ELSEVIER

Alcohol 38 (2006) 165–172

ALCOHOL

Decreased reward during acute alcohol withdrawal in rats selectively bred for low alcohol drinking

Julia A. Chester[a,*], Edward J. Rausch[a], Harry L. June[b], Janice C. Froehlich[a]

[a]*Department of Medicine, Indiana University School of Medicine, IB 424B, 975 W. Walnut Street, Indianapolis, IN 46202, USA*
[b]*Department of Psychology, Indiana University-Purdue University, Indianapolis, IN 46202, USA*

Received 4 October 2005; received in revised form 16 June 2006; accepted 16 June 2006

Abstract

We have previously hypothesized that increased sensitivity to the dysphoric-like or aversive effects of alcohol withdrawal following an initial exposure to alcohol might be associated with a genetic propensity to avoid alcohol. A decrease in brain reward function, as measured by an elevation in intracranial self-stimulation (ICSS) reward threshold, is one of the few methods available to model dysphoric-like or aversive effects of drug withdrawal in rats. We compared brain reward function during withdrawal following an initial exposure to alcohol in alcohol-naïve rats selectively bred for high (HAD1 line) versus low (LAD1 line) voluntary alcohol consumption. Male HAD1 ($n = 5$) and LAD1 ($n = 6$) rats were implanted with unilateral electrodes in the medial forebrain bundle and trained to bar press for delivery of a 100 μA current that varied in frequency from 45 to 200 Hz. Responding for ICSS was generally stable within subjects across multiple experimental sessions on a given day and across several consecutive days prior to alcohol or water administration. ICSS responding was assessed in both rat lines prior to and at 12, 14, 16, 18, 20, and 24 h following a single intragastric infusion of alcohol (4.0 g/kg body weight) or water. Rats of the LAD1 line, but not those of the HAD1 line, exhibited a decrease in brain reward function as evidenced by a decrease in bar-press responding for ICSS and an increase in ICSS stimulation threshold during alcohol withdrawal. The results suggest that rats selectively bred for low alcohol drinking may experience dysphoric-like effects during withdrawal from an initial exposure to alcohol, while rats selectively bred for high alcohol drinking may not.

Keywords: Intracranial self-stimulation (ICSS); Alcohol withdrawal; Aversion; Dysphoria; Selectively bred rat lines

1. Introduction

Alcohol withdrawal occurs in response to a reduction or termination of alcohol exposure in both rats and humans (American Psychiatric Association, 2000; Becker, 2000; Edwards et al., 1981). Many of the signs of alcohol withdrawal found in rats such as CNS hyperexcitability, body temperature disruption, and anxiety (Baldwin et al., 1991; Becker, 2000; Gallaher & Egner, 1987; Gatch & Lal, 1999; Holloway et al., 1993; Majchrowicz, 1975; Rassnick et al., 1993; Spanagel et al., 1996) resemble those observed in humans (Becker, 2000; Kalant, 1977). In both rodents and humans, the magnitude of alcohol withdrawal is influenced by genetics (McCaul et al., 1991; Newlin & Pretorius, 1990; Schmidt & Sander, 2000). Investigations of the genetic relationship between alcohol withdrawal magnitude and alcohol drinking in humans have reported mixed results. On the one hand, individuals who are at low risk for developing alcoholism because they carry a gene mutation (ALDH2) show greater signs of alcohol withdrawal than do individuals without this gene mutation (Wall et al., 2000). On the other hand, individuals with an increased genetic risk for alcoholism (sons of alcoholics) show stronger signs of alcohol withdrawal than do individuals without a genetic risk for alcoholism (sons of nonalcoholics) (McCaul et al., 1991; Newlin & Pretorius, 1990; Span & Earleywine, 1999). This discrepancy may be due to differences in alcohol-drinking history in these studies, which is known to influence the severity of alcohol withdrawal. The amount, duration, and pattern of alcohol exposure prior to alcohol withdrawal, as well as the extent of prior alcohol withdrawal experience, can influence the severity of alcohol withdrawal and the probability of subsequent drinking in both rodents and humans (Becker & Hale, 1993; Becker, 1994, 2000; Chapman, 1970; Hunter et al., 1975; Kauhanen et al., 1997; Pawan, 1973; Swift & Davidson, 1998). Rats selectively bred for high voluntary alcohol drinking (high alcohol drinking [HAD] rat lines) may be viewed as analogous to individuals at genetic risk

* Corresponding author. Purdue University, Psychological Sciences, 703 Third Street, West Lafayette, IN 47907-2081, USA. Tel.: +1-765-494-6863; fax: +1-765-496-1264.
E-mail address: jchester@psych.purdue.edu (J.A. Chester).

0741-8329/06/$ – see front matter
doi: 10.1016/j.alcohol.2006.06.009

for alcoholism who are "family history positive," and rats selectively bred for low voluntary alcohol drinking (low alcohol drinking [LAD] rat lines) may be viewed as analogous to individuals at low genetic risk for alcoholism who are "family history negative." Because alcohol-drinking history can be controlled in rat lines selectively bred for differences in alcohol preference, these lines are particularly useful for exploring the relationship between alcohol withdrawal magnitude and genetic differences in propensity toward alcohol drinking.

Several years ago, we began to assess the role of genetics in determining sensitivity to alcohol withdrawal by comparing the magnitude of alcohol withdrawal in rat lines selectively bred for differences in voluntary alcohol drinking that were alcohol naïve and hence had no prior experience with alcohol or alcohol withdrawal (Chester et al., 2002, 2003, 2004). We found that rats bred for low alcohol drinking (LAD and alcohol nonpreferring [NP] rat lines) showed an alcohol withdrawal response following a single exposure to alcohol, whereas rats bred for high alcohol drinking (HAD and preferring [P] lines) did not when a behavioral rating scale and acoustic startle reactivity were used to index alcohol withdrawal (Chester et al., 2002, 2003). These results suggested that a genetic propensity for low alcohol drinking is associated with a greater probability of experiencing withdrawal following an initial exposure to alcohol. These findings are congruent with reports that alcohol-naïve mice that voluntarily drink low amounts of alcohol exhibit strong signs of alcohol withdrawal following termination of acute forced alcohol exposure (Crabbe et al., 1983; Metten et al., 1998; Rodgers, 1966). Taken together, these results suggest that an increased probability of experiencing alcohol withdrawal following an initial exposure to alcohol may be a genetic trait that, when inherited, protects against subsequent high alcohol drinking.

This hypothesis is difficult to test using conventional indices of alcohol withdrawal because such indices do not directly assess the motivational state of the animal during withdrawal. The extent to which an animal finds the alcohol withdrawal experience to be aversive can only be inferred. However, intracranial self-stimulation (ICSS) is one method that can be used to assess the rewarding effects of drugs of abuse and the aversive effects of drug withdrawal (Esposito & Kornetsky, 1977; Hine & Lopez, 1990; Kornetsky & Bain, 1992). Drugs of abuse that are rewarding or euphoric lower the stimulation threshold for ICSS (Bozarth & Wise, 1981; Esposito & Kornetsky, 1977; Hine & Lopez, 1990; Hubner et al., 1987; Kornetsky & Bain, 1992; Kornetsky & Esposito, 1979; Lewis, 1993; Wise, 1996). Conversely, withdrawal from drugs of abuse increases the threshold for ICSS and decreases bar-press responding for ICSS (Wise, 1996). Consequently, an increase in ICSS stimulation threshold, and a decrease in bar-press responding for ICSS, have been used to index aversive, dysphoric-like, negative affective states during withdrawal following termination of administration of several classes of abused drugs (Koob, 2003; Koob et al., 1991; Leith & Barrett, 1976; Markou & Koob, 1991b; Schaefer & Michael, 1986; Schulteis et al., 1995).

Currently nothing is known about potential genetic differences in sensitivity to alcohol withdrawal that may influence alcohol-drinking behavior in rats. To determine whether rats bred for low alcohol drinking are more sensitive to the dysphoric-like or aversive effects of alcohol withdrawal than those bred for high alcohol drinking, this study compared brain reward function in alcohol-naïve rats selectively bred for high (HAD1 line) versus low (LAD1 line) alcohol drinking during withdrawal following an initial exposure to alcohol.

2. Materials and methods

2.1. Subjects

Subjects were alcohol-naïve, adult, male rats selectively bred for high alcohol drinking (HAD1, $n = 5$) or low alcohol drinking (LAD1, $n = 6$). The selectively bred HAD1 and LAD1 rat lines were derived from a foundation stock of N/NIH outbred rats (Li et al., 1988). Selection of breeders for these lines was based on the outcome of an alcohol preference test administered in each generation. At 60–70 days of age rats in both lines were given alcohol (10% v/v) as the sole source of fluid for 4 days with food freely available, followed by 4 weeks of 24-h free choice between a 10% (v/v) alcohol solution and water, with food freely available. Alcohol intake (grams [g] alcohol per kilogram body weight [BW] per day) was calculated for each rat during the 4-week free-choice period. Rats consuming more than 5.0 g alcohol/kg BW per day, and demonstrating a preference ratio of alcohol to water of at least 2:1, were selected as breeders for the next generation of the HAD1 line. Rats consuming less than 1.5 g alcohol/kg BW per day, and demonstrating an alcohol preference ratio that did not exceed 0.2:1, were selected as breeders for the next generation of the LAD1 line.

All rats in this study were from the 39th generation of selection for high or low alcohol drinking, were alcohol naïve, and were approximately 4 months old at the beginning of the experiment. All rats were individually housed in solid-floor plastic tubs, which were located in a vivarium that was maintained at 21°C with a 12-h light/dark cycle (lights on at 0700 h). All rats were provided with ad libitum access to food and water except during the first two sucrose training sessions when rats were water deprived as described below. All experimental procedures were conducted between 0800 and 2000 h. Experimental procedures were performed in accordance with the Guide for the Care and Use of Laboratory Animals and were approved by the Animal Care and Use Committee at Indiana University-Purdue University at Indianapolis.