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Repeated episodes of chronic intermittent ethanol promote insensitivity to devaluation of the reinforcing effect of ethanol

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A B S T R A C T

Studies in animal models have shown that repeated episodes of alcohol dependence and withdrawal promote escalation of drinking that is presumably associated with alterations in the addiction neurocircuitry. Using a lithium chloride-ethanol pairing procedure to devalue the reinforcing properties of ethanol, the present study determined whether multiple cycles of chronic intermittent ethanol (CIE) exposure by vapor inhalation also alters the sensitivity of drinking behavior to the devaluation of ethanol's reinforcing effects. The effect of devaluation on operant ethanol self-administration and extinction was examined in mice prior to initiation of CIE (short drinking history) and after repeated cycles of CIE or air control exposure (long drinking history). Devaluation significantly attenuated the recovery of baseline ethanol self-administration when tested either prior to CIE or in the air-exposed controls that had experienced repeated bouts of drinking but no CIE. In contrast, in mice that had undergone repeated cycles of CIE exposure that promoted escalation of ethanol drinking, self-administration was completely resistant to the effect of devaluation. Devaluation had no effect on the time course of extinction training in either pre-CIE or post-CIE mice. Taken together, these results are consistent with the suggestion that repeated cycles of ethanol dependence and withdrawal produce escalation of ethanol self-administration that is associated with a change in sensitivity to devaluation of the reinforcing properties of ethanol.

Introduction

Alcoholism and alcohol abuse are a major problem worldwide with devastating health and societal consequences. While most individuals who consume alcohol can control their intake, a significant proportion of individuals cannot control their consumption and subsequently develop an addiction to alcohol that is characterized by uncontrollable and compulsive consumption. While studies have demonstrated that both positive and negative reinforcing properties of ethanol contribute to and promote self-administration (Becker, 2013; Heilig, Egli, Crabbe, & Becker, 2010; Koob, 2003; Meisch, 1982, 1984), accumulating evidence in rodents indicates that prolonged self-administration of ethanol is also associated with the development of ~~a~~ resistance to aversive stimuli associated with ethanol. For example, a study conducted in C57BL/6J mice showed that addition of quinine (an aversive tastant) to the ethanol solution lowered ethanol intake in mice with a short (2-week) history of voluntary ethanol intake. In contrast, when mice were allowed to self-administer ethanol for a longer period of time (8 weeks), they were no longer affected by this quinine-induced adulteration of ethanol, and continued to self-administer it despite the aversive taste (Lesscher, van Kerkhof, & Vanderschuren, 2010). Similar results were obtained in rats that had been drinking ethanol adulterated with quinine after a short (1.5 months) versus a long (3–4 months) history of ethanol self-administration (Hopf, Chang, Sparta, Bowers, & Bonci, 2010).

In addition to the differences in drinking behaviors observed in animals with a short versus long history of drinking, recent evidence has demonstrated that models of ethanol dependence that involve multiple episodes of withdrawal also promote changes in drinking behavior. For example, it was reported that subjecting rats to repeated cycles of chronic ethanol exposure and withdrawal resulted in resistance to the effect of adulteration of ethanol with quinine (Vendruscolo et al., 2012). In addition, studies in mice have shown that repeated cycles of chronic intermittent ethanol (CIE) exposure promote increases in voluntary ethanol consumption when tested using various 2-bottle choice drinking procedures (Becker & Lopez, 2004; Finn et al., 2007; Griffin, Lopez, & Becker, 2009; Griffin, Lopez, Yanke, Middaugh, & Becker, 2009; Lopez & Becker, 2005; Lopez, Griffin, Melendez, & Becker, 2012). Importantly, this heightened ethanol intake after CIE exposure is associated with increased blood

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(Becker & Lopez, 2004) and brain (Griffin, Lopez, Yanke, et al., 2009) ethanol concentrations compared to that measured in non-dependent mice that consume more moderate amounts of ethanol. In a recent study, we further observed that mice trained to lever press for ethanol using a fixed-ratio (FR) schedule exhibited significant increases in ethanol self-administration after CIE exposure (Lopez & Becker, under review). This CIE-induced elevation of operant oral ethanol self-administration engendered responding that was resistant to extinction and more sensitive to cue-induced reinstatement. While CIE-exposure models have clearly demonstrated escalated ethanol self-administration, it is not clear whether this augmented consumption reflects a change in the reinforcing value of ethanol. To begin to address this question, the present study examined whether the CIE-induced escalation of operant self-administration is also associated with changes in response to devaluation of the reinforcing properties of ethanol.

Methods

Subjects

Adult male C57BL/6 mice purchased from Jackson Laboratories (Bar Harbor, ME) were individually housed with free access to food (Harland Teklad, Madison, WI) and water throughout all phases of the experiments. Body weights were recorded weekly during ethanol self-administration or daily during chronic intermittent ethanol (CIE) or air exposure (detailed below). Mice were housed in a temperature- and humidity-controlled animal facility under a reversed 12-h light/dark cycle (lights on at 1800 h). All procedures were approved by the Institutional Animal Care and Use Committee and followed the NIH Guide for the Care and Use of Laboratory Animals (8th edition, National Research Council, 2011).

Study design

The general study design (Fig. 1) involved examination of the effects of devaluation on operant ethanol self-administration and extinction before or after repeated cycles of CIE or air control exposure. Mice tested before CIE exposure had 6 weeks of ethanol self-administration and are referred to as short-drinking history mice, and those tested after repeated CIE or air exposure as long-drinking history mice (10 weeks of ethanol self-administration). The study involved first establishing stable baseline levels of operant ethanol responding and intake, as described below. Mice were then separated into 2 groups to be exposed to either weekly cycles of CIE exposure (CIE group) or air control (CTL group) exposure. Seventy-two hours after each cycle of CIE (or air control) exposure, mice resumed ethanol self-administration for 5 consecutive days. This pattern of exposure followed by 5 days of ethanol self-administration was repeated for 4 cycles until the mice were used in studies to evaluate the effect of devaluation of ethanol on drinking behavior. Separate groups of mice received devaluation treatment after either baseline or a fifth cycle of CIE (or air control) exposure (see schema in Fig. 1). Mice were first evaluated for ethanol self-administration or extinction responding the day before initiation of the devaluation procedure. Seventy-two hours after the last devaluation session, mice were tested under regular self-administration or extinction conditions.

Operant ethanol self-administration

Standard chambers for mouse operant conditioning were used (Med Associates, Inc., St. Albans, VT). The operant boxes were housed in sound-attenuating boxes with exhaust fans. Stimulus events and responses were controlled and monitored using Med PC,

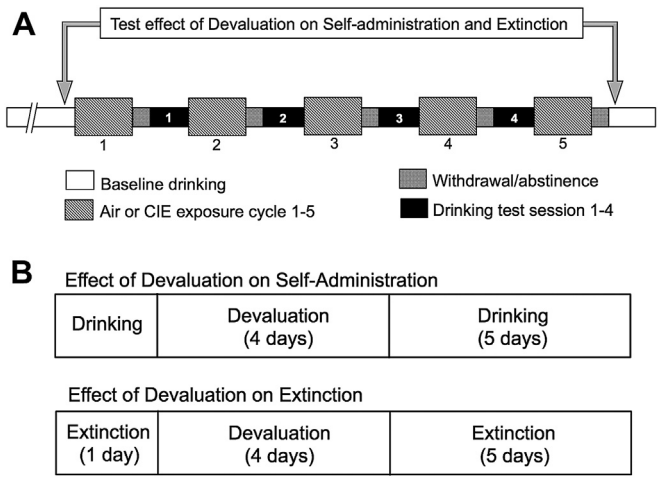

Fig. 1. Schematic depiction of the experimental design of the study. **A**. The effect of ethanol devaluation on ethanol self-administration and extinction was examined in mice with a short history of drinking prior to initiation of CIE and in mice with a long history of drinking after 5 cycles of CIE or air control exposure. **B**. In separate groups of mice, the effect of devaluation of the rewarding properties of ethanol was examined on operant ethanol self-administration (top) and extinction (bottom).

Version IV software (Med Associates, Inc., St. Albans, VT). Mice were not food- or water-deprived and were trained to self-administer ethanol using a modified sucrose fading procedure (Samson, 1986). All operant self-administration sessions were 30 min and were conducted 5 days per week (Mon–Fri) during the dark period of the light/dark cycle. Mice were placed in the operant box and the session began by introducing 2 levers into the box and turning on the house light. Once the subject pressed the active lever, an infusion pump was activated for 2 s to deliver the reinforcer into the well between the 2 retractable levers. For the duration of pump activation, ethanol delivery was cued by turning off the house light and presentation of a tone (80 dB) and yellow stimulus light. Responses on the inactive lever had no consequences. Initially, mice were trained to lever press under a Fixed Ratio 1 (FR1) schedule for the delivery of 20 μL of a 10% (v/v) ethanol solution combined with 5% (w/v) sucrose (10E/5S) during the daily 30-min sessions. Over successive days, the FR requirement was increased to 2 and finally to 4 responses on the active lever (FR4). After this initial period (4–5 days), the ethanol solution was increased and the sucrose solution reduced using 12E/5S, 12E/2S for 2 or 3 days each, and then 12E/1S was used for the remainder of the study. At the end of each session, any residual ethanol that was left in the well was measured and the amount was subtracted from the total self-administration volume. This corrected volume was used to calculate g/kg of ethanol intake during the session. Ethanol intake (g/kg) and number of responses on the active and inactive levers were recorded. After 2 weeks of sucrose fading, daily (Mon-Fri) ethanol self-administration sessions continued until mice reached stable ethanol self-administration (<15% change over 3 consecutive days in the number of responses). The final week of FR4 responding was used as a baseline for data analysis purposes. Mice resumed ethanol self-administration under the same conditions for 5 consecutive days after each CIE exposure cycle. During extinction sessions, neither ethanol nor ethanol-associated cues (tone and lights) were presented after lever pressing.

CIE exposure

Mice in the CIE group were exposed to ethanol vapor in inhalation chambers for 16 h a day separated by an 8 h withdrawal