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The effect of prior alcohol consumption on the ataxic response to alcohol in high-alcohol preferring mice

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ABSTRACT

We have previously shown that ethanol-naïve high-alcohol preferring (HAP) mice, genetically predisposed to consume large quantities of alcohol, exhibited heightened sensitivity and more rapid acute functional tolerance (AFT) to alcohol-induced ataxia compared to low-alcohol preferring mice. The goal of the present study was to evaluate the effect of prior alcohol self-administration on these responses in HAP mice. Naïve male and female adult HAP mice from the second replicate of selection (HAP2) underwent 18 days of 24-h, 2-bottle choice drinking for 10% ethanol vs. water, or water only. After 18 days of fluid access, mice were tested for ataxic sensitivity and rapid AFT following a 1.75 g/kg injection of ethanol on a static dowel apparatus in Experiment 1. In Experiment 2, a separate group of mice was tested for more protracted AFT development using a dual-injection approach where a second, larger (2.0 g/kg) injection of ethanol was given following the initial recovery of performance on the task. HAP2 mice that had prior access to alcohol exhibited a blunted ataxic response to the acute alcohol challenge, but this pre-exposure did not alter rapid within-session AFT capacity in Experiment 1 or more protracted AFT capacity in Experiment 2. These findings suggest that the typically observed increase in alcohol consumption in these mice may be influenced by ataxic functional tolerance development, but is not mediated by a greater capacity for ethanol exposure to positively influence within-session ataxic tolerance.

Introduction

Alcohol use disorders have been demonstrated to have a substantial genetic component (Ducci & Goldman, 2008; Mayfield, Harris, & Schuckit, 2008; Schuckit, 2009), with a positive family history having significant predictive value. Recognizing a genetically predisposed state has significant clinical importance; however, the ultimate health concern is whether these individuals, if they choose to consume alcohol, escalate their consumption to dangerous levels (Warner, White, & Johnson, 2007). Exploring the adaptive processes (i.e., tolerance) that may be positively influenced by alcohol exposure and ultimately, allow these individuals to significantly increase their alcohol consumption over time, will enhance our understanding of how these processes *themselves* may adapt and drive continued drinking. As it is difficult to account for environmental variables and the subjects' alcohol use history in human studies, animal models offer a powerful approach for addressing this issue.

Numerous lines of rodents have been selectively bred for divergent alcohol intake (i.e., high/low). Similar to the human literature, studies have shown that these opposite genetic predispositions can associate with highly different responses to alcohol in these lines of rodents (Chester, Lumeng, Li, & Grahame, 2003; Crabbe, Colville, et al., 2012; Crabbe, Kruse, et al., 2012; Fritz et al., 2014; Fritz, Grahame, & Boehm, 2013; Grahame, Rodd-Henricks, Li, & Lumeng, 2000; Waller, McBride, Lumeng, & Li, 1983), suggesting that these responses 'genetically correlate' with the alcohol consumption phenotype. In other words, these associations can be indicative of common underlying genes for the response(s) of interest and form of alcohol consumption. One interpretation is that these various responses (ataxia, stimulation, etc.) are components of the complex phenotypes that are high/low alcohol consumption (Crabbe, Phillips, Kosobud, & Belknap, 1990).

Recently, we have shown that selectively bred high- and low-alcohol preferring mice (HAP and LAP) differ in their sensitivity

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and capacity to develop acute functional tolerance (AFT) to alcohol's ataxic effects. HAP mice are particularly sensitive to these effects on the ascending limb of the blood ethanol concentration (BEC) curve, as ethanol is being absorbed (Fritz et al., 2013). Furthermore, HAP mice have a significantly greater AFT capacity than do LAP mice. These findings appear to support the alcohol consumption phenotype of HAP mice because alcohol's intoxicating effects may become salient more rapidly, thereby tightening the temporal relationship between alcohol exposure and its effects. In addition, these mice are able to rapidly (<30 min) overcome impairment at significantly higher BECs, suggesting greater AFT capacity. The high ethanol intake of HAP mice may reflect, in part, a significant ability to rapidly overcome this alcohol-induced motor impairment, with sustained drinking throughout their active circadian phase in an attempt to achieve an earlier intoxication state that can quickly be masked by AFT.

One question raised by this previous study was whether an alcohol consumption history altered these ataxic responses to ethanol in HAP mice. These lines typically demonstrate an increase in 10% ethanol intake/preference over days in a continuous-access 2-bottle choice paradigm (Grahame, Li, & Lumeng, 1999; Matson & Grahame, 2011; Oberlin, Best, Matson, Henderson, & Grahame, 2011). Given the already demonstrated impressive rapid AFT capacity in ethanol-naïve HAP mice (Fritz et al., 2013), their capacity to escalate ethanol consumption over days may also be reflective of an enhanced ability for alcohol exposure to positively influence this response. This notion is supported by a previous study demonstrating that the AFT capacity of a mouse line selectively bred to develop a high degree of AFT (HAFT) following acute ethanol administration was augmented by alcohol pre-exposure (Wu, Tabakoff, Szabó, & Hoffman, 2001). We hypothesized that a history of alcohol consumption would enhance AFT to alcohol-induced ataxia in HAP mice.

Materials and methods

Animals

Naïve adult (postnatal day 60–95) male and female mice from the second replicate of a line selected for high (HAP2) alcohol preference drinking were bred on site at the IUPUI School of Science, Indianapolis, IN (for an in-depth description of the selection process and characterization of these lines, see Oberlin et al., 2011). Three replicates of the HAP/LAP lines now exist and there are extreme differences in alcohol intake and preference with the replicate HAP lines consuming high, intoxicating amounts of alcohol, and replicate LAP lines demonstrating relative avoidance (Oberlin et al., 2011). Only HAP2 mice were used as we previously demonstrated that the genetic differences in ataxic ethanol sensitivity and AFT were present in both replicates 2 and 3 (Fritz et al., 2013). Therefore, testing replicate 3 was deemed unnecessary. Furthermore, the ethanol intake of HAP2 mice is greater and more stable than HAP3 mice (Matson & Grahame, 2011; Oberlin et al., 2011), perhaps because the selection process is further advanced.

All mice were from generations 43–44 of selection. Animals were singly housed and maintained on a 12-h light/dark cycle with lights on at 2300; testing took place between 2300 and 0500. Temperature and relative humidity were held constant near 20 °C and 50%, respectively. Food was available *ad libitum* and fluids were provided as described below. All experiments were performed under a protocol approved by the IUPUI Institutional Animal Care and Use Committee and were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Ethanol administration

One hundred ninety proof ethanol was purchased from Pharmco Inc. (Brookfield, CT) and diluted in sterile 0.9% physiological saline to a concentration of 15% v/v. The solution was freshly mixed each test day. Ethanol was administered via intraperitoneal (i.p.) injection in weight-based doses of 1.75 g/kg or 2.0 g/kg.

Two-bottle choice drinking

All mice were exposed to the 2-bottle choice drinking procedure, in the same manner in which the lines were selected (Grahame et al., 1999), for 18 days. This duration was chosen because ethanol intake typically plateaus for HAP2 mice by this point (Oberlin et al., 2011). One group of HAP2 mice (E) had access to 10% (v/v) ethanol and tap water in the home cage via modified 25-mL graduated cylinders, and another group (W) had access to tap water only. Volume readings were taken at 1000, 1 h before lights-out, every other day, and the designated fluids were replaced. The position of the tubes (left or right side of the cage) was also rotated every other day to avoid the development of a side preference.

Static dowel task

Details concerning this behavioral assessment have been previously published (Fritz et al., 2013; Grahame et al., 2000). This task was employed to evaluate ethanol-induced ataxia by requiring mice to balance on an elevated wooden dowel horizontally centered in a Plexiglas® box (32 × 32 × 60 cm; l × w × h) to prevent falling. Ethanol interferes with the ability to perform this task and 'loss of function' (LOF) was declared live by a trained researcher when the majority of the mouse's body was observed to swing below the imaginary horizontal plane that bisects the dowel (Fritz et al., 2013).

Experiment 1: Mellanby (single recovery) approach

As previously published (Fritz et al., 2013, 2014), this assessment is referred to as the 'Mellanby' approach to AFT quantification as it employs his original conceptualization of the phenomenon, based on observations in canines, by comparing intoxication on the ascending and descending limbs of the time-BEC curve over the course of a *single alcohol exposure* (Mellanby, 1919). In this manner, AFT can be considered 'within-session tolerance' and is herein referred to as 'M-AFT'. This form of tolerance may be instrumental in the ability of an individual to engage in long, excessive drinking sessions.

Immediately following the fluid reading after the 18th day of 2-bottle choice drinking, mice that had previously had access to ethanol had this tube removed, leaving only water. The other groups had one of their water bottles removed. This was done to ensure that the mice had no ethanol in their systems during the static dowel assessment. At lights-on (2300), mice were moved into the testing room to habituate for 1 h. All animals then received 3 training trials by placing them on the dowel for 1 min approximately every 5–8 min to ensure that they could perform the task. Mice were then individually injected with a 1.75 g/kg dose of ethanol (i.p.) and immediately placed on the dowel. At the point of LOF, a periorbital blood sample (25 μL) was rapidly collected and this value served as the index of sensitivity. Because BEC rises very rapidly following an i.p. injection (on the ascending limb), care was taken to include only samples that were obtained within 8 s of LOF in the analyses. Mice were then returned to their home cage and retested approximately every 5–8 min until they were able to