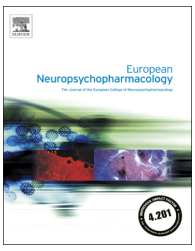
European Neuropsychopharmacology (2014) 24, 856–864



www.elsevier.com/locate/euroneuro

Adolescent intermittent ethanol exposure diminishes anhedonia during ethanol withdrawal in adulthood

Nathalie Boutros, Svetlana Semenova, Athina Markou*

University of California San Diego, La Jolla, CA, United States

Received 25 October 2013; received in revised form 18 December 2013; accepted 28 January 2014

KEYWORDS
Adolescent;
Binge drinking ethanol;
Self-stimulation;
Wistar rats

Abstract
Adolescent alcohol use may interfere with neurodevelopment, increasing the likelihood of adult alcohol use disorders (AUDs). We investigated whether adolescent intermittent ethanol (AIE) exposure alters the adult reward response to ethanol. Adolescent rats were administered ethanol once (moderate exposure; Cohort 1) or three times per day (severe exposure; Cohort 2) in a 2 days on/2 days off pattern. In adulthood, subjects responded for electrical stimulation directed at the posterior lateral hypothalamus in a discrete-trial intracranial self-stimulation (ICSS) procedure that provides current-intensity thresholds as a measure of brain reward function. The effects of ethanol administration and withdrawal were assessed. Control rats showed dose-dependent threshold elevations after acute ethanol, indicating reward deficits. A majority of moderately AIE-exposed rats (Cohort 1) showed threshold lowering after ethanol, suggesting ethanol-induced reward enhancement in this sub-set of rats. Rats exposed to severe AIE (Cohort 2) showed no threshold elevation or lowering, suggesting a blunted affective ethanol response. Daily ethanol induced threshold elevations 24 h after administration in control rats but not in either group of AIE-exposed rats, suggesting decreased sensitivity to the negative affective state of ethanol withdrawal. Withdrawal from a 4-day ethanol binge produced robust and enduring threshold elevations in all rats, although threshold elevations were diminished in rats exposed to severe AIE. These results indicate that AIE exposure diminished reward deficits associated with ethanol intoxication and withdrawal and may have increased ethanol-induced reward enhancement in a sub-set of rats. In humans, enhanced ethanol reward accompanied by reduced withdrawal severity may contribute to the development of AUDs.

*Correspondence to: Department of Psychiatry, M/C 0603, School of Medicine, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0603, USA. Tel.: +1 858 534 1572; fax: +1 858 534 9917.
E-mail address: amarkou@ucsd.edu (A. Markou).

http://dx.doi.org/10.1016/j.euroneuro.2014.01.022
0924-977X

1. Introduction

A large proportion of adolescents worldwide engage in regular heavy alcohol use. The proportion of 16 year olds who report having consumed five or more drinks on a single occasion in the last 30 days exceeds 30% in most countries of Europe, with 17% of students reporting that they engage in such binge drinking episodes at least once per week (Hibell et al., 2009). Similarly, nearly a quarter of American 12th grade students report at least one binge drinking episode in the last 2 weeks (Johnston et al., 2013). This heavy alcohol use is a major public health concern because early alcohol use initiation predicts later alcohol abuse and the development of alcohol use disorders (AUDs) in adulthood (Grant & Dawson, 1997). Adolescent alcohol use may increase adult AUDs by altering the cortical and subcortical brain reward circuits that mature during adolescence (Spear, 2000). High sensitivity to the rewarding effects of alcohol and low sensitivity to the aversive effects of alcohol predict later heavy alcohol use (King et al., 2011; Schuckit, 1994), demonstrating a relationship between alcohol sensitivity and AUDs but leaving open the question of causality. Altered sensitivity to ethanol may be an inherited phenotype or may reflect neuroadaptations engendered by alcohol exposure during developmentally sensitive periods. While ethical considerations prohibit assessment of alcohol sensitivity in human adolescents, animal studies can dissociate the consequences of heavy adolescent alcohol exposure from preceding or accompanying predispositions.

In animals, the discrete-trial intracranial self-stimulation (ICSS) procedure is used to assess brain reward function. In this procedure, intracranial electrical stimulation is delivered contingent on an operant response. The rewarding electrical current is varied to determine the brain reward threshold or minimal current intensity that maintains responding (Kornetsky et al., 1979; Markou and Koob, 1992). This reward threshold is a direct measure of brain reward function. Acute administration of drugs that humans find rewarding lowers reward thresholds, reflecting enhanced brain reward function (Markou and Koob, 1992). Drug withdrawal, associated with a negative affective state in humans, elevates reward thresholds, reflecting brain reward deficits or anhedonia (Markou and Koob, 1991).

The literature on the effects of acute ethanol administration on brain reward function in adult rats without a history of previous ethanol exposure is equivocal, while ethanol withdrawal reliably produces threshold elevations (see Section 4). However, the long-term effects of adolescent ethanol exposure on brain reward function during re-exposure to ethanol in adulthood have not been studied. Interestingly, rodent strains bred for high ethanol consumption exhibit heightened sensitivity to the reward-enhancing effects of ethanol and blunted sensitivity to the anhedonia associated with ethanol withdrawal (Chester et al., 2006; Eiler et al., 2007; Fish et al., 2012). These findings suggest that heightened sensitivity to the reward-enhancing effects of ethanol or blunted sensitivity to the anhedonia of ethanol withdrawal accompany and may predict increased ethanol consumption. For example, adolescent ethanol exposure, similar to selective breeding for high ethanol consumption, can result in increased adult ethanol self-administration under some conditions (Gilpin et al., 2012; Pascual et al., 2009; Sherrill et al., 2011). Based on the above findings, we hypothesized that adolescent ethanol exposure may decrease sensitivity to ethanol-induced anhedonia and may increase sensitivity to ethanol-induced reward enhancement in adulthood.

The goal of the present study was to investigate the long-term effects of adolescent intermittent ethanol (AIE) exposure on brain reward function in response to ethanol intoxication and ethanol withdrawal using the ICSS procedure. Human adolescence has been defined as the second decade of life and is characterized by hormonal, physiological, psychological and social changes that mark the transition from childhood to adulthood. Rodent adolescence has been defined as occurring between post-natal day (PND) 28 and 42 (Spear, 2000). Others have considered the adolescent period to extend to PND 60 (Brenhouse and Andersen, 2011). Thus, we used a relatively broad definition of adolescence (PND 28–57) to ensure ethanol exposure during developmentally sensitive periods. We used an AIE exposure regimen consisting of experimenter-administered ethanol for 2 consecutive days, followed by 2 days of abstinence throughout adolescence to model the high levels of alcohol intoxication during alcohol binges reported in human adolescents. Similar AIE exposure regimens in rodents have induced neurochemical and behavioral effects, such as neuroinflammation accompanied by reversal learning deficits (Vetreno and Crews, 2012), altered expression of dopamine receptors and extended dopamine release after ethanol (Pascual et al., 2009), and increased ethanol sensitivity of hippocampal extrasynaptic γ-aminobutyric acid-A ($GABA_A$) receptors (Fleming et al., 2012). Notably, adolescent binge-like intermittent ethanol exposure altered the affective valence of ethanol in adulthood as measured by increased ethanol self-administration (Alaux-Cantin et al., 2013; Pascual et al., 2009) and in conditioned taste aversion procedures (Alaux-Cantin et al., 2013). In the present work, the ICSS procedure was used to assess brain reward function in AIE-exposed and control rats during adulthood in response to acute ethanol, repeated daily ethanol withdrawals (to model human “hangover“), and withdrawal from a more severe 4-day ethanol binge.

2. Experimental procedures

2.1. Subjects

Timed-pregnant female Wistar rats (Charles River, Raleigh, NC) arrived in the vivarium on gestational day 13. Male pups were weaned on PND 21 and pair-housed in a humidity- and temperature-controlled vivarium on a 12 h/12 h reverse light/dark cycle. Food and water were available *ad libitum* at all times except when the rats were tested in the ICSS procedure. All of the procedures were conducted in accordance with the guidelines of the American Association for the Accreditation of Laboratory Animal Care and the National Research Council's Guide for Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee.

2.2. Adolescent intermittent ethanol exposure

From PND 28 to PND 57 (Cohort 1) or PND 28 to PND 53 (Cohort 2), the rats were administered 5 g/kg of 25% (v/v) ethanol or an equivalent volume of water intragastrically (IG) via oral gavage in a 2 days on/2 days off pattern. A relatively moderate AIE exposure