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Dependence-induced increases in ethanol self-administration in mice are blocked by the CRF_1 receptor antagonist antalarmin and by CRF_1 receptor knockout

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Abstract

Models of dependence-induced increases in ethanol self-administration will be critical in increasing our understanding of the processes of addiction and relapse, underlying mechanisms, and potential therapeutics. One system that has received considerable attention recently is the CRF_1 system that may mediate the link between anxiety states and relapse drinking. C57BL/6J mice were trained to lever press for ethanol, were made dependent and then were allowed to self-administer ethanol following a period of abstinence. The effect of the CRF_1 antagonist, antalarmin, was examined on this abstinence-induced self-administration in a separate group of mice. Finally, dependence-induced changes in ethanol self-administration were examined in CRF_1 knockout and wild type mice. The results indicated that ethanol self-administration was increased following the induction of dependence, but only after a period of abstinence. This increase in ethanol self-administration was blocked by antalarmin. Furthermore, CRF_1 knockout mice did not display this increased ethanol self-administration following dependence and abstinence. These studies, using both a pharmacological and genetic approach, support a critical role for the CRF_1 system in ethanol self-administration following dependence. In addition, a model is presented that may be useful for studies examining underlying mechanisms of the ethanol addiction process as well as for testing potential therapeutics.
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1. Introduction

There is a growing necessity to produce models of ethanol intake in dependent animals in order to investigate the changes that occur through the process of addiction that lead to excessive ethanol consumption, loss of control and relapse drinking. Several rat models have been developed in which increased ethanol self-administration is observed following dependence induction (Roberts et al., 1996, 2000a, Rimondini et al., 2003; O'Dell et al., 2004). More recently, several groups have been developing mouse models of dependence-induced drinking. C57BL/6J mice exposed to repeated cycles of ethanol vapor increased ethanol drinking following withdrawal (Becker and Lopez, 2004; Lopez and Becker, 2005; Finn et al., 2007).

One system that appears to play a critical role in the enhanced ethanol self-administration subsequent to dependence involves the stress neuropeptide, corticotropin-releasing factor (CRF). This is not surprising considering that the affective signs of ethanol withdrawal and abstinence such as anxiety, increased responsiveness to stressors, and depressed mood, appear to be critically important in relapse to drinking in alcoholics (Hershon, 1977; Mossberg et al., 1985; De Soto et al., 1989; Parsons et al., 1990; Miller and Harris, 2000) and ethanol withdrawal is associated with disruptions in CRF functioning (Wilkins et al., 1992; Pich et al., 1995; Adinoff et al., 1996; Ehrenreich et al., 1997; Kreek and Koob, 1998; Olive et al., 2002; Valdez et al., 2003). The CRF receptor antagonist, d-Phe-CRF(12–41), attenuated dependence-induced increases in

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ethanol self-administration without affecting ethanol self-administration in non-dependent rats (Valdez et al., 2002).

The CRF_1 receptor appears to mediate anxiety responses and also behavioral consequences of ethanol withdrawal. CRF_1 knockout mice display decreased anxiety-like behavior (Smith et al., 1998; Contarino et al., 1999; Timpl et al., 1998) and may be less sensitive to the anxiogenic-like effects of ethanol withdrawal (Timpl et al., 1998). CRF_1 antagonists have been shown to decrease anxiety-like behavior of rats undergoing repeated ethanol withdrawal (Overstreet et al., 2004, 2005) and specifically decrease ethanol self-administration associated with withdrawal in rats (Funk et al., 2007). There is some suggestion that CRF_1 also mediates the association between anxiety and ethanol consumption. The blood–brain barrier penetrating CRF_1 antagonist, antalarmin, decreased voluntary ethanol consumption in isolation-reared Fawn-Hooded rats (Lodge and Lawrence, 2003). In contrast, non-dependent mice lacking CRF_1 receptors displayed increases in ethanol drinking following repeated exposures to stressors (Sillaber et al., 2002). These findings suggest that the effects of decreased CRF_1 functioning on ethanol consumption may depend on the stress and/or dependence state of the animal.

The purpose of this study was to examine the role of CRF_1 in dependence-induced increases in ethanol self-administration using both a pharmacologic and a genetic approach. First, a model of ethanol intake in dependent mice using an operant self-administration paradigm is presented. This is an important contribution to the existing mouse models as the operant procedure involves both consummatory and appetitive/motivational aspects of ethanol self-administration, whereas the more traditionally employed bottle drinking studies (for example two bottle choice) primarily focus on the consummatory aspects of ethanol. Second, the effect of a CRF_1 antagonist on baseline and dependence-induced increases in operant ethanol self-administration was assessed. Finally, ethanol self-administration was investigated in CRF_1 knockout mice before and after dependence induction.

2. Materials and methods

2.1. General methods

2.1.1. Subjects

Mice were housed 2–4 per cage in a temperature controlled reverse light cycle room (lights off between 8:00 am and 8:00 pm). Testing occurred during the dark phase of the circadian cycle. Mice received ad libitum access to food and water throughout the experiment with the following exception. Mice tested in the operant self-administration paradigm were water restricted prior to the first 3 training sessions in order to motivate the mice to press the levers. Water bottles were removed 16 h prior to testing on these first 3 days and then replaced immediately following testing. All procedures were conducted in accordance with the guidelines established by the USDA and the National Institutes of Health in the *Guide for the Care and Use of Laboratory Animals* and were approved by the Institutional Animal Care and Use Committee of The Scripps Research Institute.

2.1.2. Operant ethanol self-administration

Operant testing chambers outfitted for lever responding for liquid reinforcement were used in this study. Each of these clear Plexiglas chambers measures 14.9 × 15.2 × 18.3 cm and is housed within a larger exterior box equipped with an exhaust fan serving to ventilate the chamber and to mask background noise. One wall of each operant chamber is equipped with two levers (2.5 cm in width, 5 cm apart and 2.5 cm from the grid floor). Between the levers there are two plastic drinking cups separated by a clear Plexiglas divider (7.5 × 10 cm). A lever press requires 5 ± 1 g of downward force and results in the disruption of a photocell beam. A continuous reinforcement schedule (FR1) was used initially, whereby a single lever press resulted in the delivery of 0.01 ml of fluid into one of the two drinking cups. The FR requirement was increased on an individual mouse basis so that responding matched consumption (i.e. no ethanol fluid was left in the drinking cups at the end of the sessions) up to a maximum of FR4. Fluid delivery and recording of operant responses (photocell beam breaks) were controlled by microcomputer. Mice were trained in daily 30-min sessions, 5 days per week. Test sessions were extended to 60 min following the training phase of the experiment.

A saccharin fading procedure used previously in mice (Roberts et al., 2000b) to establish ethanol as a reinforcer was employed. Both levers were available and responding on one lever resulted in the delivery of saccharin/ethanol and responding on the other resulted in the delivery of nothing or water. The progression of saccharin fading training was as follows: 7 days of saccharin vs. nothing (first 3 days following water restriction), 3 days of 5% ethanol + saccharin vs. nothing, 3 days of 5% ethanol + saccharin vs. water, 3 days of 5% ethanol vs. water, 4 days of 8% ethanol + saccharin vs. water, 4 days of 8% ethanol vs. water, and 6 days of 10% ethanol + saccharin vs. water. For the final 20 days prior to ethanol or control vapor exposure, unsweetened 10% ethanol and water were available. Throughout operant training, the lever associated with saccharin/ethanol and the lever associated with nothing/water were kept constant.

Ethanol dilutions (5, 8, and 10% w/v) were made using 95% ethyl alcohol and water. Sodium saccharin (Sigma Chemical Co., St. Louis, MO, USA) was added to water or the ethanol solutions to achieve a final concentration of 0.2%.

2.1.3. Blood alcohol determination

Approximately 40 µl of blood was obtained by cutting 0.5 mm from the tip of each mouse's tail with a clean razor blade. With repeated sampling, the scabs were nicked in lieu of cutting additional tail. Blood was collected in capillary tubes and emptied into Eppendorf tubes containing evaporated heparin and kept on ice. Samples were centrifuged and serum decanted into fresh Eppendorf tubes. The serum was injected into an oxygen-rate alcohol analyzer (Microstat GM7, Analox Instruments, Inc., Lunenburg, MA) for blood alcohol determination.

2.2. Dependence induction and abstinence testing

Following ethanol self-administration training, mice were separated into two groups based on equal responding across the

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