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Chronic intermittent ethanol inhalation increases ethanol self-administration in both C57BL/6J and DBA/2J mice

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ABSTRACT

Inbred mouse strains provide significant opportunities to understand the genetic mechanisms controlling ethanol-directed behaviors and neurobiology. They have been specifically employed to understand cellular mechanisms contributing to ethanol consumption, acute intoxication, and sensitivities to chronic effects. However, limited ethanol consumption by some strains has restricted our understanding of clinically relevant endpoints such as dependence-related ethanol intake. Previous work with a novel tastant-substitution procedure using monosodium glutamate (MSG or umami flavor) has shown that the procedure greatly enhances ethanol consumption by mouse strains that express limited drinking phenotypes using other methods. In the current study, we employ this MSG-substitution procedure to examine how ethanol dependence, induced with passive vapor inhalation, modifies ethanol drinking in C57BL/6J and DBA/2J mice. These strains represent 'high' and 'low' drinking phenotypes, respectively. We found that the MSG substitution greatly facilitates ethanol drinking in both strains, and likewise, ethanol dependence increased ethanol consumption regardless of strain. However, DBA/2J mice exhibited greater sensitivity dependence-enhanced drinking, as represented by consumption behaviors directed at lower ethanol concentrations and relative to baseline intake levels. DBA/2J mice also exhibited significant withdrawal-associated anxiety-like behavior while C57BL/6J mice did not. These findings suggest that the MSG-substitution procedure can be employed to examine dependence-enhanced ethanol consumption across a range of drinking phenotypes, and that C57BL/6J and DBA/2J mice may represent unique neurobehavioral pathways for developing dependence-enhanced ethanol consumption.

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Introduction

Inbred mouse strains have been employed by alcohol researchers to understand the genetic basis for ethanol consumption, sensitivity, and reward. For example, C57BL/6J (B6) and DBA/2J (D2) represent extremes in both drinking phenotype (B6 > D2; see Belknap & Atkins, 2001; Rhodes et al., 2007; Yoneyama, Crabbe, Ford, Murillo, & Finn, 2008) and behavioral/physiological sensitivity to ethanol (generally D2 > B6; reviewed by Crabbe, Phillips, Buck, Cunningham, & Belknap, 1999; Crawley et al., 1997). Recombinant inbred lines (BXD lines) and more recently F(2) populations derived from crosses between B6 and D2 mice have been used to understand genetic mechanisms controlling ethanol consumption/preference, reward, and sensitivity to both acute and chronic withdrawal. While these complex behaviors are clearly controlled by many gene products, several gene candidates strongly influence many of these phenotypes. For example, synaptic trafficking/scaffolding molecules including Syntaxin 12 (Weng, Symons, & Singh, 2009) and Munc18-1 (Fehr et al., 2005) help control ethanol consumption/preference. Additionally, dopamine D2 receptors appear to regulate ethanol reward, as represented by conditioned place preference (Hitzemann et al., 2003). Notably, dependence-enhanced ethanol drinking has not been as extensively studied using recombinant inbred lines. This likely reflects the strong negative correlation between ethanol consumption and withdrawal sensitivity (Metten et al., 1998).

We have recently described a tastant-substitution procedure using monosodium glutamate that initiates considerable ethanol drinking by traditionally low-drinking/preferring strains such as DBA/2J (D2) mice (McCool & Chappell, 2012, 2014). Although sucrose/saccharine substitution procedures are well established (Samson, 1986), they have limited efficacy in initiating ethanol drinking by D2 mice despite robust ethanol-seeking behaviors expressed by this strain (Chester & Cunningham, 1999). Since ethanol taste contains both sweet and bitter components (Blizard,

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2007), the drinking versus seeking dichotomy in D2 mice may reflect their diminished ability to sense both the sweet components in ethanol itself as well as the sucrose/saccharine used to mask the bitter (aversive) components. Monosodium glutamate, the principle chemical component of umami flavor, is not only rewarding (Jones, Chappell, & Weiner, 2007; Uematsu et al., 2011), but also interacts with several different potential taste receptors (Delay et al., 2000; Inoue et al., 2007; Nakashima, Eddy, Katsukawa, Delay, & Ninomiya, 2012), which would theoretically limit effects of single-gene polymorphisms. Further, monosodium glutamate also conditions taste preference via post-ingestion mechanisms (Ackroff & Sclafani, 2013; Niijima, 1991; Shibata, Kameishi, Kondoh, & Torii, 2009). These characteristics may favorably interact with ethanol during the substitution procedure for mice like the D2 strain.

Ethanol dependence consistently enhances voluntary ethanol drinking both in humans and in a number of animal models. In rodents, ethanol dependence models have included forced consumption of an ethanol-containing liquid diet and passive inhalation of ethanol vapor. As long as ethanol taste aversion is avoided in the experimental design, these dependence models enhance ethanol drinking, seeking, and preference. In rats, for example, ethanol dependence via vapor exposure enhances operant responding for ethanol across a range of chronic exposure and abstinence periods (Ciccocioppo, Lin, Martin-Fardon, & Weiss, 2003; Roberts, Heyser, Cole, Griffin, & Koob, 2000; Sidhpura, Weiss, & Martin-Fardon, 2010). Ethanol drinking in dependent rats is also characterized by a distinct sensitivity to various pharmacological manipulations (de Guglielmo, Martin-Fardon, Teshima, Ciccocioppo, & Weiss, 2014; Funk, O'Dell, Crawford, & Koob, 2006; Gilpin & Koob, 2010; Rimondini, Thorsell, & Heilig, 2005; Sidhpura et al., 2010), suggesting that dependence exerts a unique influence on the neurobiological mechanisms controlling ethanol self-administration. Ethanol dependence also increases ethanol consumption in mouse strains such as C57BL/6J (B6) (Griffin, Lopez, & Becker, 2009), and shares some of the same pharmacology as in dependent rats (Chu, Koob, Cole, Zorrilla, & Roberts, 2007). While most studies have focused on B6 mice due to robust 'baseline' drinking, recent work using intragastic delivery has shown that dependence can in fact increase D2 ethanol self-administration (Cunningham, Fidler, Murphy, Mulgrew, & Smitasin, 2013; Fidler et al., 2012). However, the question remains whether oral consumption would be impacted in this strain. Further, the genetic diversity of mouse models has not been brought significantly to bear on dependence-enhanced drinking because of limited oral consumption by mice such as the D2 strain. The purpose of the current study was to employ a recently described substitution procedure with monosodium glutamate to ascertain whether ethanol dependence will increase ethanol drinking in D2 mice.

Materials and methods

Animals

Adult male C57BL/6J (B6, $n = 44$) and DBA/2J (D2, $n = 44$) mice were obtained from The Jackson Laboratory (Bar Harbor, ME) at approximately 5 weeks of age. Mice were housed individually in a reversed 12 h light cycle (7:00 AM lights off), with water and standard mouse chow offered *ad libitum*. Four days after arrival at our facility, we divided mice into two experimental groups. We subjected one group of mice to the substitution procedures followed by chronic intermittent ethanol vapor inhalation (Study 1) to measure dependence-related ethanol drinking. To avoid confounds between the extensive handling required for the drinking study and the negative affective states potentially produced by the dependence procedure, a separate experimental group of mice received only the chronic intermittent ethanol vapor inhalation, followed by exposure to the light/dark box assay to measure anxiety-like behaviors (Study 2). The experimental design for both experimental groups is shown in Fig. 1. All animal procedures were approved by the Wake Forest School of Medicine IACUC in accordance with the NIH Guide for the Care and Use of Laboratory Animals.

Drinking and substitution procedures

Mice were exposed to 100 mM monosodium glutamate (MSG in water; Sigma–Aldrich, St. Louis, MO) in the home cage using either a limited-access (2 h) or unlimited-access (24 h) two-bottle choice procedure (versus water alone) as described previously (McCool & Chappell, 2012, 2014). We used 5 mL serological pipettes (0.05 mL accuracy) to measure drinking during the 2 h limited-access, and 25 mL serological pipettes (0.2 mL accuracy) for the 24 h continuous-access drinking. Following this preference test, we employed an MSG-substitution procedure using a modified single-bottle, drinking-in-the-dark (DID) procedure (Rhodes, Best,

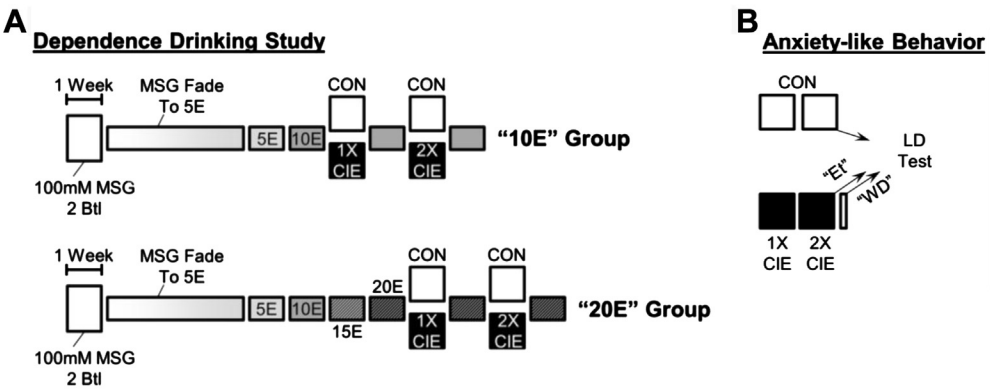

Fig. 1. *Experimental design.* (A) In the drinking study, animals were first subjected to a two-bottle preference test with 100-mM MSG during either 2 h or 24 h drinking sessions. We then used the MSG-substitution procedure as described previously (McCool & Chappell, 2012) to initiate drinking of 5% ethanol and subsequent increase in ethanol concentrations. Two cohorts, one drinking 10% ("10E" group) and another drinking 20% ethanol ("20E" group), were subjected to two separate exposures to either room air (CON) or chronic intermittent ethanol (CIE) inhalation to establish ethanol dependence (Becker & Hale, 1993). Ethanol drinking was measured 72 h after each dependence exposure. (B) In the anxiety study, animals were subjected to the two ethanol-dependence exposures. Anxiety-like behaviors were measured in the light/dark transition assay following the control exposure (CON), immediately after the last ethanol inhalation exposure while animals were still intoxicated (Et), or 72 h after the last ethanol inhalation (WD).

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