethanol self-administration (Volpicelli et al., 1990) whereas other studies have demonstrated that footshock does not increase ethanol self-administration (Fidler & LoLordo, 1996; Ng Cheong Ton et al., 1983). Interestingly, two recent reports have shown that footshock stress increases ethanol self-administration in various rat strains (Funk et al., 2004; Vengeliene et al., 2003). Although promising, footshock in the later study occurred following both ethanol deprivation and swim stress whereas in the former, footshock stress occurred during ethanol deprivation. These results raise the possibility that footshock may be an effective stressor only during or after a period of ethanol deprivation. In fact, although footshock stress increased the amount of ethanol drinking when administered during ethanol deprivation, it did not alter self-administration levels if applied without a corresponding deprivation period (Funk et al., 2004).

The widely varying effects of footshock on ethanol self-administration may be due to many factors. One factor could be the intensity of the footshock used. For example, most previous studies have used a high level of footshock (0.8–1.0 mA) to investigate the effect of stress on ethanol consumption (Fidler & LoLordo, 1996; Funk et al., 2004; Ng Cheong Ton et al., 1983; Vengeliene et al., 2003; Volpicelli et al., 1990). Although these high levels of footshock can reliably reinstate ethanol responding under extinction (Le & Shaham, 2002; Le et al., 1998; Liu & Weiss, 2003; Martin-Fardon et al., 2000) it is possible that these levels are too intense to alter ongoing ethanol drinking, particularly in mice.

The following studies were designed to develop a procedure to directly investigate the effect of a mild footshock stress on ethanol self-administration in three commonly used inbred mouse strains, C57BL/6J (B6), DBA/2J (D2), and A/J. Specifically, to equate the intensity (mA) of footshock across strains, the intensity of footshock was set at the level which produced an audible vocalization within each strain. It should be noted that vocalization elicited by footshock is a complex trait that has an identifiable QTL on Chromosome 1 (Matthews et al., data under review). In addition to investigating the effect of a mild footshock stress on ethanol self-administration, plasma corticosterone levels were determined in ethanol naïve mice. It was found that acute footshock stress can modulate ethanol self-administration and plasma corticosterone levels but such changes are strain dependent.

Materials and methods

Subjects

Ninety-eight male mice (28 B6 mice; 32 D2 mice; 38 A/J mice) were used in these studies. Animals were either purchased from Jackson Laboratories (Bar Harbor, Maine) or bred and raised at the University of Memphis from Jackson Laboratories stock. All animals were 56 days of age at the beginning of each study. Animals were individually housed for at least 7 days prior to use in an approved animal colony at the University of Memphis and were treated in accordance with NIH guidelines on animal care following approved University of Memphis IACUC protocols. Animals had free access to food and water. Animals were housed in a 12:12 light:dark cycle with lights off at 3:00 p.m.

Acute footshock procedure

Subjects in the footshock procedures were exposed to a single session of 15 min of inescapable footshock via operant shock chambers (MED Associates, Inc) following a modified paradigm that has been demonstrated to reinstate ethanol-seeking behavior during extinction in rodents (Le et al., 1998). Briefly, mice received intermittent foot-shock at the average shock intensity in which each strain vocalized, as previously determined (Matthews et al., data under review). Specifically, the shock value for B6 animals was 0.23 mA, D2 animals was 0.42 mA, and A/J animals was 0.34 mA. During the shock procedure, shock duration was 0.5 s with a mean off time of 40 s (range of shock off varied from 10 to 70 s). Mice received footshock for 15 min. Animals in the no shock conditions were placed in the operant chambers but did not receive footshock. Following completion of the shock procedure, animals were immediately returned to the home cage in the housing room for the ethanol self-administration procedure or plasma collected for corticosterone determination (see below).

Ethanol self-administration

Subjects were allowed to administer ethanol in a standard two-bottle choice paradigm. Briefly, animals could consume either a 10% (wt/vol) ethanol solution or tap water 23-h per day for 12 days. The amount of ethanol consumed in ml was determined every day between 2:00 pm and 3:00 pm and the bottles refilled with fresh solution and alternated to prevent a positional bias. Animals were weighed at the beginning and the end of the experiment and the daily weight was estimated by using the difference between these two values in a cumulative fashion over the 12 days. Following 12 days of ethanol self-administration, animals were randomly assigned to either shock or no shock. Animals received foot-shock immediately before the initiation of the dark cycle and access to fresh ethanol solutions. Following footshock, subjects had the opportunity to self-administer ethanol for an additional 23 h. Ethanol consumption was expressed as g/kg ethanol consumed while ethanol preference was defined as the ratio of ethanol intake (in ml) divided by total fluid consumption (ethanol intake plus water intake).

Plasma corticosterone levels

Ethanol naïve subjects, 56 days of age, were exposed to 15 min of footshock or no footshock immediately before rapid decapitation and collection of trunk blood. Corticosterone was determined by RIA using a standard kit from (MP Biomedicals, Solon, OH) following the manufacturer's directions.

Data analysis

Data collection did not occur for each strain at the same time of the year. Therefore, data per strain were analyzed separately. Changes in ethanol drinking (g/kg consumption) and preference following footshock were determined by analyzing absolute values of drinking.

Results

C57BL/6J

Ethanol self-administration—A total of 18 (n = 9 in the shock condition and n = 9 in the control condition) B6 male mice were used to investigate the effect of mild footshock on ethanol-self administration. Animals consumed ethanol for 12 days prior to footshock exposure. To insure that animals in the shocked condition consumed similar amounts of ethanol compared to animals in the no shock condition, a two-way analysis of variance (ANOVA) repeated measures (Condition × Day) was conducted on the initial 12 days of ethanol consumption. As expected, before footshock animals in the two conditions consumed similar amounts of g/kg ethanol during the first 12 days of the project (main effect of Day, $F(11,176) = 2.18$, $P < .05$; no main effect of Condition, $P > .70$ or significant interaction $P > .50$ or see Fig. 1A). When ethanol consumption following footshock (test day) was compared to ethanol drinking on the day prior to footshock (day 12) it was found that footshock altered ethanol consumption (two-way repeated measures ANOVA [Condition × Day], $F(1,16) = 7.76$, $P < .02$). Specifically post hoc comparisons revealed that prior to footshock no difference in ethanol consumption was found ($P > .40$), but following footshock, male B6 mice consumed 34% more ethanol compared to the no shock controls during the next 23-h period (t-test, $t(16df) = 2.4$, $P < .05$; see Fig. 1B). Interestingly, the significant difference in ethanol consumption following footshock was due to both a modest increase (10%) in consumption in animals that had received footshock, as well as a significant decrease (–27%) in ethanol consumption in animals placed in the shock box that did not receive footshock (paired t-test, $t(8df) = 3.02$, $P < .05$; see Fig. 1C).

Baseline (prior to shock) ethanol preference in mice in the shock and control conditions was very similar (two-way repeated measures ANOVA, main effect of Day, $F(11,176) = 2.497$, $P < .01$; no main effect of condition, $P > .60$ and no significant interaction $P > .50$ or). Following footshock stress those mice that received shock tended to have a higher preference ratio compared to control animals (independent t-test, $t(16df) = 1.803$, $P < .10$), although this effect did not reach significance (data not shown).

Plasma corticosterone level—A total of 10 (n = 5 in the shock condition and n = 5 in the control condition) B6 male mice were used to investigate if mild footshock increased plasma corticosterone levels. Mild footshock increased plasma corticosterone by 105% compared to the no footshock control animals (t-test, $t(8df) = 3.28$, $P < .05$) (see Table 1).

DBA/2J

Ethanol self-administration—A total of 20 D2 (n = 10 in the shock condition and n = 10 in the control condition) male mice were used to investigate the effect of mild footshock on ethanol-self administration. Animals consumed ethanol for 12 days prior to footshock exposure. As expected, no significant difference was found in g/kg consumption of animals that were to be shocked compared to the drinking levels of control animals on day 12; however, there was a significant difference between the two conditions on day 2 (two-way repeated measures ANOVA, Day × Condition interaction, $F(11,198) = 2.134$, $P < .05$; post hoc analysis by independent t-test, all P's < .05). Unlike B6 male mice, acute footshock stress did not alter ethanol self-administration in D2 males during the 23-h period following footshock compared to drinking the day prior to the footshock (two-way ANOVA with repeated measures [Day × condition], $F(1,18) = 1.08$, (1,18) $P > .30$; see Fig. 2A–C).

There was no significant difference in baseline preference between animals in the shock and control conditions (two-way ANOVA, no main effect of condition, $F(1,18) = 1.72$, $P > .10$; no main effect of Condition, $P > .20$ or significant interaction $P > .10$ or). Furthermore, ethanol

preference was not significantly affected by acute footshock stress in D2 male mice (independent *t*-test, $t(18df) = 1.08$, $P > .10$; data not shown).

Plasma corticosterone level—A total of 12 ($n = 6$ in the shock condition and $n = 6$ in the control condition) D2 male mice were used to determine if mild footshock increased plasma corticosterone levels. Unlike B6 mice, mild footshock did not significantly increase plasma corticosterone in D2 mice compared to the no foot-shock control animals (*t*-test, $t(12df) = 0.74$, $P > .10$; see Table 1).

A/J

Ethanol self-administration—A total of 25 A/J ($n = 13$ for no shock and $n = 12$ for shock) male mice were used to investigate the effect of mild footshock on ethanol-self administration. Animals consumed ethanol for 12 days prior to footshock exposure. During this baseline period there were no significant differences in g/kg ethanol consumption between animals in the shock and control conditions (two-way repeated measures ANOVA, Day × Condition interaction, $F(11,253) = 1.69$, $P > .05$; The significant effect of day was due to higher drinking levels on day 1, $P < .05$ but no significant effect of condition, $P > .50$ or significant interaction $P > .01$). Similar to D2 mice, acute footshock stress did not alter ethanol self-administration in the ensuing 23-h period compared to ethanol consumption the day prior to the footshock (two-way ANOVA with repeated measures [Day × Condition], $F(1,23) = 0.97$, $P > .50$; see Fig. 3A–C).

To assess if footshock stress altered ethanol preference, the baseline preference for the first 12 days of ethanol self-administration were examined. As expected, no difference in baseline preference was found between the to be shocked animals and control animals (two-way repeated measures ANOVA, Day × Condition interaction, $F(11,253) = 1.35$, $P > .05$; significant effect of day, $P < .05$ due to high ethanol drinking on day 1, but no significant effect of condition, $P > .50$ or the interaction $P > .10$). Furthermore, ethanol preference was not significantly affected by acute footshock stress in A/J male mice (independent *t*-test, $t(13df) = 0.23$, $P > .10$; data not shown).

Plasma corticosterone level—A total of 13 A/J male mice were used to investigate if mild footshock increased plasma corticosterone levels. Similar to D2 mice, mild footshock did not significantly increase plasma corticosterone in males of the A/J strain compared to the no footshock control animals (*t*-test, $t(11df) = 0.619$, $P > .10$; see Table 1).

Discussion

Acute footshock stress produced a significant increase in the amount of ethanol consumed by male B6 mice in the 23-h period following the footshock procedure compared to control (nonshocked) animals. In addition, the mild foot-shock increased plasma corticosterone levels in the B6 mouse strain. However, these effects were selective to B6 mice in that no significant change was observed in either A/J or D2 male mice on any of the measures (ethanol consumption or plasma corticosterone).

The significant difference in ethanol consumption following the acute footshock procedure in B6 mice is due to two related factors. First, simply being placed in the shock chamber, but not actually undergoing the footshock procedure, resulted in a significant decrease in ethanol intake in the following 23-h period. Secondly, undergoing the shock procedure produced an increase in ethanol intake compared to the prior 12 days; however, this increase was not statistically significant.

It is unclear what factors could have influenced the significant decrease in ethanol self-administration in B6 mice following placement in the shock chamber. Animals were randomly

assigned to either the shock or no shock condition, shock chambers were cleaned between each animal and subjects all received the ethanol-containing bottles at the same time in the light/dark phase. In addition, the shock chamber was novel for both animals in the shock condition and animals in the no shock condition. It is interesting to speculate about the relationship of this data to other previous reports about the effect of footshock stress on ethanol self-administration. In previous studies, relatively high footshock intensity produced a reduction in ethanol self-administration (Fidler & LoLordo, 1996; Ng Cheong Ton et al., 1983; however, see Volpicelli et al., 1990) whereas the current results demonstrate that simply being placed in the shock chamber (without footshock) also decreased ethanol self-administration. In contrast to these reductions, a mild footshock resulted in a modest increase in self-administration in B6 mice. This pattern is similar to that of a Yerkes–Dodson relationship (Yerkes & Dodson, 1908) where little to no stimulation and high levels of stimulation result in a decrease in behavior whereas a moderate amount of stimulation can increase responding (i.e., an inverted-U function). Probably the only way to understand this surprising relationship is to conduct a systematic and parametric study of footshock intensity on ethanol self-administration in B6 mice and allow animals to consume ethanol for longer periods of time following exposure to the shock chamber. Such a set of studies will provide further evidence to understand not only the effect of footshock on ethanol consumption but also if such effects are long lasting.

Mild footshock stress increased plasma corticosterone levels in B6 male mice but this effect was strain dependent in that the footshock stress did not increase plasma corticosterone in either male D2 mice or A/J mice. The B6 mice were also the only strain that demonstrated a significant effect of footshock stress on ethanol self-administration. Previous work has shown that acute injection of corticosterone can increase ethanol self-administration (Fahlke & Eriksson, 2000; Fahlke & Hansen, 1999; Fahlke et al., 1996). Given that B6 mice showed increases in plasma corticosterone as well as ethanol self administration it is possible that footshock either increased corticosterone levels which directly resulted in greater ethanol consumption, or that plasma corticosterone levels and ethanol intake were directly and simultaneously increased by footshock-induced activation. However, it must be noted that corticosterone levels in the current study were collected in ethanol naive animals and as such this limits the predictive validity of how footshock affects corticosterone levels in animals that have self-administered ethanol for 12 days. In addition, plasma for corticosterone determination was collected immediately following termination of the footshock procedure and therefore may have missed the peak corticosterone response, which has been shown to differ as a function of the mouse strain tested (Jones et al., 1998; Treiman et al., 1970). Finally, identified corticosterone levels cannot be compared to a ‘‘cage’’ control (animals that were not placed into the shock chambers) and therefore the exact increase in plasma corticosterone is unknown.

The effect of mild footshock on ethanol drinking and plasma corticosterone levels was strain dependent. Such an effect is likely not due to shock intensity as the B6 animals received ~50% less shock than did the D2 and A/J animals. Given that the shock intensity used was yoked to the intensity that each strain vocalized, it is likely that genetic variation between strains influences the effect of footshock on these responses. Recently, we have demonstrated a QTL for vocalization sensitivity to footshock intensity on chromosome 1 (Matthews et al., data under review). Furthermore, it is possible that mice in the ethanol self-administration condition had measureable amounts of ethanol in their blood when placed into the shock chamber and this might have altered response to the footshock. Future studies need to include a set of animals where blood ethanol concentrations are measured at this time to investigate the effect of this potential confound. These data suggest that the relationship between footshock intensity, genetics, and ethanol self-administration is complex.

The effect of mild footshock stress on ethanol self-administration is not dramatic. For example, mild footshock stress did not alter ethanol drinking in either D2 or A/J male mouse strains.

Furthermore, preliminary data from our lab indicates that mild footshock does not alter ethanol self-administration in female C57, D2, or A/J mice. In fact, the significant change in B6 ethanol self-administration in the current work was due to a mild increase in ethanol self-administration following footshock coupled with a significant decrease in drinking among animals that were placed in the shock boxes but did not receive footshock. In the current experiment, the relatively moderate effectiveness of footshock on ethanol consumption is surprising considering footshock stress is a common procedure to reinstate ethanol self-administration (for review see Le & Shaham, 2002; Le et al., 1998; Liu & Weiss, 2003; Martin-Fardon et al., 2000). These results are therefore suggestive that footshock may not be an optimal stressor for investigating ongoing ethanol consumption in mice.

Humans frequently report stress reduction is one reason for ethanol consumption (Conger, 1956; Goeders & Goeders, 2004; Volpicelli, 1987). The current studies sought to investigate if mild footshock is a useful procedure to study the relationship between stress and ethanol consumption in three commonly used mouse strains. Given that high shock intensities often produces mixed results on ethanol consumption (Fidler & LoLordo, 1996; Ng Cheong Ton et al., 1983; Volpicelli et al., 1990) and mild shock intensities produce minimal effects (current data), additional research is needed to establish procedures beyond footshock to investigate the relationship between stress and ongoing ethanol consumption in rodents.

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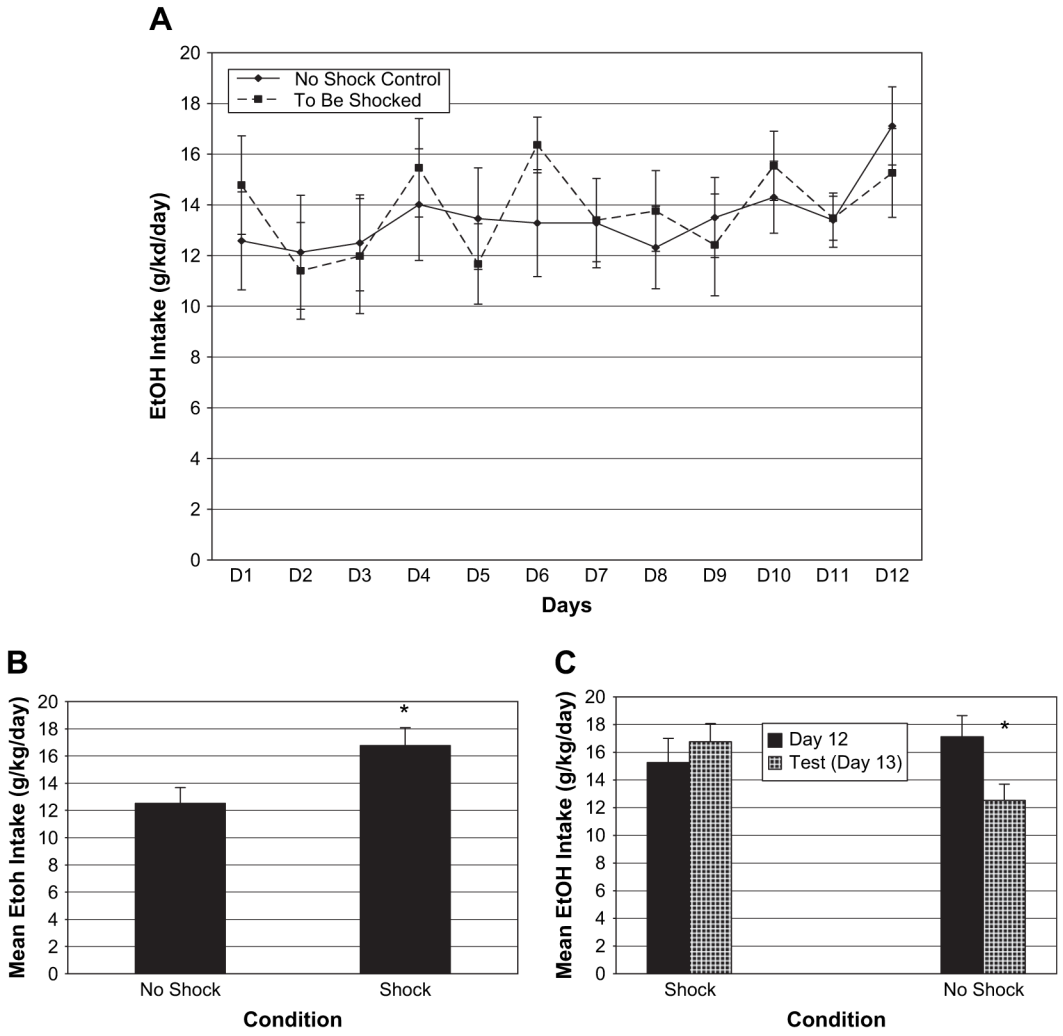

Fig. 1.

(A) Mean ethanol intake in C57BL/6J (B6) mice as a function of shock or no shock condition. Animals consumed ethanol for 12 days prior to foot-shock. As expected, no significant difference in ethanol intake was found across the 12 days of consumption. Error bars denote standard error of the mean. (B) Twenty-three h ethanol intake in B6 mice was significantly affected by 15 min of inescapable footshock. Specifically, a significant difference in the amount of ethanol consumed was found between B6 mice that received footshock compared to B6 mice that did not receive footshock. * denotes $P < .05$, error bars denote standard error of the mean. (C) The significant change in ethanol intake by footshock is due to a small increase in ethanol consumption in the B6 mice that received footshock and a significant reduction in ethanol intake in the B6 mice that were placed in the shock chambers but did not receive footshock. * denotes $P < .05$, error bars denote standard error of the mean.

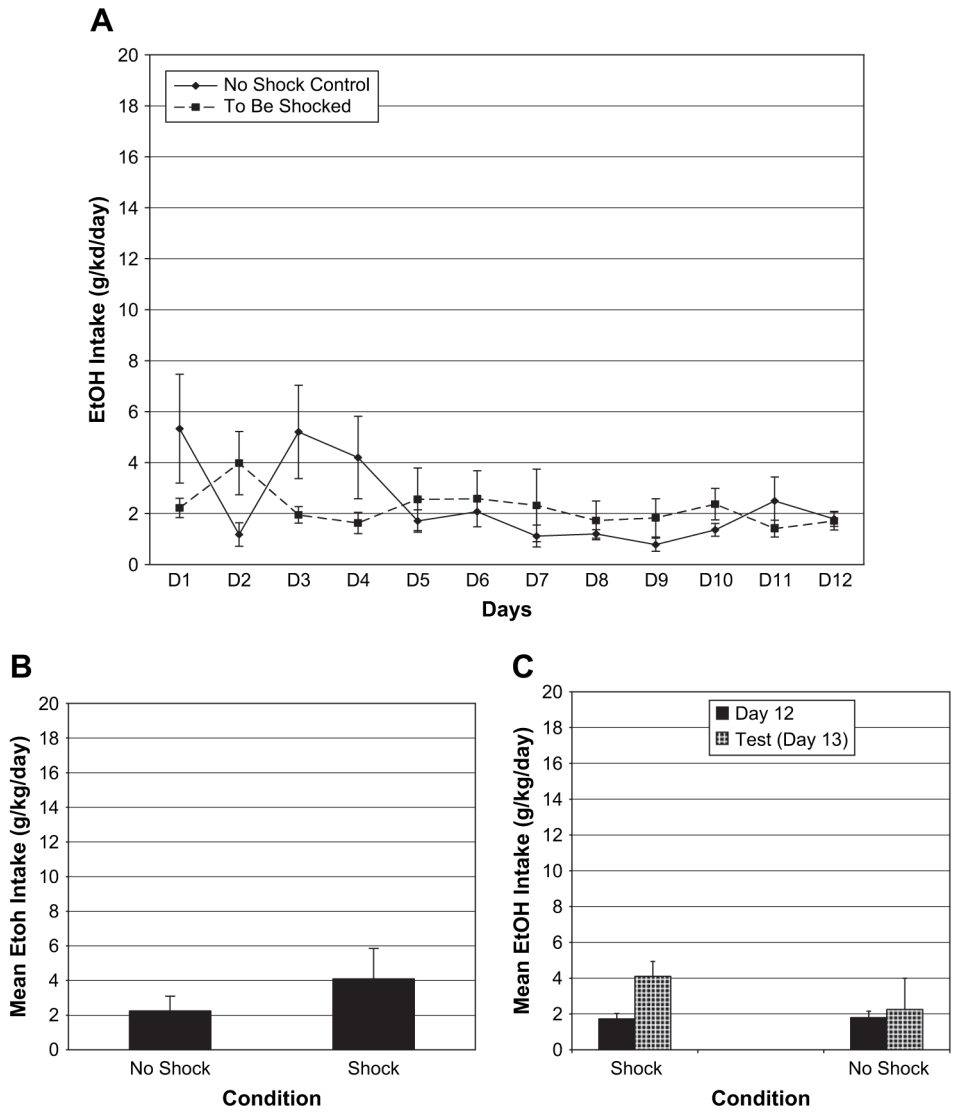

Fig. 2.

(A) Mean ethanol intake in DBA/2J mice as a function of shock or no shock condition. Animals consumed ethanol for 12 days prior to footshock. A significance difference in ethanol consumption was found on day 2; however, no significance difference in consumption between the two groups was found on the remaining 11 days. * denotes $P < .05$, error bars denote standard error of the mean. (B) Twenty-three h ethanol intake in DBA/2J mice was not significantly affected by 15 min of inescapable footshock. (C) Footshock stress did not significantly alter ethanol intake in either the shock or no shock condition in DBA/2J male mice.

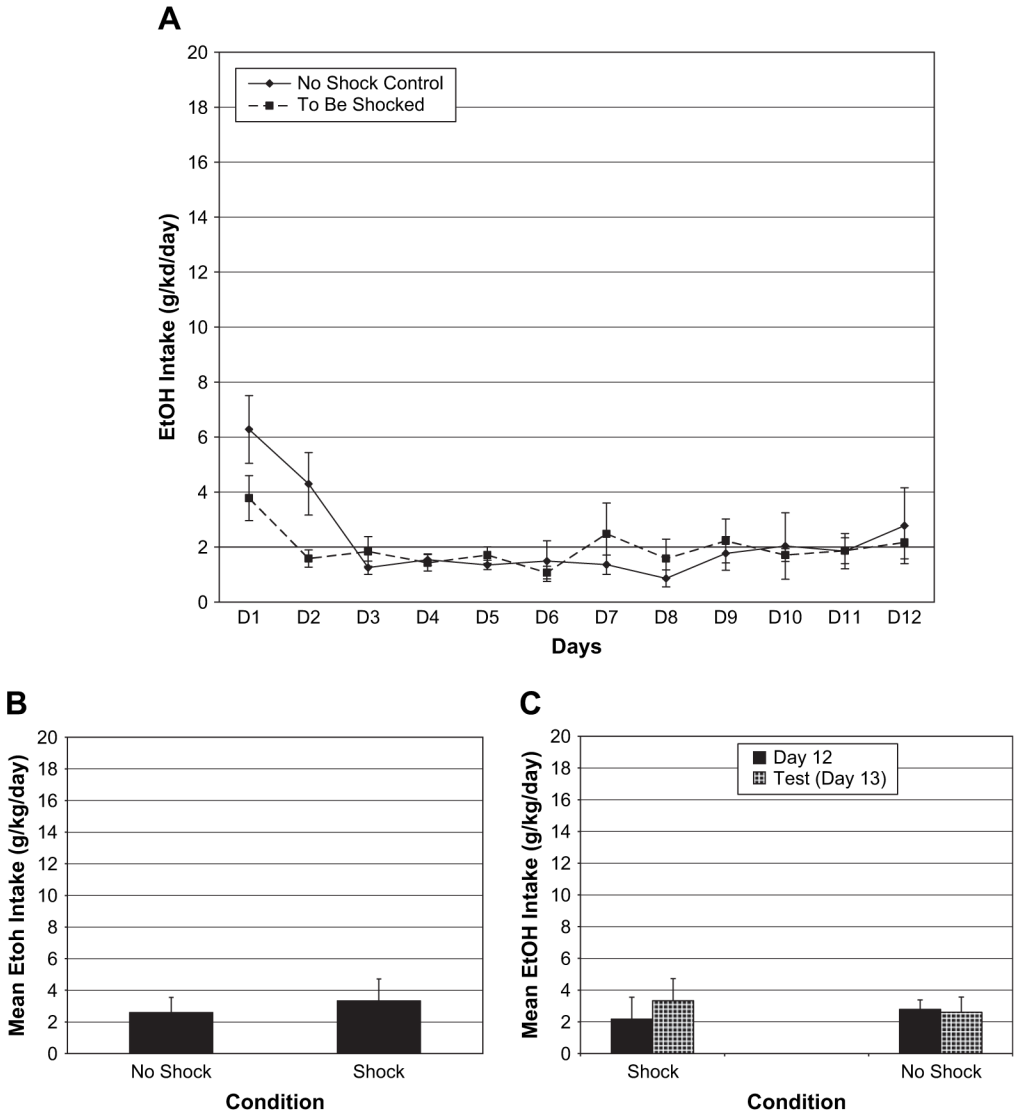

Fig. 3.

(A) Mean ethanol intake in A/J mice as a function of shock or no shock condition. Animals consumed ethanol for 12 days prior to footshock. A significance difference in ethanol consumption was found as a function of day; however, no significance difference in consumption between the two groups was found on any day of ethanol self-administration. (B) Twenty-three h ethanol intake in A/J mice was not significantly affected by 15 min of inescapable footshock. (C) Footshock stress did not significantly alter ethanol intake in either the shock or no shock condition in A/J male mice.

Table 1

Effect of mild footshock on plasma corticosterone levels in three mouse strains[a]

Strain	Corticosterone in shocked animals (ng/ml)	Corticosterone in not shocked animals (ng/ml)
C57BL/6J	80.6 (9.4)[a]	39.2 (8.4)
DBA/2J	127.3 (17.87)	86.1 (36.92)
A/J	50.7 (10.96)	73.5 (37.8)

[a]Levels of plasma corticosterone were significantly elevated in shocked animals (*t*-test, $P < .05$). Values in parentheses indicate the standard error of the mean.