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Effects of acute alcohol withdrawal on nest building in mice selectively bred for alcohol withdrawal severity

Gian D. Greenberg [a,b,d,*], Tamara J. Phillips [a,b,c,d], John C. Crabbe [a,b,c,d]

[a] Department of Behavioral Neuroscience, Oregon Health & Science University, Portland, OR, USA
[b] Portland Alcohol Research Center, Portland, OR, USA
[c] Methamphetamine Abuse Research Center, Portland, OR, USA
[d] VA Portland Health Care System, Portland, OR, USA

HIGHLIGHTS

- Nest building is dose-dependently impaired by acute ethanol withdrawal in mice.
- Nest building deficits were present in mice selectively bred for high and low withdrawal severity from chronic ethanol vapor.
- Nest building deficits could not be explained by a general decrease in locomotor activity.

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ABSTRACT

Nest building has been used to assess thermoregulatory behavior and positive motivational states in mice. There are known genetic influences on ethanol withdrawal severity as well as individual/thermoregulatory nest building. Withdrawal Seizure-Prone (WSP-1, WSP-2) and Withdrawal Seizure-Resistant (WSR-1, WSR-2) mice were selectively bred for high vs low handling-induced convulsion (HIC) severity, respectively, during withdrawal from chronic ethanol vapor inhalation. They also differ in HIC severity during withdrawal from an acute, 4 g/kg ethanol injection. In our initial study, withdrawal from an acute dose of ethanol dose-dependently impaired nest building over the initial 24 h of withdrawal in genetically segregating Withdrawal Seizure Control (WSC) mice. In two further studies, acute ethanol withdrawal suppressed nest building for up to two days in WSP-1 females. Deficits in nest building from ethanol were limited to the initial 10 h of withdrawal in WSR-1 females and to the initial 24 h of withdrawal in WSP-1 and WSR-1 males. Effects of ethanol on nest building for up to two days were found in WSP-2 and WSR-2 mice of both sexes. Nest building deficits in female mice from the first replicate could not be explained by a general decrease in locomotor behavior. These results suggest that nest building is a novel behavioral phenotype for indexing the severity of acute ethanol withdrawal, and that genes contributing to this trait differ from those affecting acute withdrawal HIC severity.

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1. Introduction

Alcohol (ethanol) withdrawal is a core component of alcohol use disorders with many genetic contributions [41]. This genetic complexity may explain why cessation of chronic ethanol exposure is associated with a wide variety of behavioral states in rodent models, including decreased locomotor activity [29], behavioral despair [30], and disrupted thermoregulation [50]. The handling-induced convulsion (HIC) index was developed over 40 years ago as a quantitative index of severity of withdrawal from chronic exposure to ethanol vapor [21], and enhanced sensitivity to convulsive treatments have been reported following a single high dose of ethanol in mice [43]. Many pharmacological [7] and genetic [44,45] studies have increased our understanding of exacerbated HICs during withdrawal following a single ethanol exposure. Although less is known about behavioral responses other than HICs during this period, there is recent evidence from mouse models suggesting acute withdrawal-associated modulations of pain sensitivity, affective state, and learning [27,58]. The genetic contributions to many behavioral responses during acute ethanol withdrawal have also not been explored. Thus, behavioral assays that can detect acute ethanol withdrawal states in mice and can provide genetic information could be of great use.

Nest building is an activity that can be observed in the home cage of mice. When a mouse of either sex is given nesting material, it will retrieve it, deposit it in a central site, and begin to build walls. Nests differ in quality, but a complete, high-quality nest has enclosing walls that can

* Corresponding author at: VA Portland Health Care System, R&D 12, 3710 SW US Veterans Hospital Rd., Portland, OR 97239, USA.
E-mail address: greenbeg@ohsu.edu (G.D. Greenberg).

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serve to provide shelter and minimize heat loss [11,17]. The latency for a mouse in a laboratory setting to retrieve nesting material and begin manipulating it for several seconds is approximately 30 min to 1 h [26], and other variations of nest-building tests indicate that nesting material is incorporated into an established nest site in under 7 min [51]. Other studies suggest that mice will work to obtain nesting material or employ it for thermoregulation. Mice will key press to dispense paper nesting material [52,53], and they will expend time and energy moving it from one cage to another held at a preferred temperature [16]. Whether nest building is an intrinsically motivated behavior or an instrumental response to the availability of a substrate for thermoregulation, these studies suggest the sequence is a highly motivated process. Decreased nest building in small mammals has been suggested to reflect anhedonic state [9,12]. Although ethanol withdrawal and nest building are complex traits, there is evidence for genetic contributions for each. Thus, nest building could be assessed during acute ethanol withdrawal to further understand the genetics that underlie withdrawal-induced impairments in affective states and thermoregulation.

Evidence for genetic influences on acute ethanol withdrawal has come from selectively-bred and inbred strains of mice [4]. With bidirectional selective breeding, individuals from a population are chosen to mate based on their high or low scores on a trait of interest (i.e., their phenotypic value). As this process is repeated across generations, a selected line eventually approaches homozygosity for all trait-relevant genes; this progression is known as allele fixation. The oppositely-selected line will fix different alleles for the same genes, and/or alleles for other influential genes. These genes can influence other traits, revealed when the divergently-selected lines differ in those genetically correlated responses to selection. Pairs of selectively-bred lines are often generated in two replicates from independent sets of families, and evidence for a genetic correlation is stronger when both replicate pairs display a difference in a correlated response in the same direction [8].

To study ethanol withdrawal severity, two replicate pairs of selected lines of mice were bred from a genetically heterogeneous founder population for increased [i.e., the Withdrawal Seizure-Prone (WSP-1 and WSP-2)] and decreased [i.e., the Withdrawal Seizure-Resistant (WSR-1 and WSR-2)] HIC scores during withdrawal after a period of chronic ethanol vapor inhalation [5]. Thus, correlated traits that are seen to differ between WSP vs WSR mice, particularly when differences are seen in both replicates in the same direction, are assumed to be influenced by genes underlying ethanol withdrawal severity [8]. WSP mice from both replicates also display greater HIC responses after withdrawal from acute ethanol than their corresponding WSR lines, which provides strong evidence for a genetic correlation between withdrawal severity from acute and chronic ethanol exposure [6,31].

Evidence for genetic influences on nest building has similarly stemmed from mice bidirectionally selected for the quantity of nesting material used at room temperature [38]. By generation 15, mice from both replicates of a high-nesting selected line had achieved an eight-fold difference in nesting compared to the low selected mice, with future generations achieving a 40-fold difference between high and low lines [39]. Tests for genetic influences on nest building have been performed for over a half decade, beginning with comparisons of inbred strains and F1 crosses [2,36]. Differences in nesting behavior across inbred strains have suggested heritable differences in the behavior [40] that also interact with environmental variables, such as changes in room temperature [36]. Although there is evidence for gene-environment interactions producing differences in nest building, we are not aware of any studies that have investigated interactions with alcohol or other drugs of abuse. Here, we investigate the interaction between genes and alcohol withdrawal for effects on qualitative nest building in mice.

We developed a rubric for scoring nest building in a genetically heterogeneous stock (HS/Npt/Pdx) of mice. HS/Npt/Pdx mice had increased HIC scores during withdrawal from 3 days of chronic ethanol vapor exposure, and chronic ethanol dose-dependently suppressed nest building for up to 32 h into withdrawal [22]. This suppression was also observed in mice after a single, acute injection of ethanol. Here, we further assessed the effects of acute ethanol withdrawal on nest building and tested for genetic influences and sex differences, with the null hypothesis that nest building would decrease after acute ethanol withdrawal. We first demonstrated dose-dependent deficits following acute ethanol withdrawal in another genetically heterogeneous mouse stock, the Withdrawal Seizure Control (WSC/Pdx) mice, which serve as the non-selected control line for the WSP and WSR mice and share their genetic background. We then tested whether there were systematic genetic differences in the nest-building deficit by studying the four WSP and WSR genotypes.

In a separate line of studies using HS/Npt/Pdx mice, we found that reduced nest building was observed up to 24 h into withdrawal from an acute 4 g/kg injection of ethanol before ethanol-withdrawn mice began to recover [22]. In earlier selected generations of WSP mice, signs of acute ethanol withdrawal as measured by HICs began to subside 12 h after injection of 4 g/kg ethanol before returning to baseline levels at 24 h [31]. HICs also returned to baseline in Swiss-Webster and inbred strains of mice (BALB/cJ and DBA/2J) 12 h after injection of 4 g/kg ethanol [44,45]. We tracked nest building during the first day of acute ethanol withdrawal when we hypothesized nest-building deficits would occur, and during the second day of withdrawal when we hypothesized nest-building deficits would subside.

Finally, we investigated whether nest-building deficits reflected overall decreases in locomotor behavior using activity monitoring chambers in combination with acute ethanol withdrawal in female WSP-1 and WSR-1 mice. We tested three hypotheses: 1) that decreased activity 10–24 h after acute ethanol withdrawal might underlie nest building deficits specific to female WSP-1 mice, 2) that decreased activity could explain the delayed recovery from withdrawal-induced nest building deficits 24–32 h after injection in female WSP-1 mice, and 3) that the decreased nest building, either due to acute ethanol withdrawal or genetic factors, in all female groups compared to female WSR-1 mice given saline evident at 10 h after injection simply reflected lower activity in those groups during hrs 6–10.

2. Materials and methods

2.1. Animals and husbandry

Naïve male and female WSP-1/Pdx and WSP-2/Pdx and WSR-1/Pdx and WSR-2/Pdx mice and their non-selected controls (WSC/Pdx) were used. The founder population for these mice were from a heterogeneous stock (HS/Ibg) derived from an 8-way cross of inbred strains (A/J, AKR, BALB/c, C3H, C57BL/6, DBA/2, RIII and AKR). The inbred strains are a mix of *M. m domesticus*, *M. m. musculus*, *M. m. castaneus*, and possibly *M. m. bactrianus*, but the most prominent strain is *M. m. domesticus* [55]. WSP and WSR mice were selectively bred for 25 generations [5], and have since been maintained under relaxed selection with quasi-random mating (within line). The tested mice were from generations $S_{26}G_{134}$ and $S_{26}G_{135}$, where S_{xx} refers to the number of selection generations, and G_{yy} refers to the total number of breeding generations that have elapsed since the beginning of selection. After weaning and prior to experiments, same-sex mice were housed 1–5 animals per plastic cage ($28 \times 17 \times 11.5$ cm; Thoren Caging Systems, Hazelton, PA, USA) lined with ECOFresh bedding (Absorption Corporation, Ferndale, WA, USA) with stainless-steel wire tops; rodent chow 5001 (PMI Nutrition International, Brentwood, MO, USA) and tap water were available ad libitum. All colony and procedure rooms were on a 12 h:12 h light:dark cycle (lights on at 0600 PDT) at a temperature of 21 ± 1 °C. We aimed to have 10 mice per sex and ethanol treatment group for each experiment. We previously reported that this number of animals produced significant ethanol effects on nest building [22]. Mice were euthanized via CO_2 asphyxiation followed by cervical dislocation after the completion

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