Alcohol 59 (2017) 43–51

Contents lists available at ScienceDirect

Alcohol

journal homepage: http://www.alcoholjournal.org/

Alcohol drinking during adolescence increases consumptive responses to alcohol in adulthood in Wistar rats

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ARTICLE INFO

Article history:
Received 3 February 2016
Received in revised form
5 December 2016
Accepted 7 December 2016

Keywords:
Adolescence
Alcohol drinking
Appetitive responses
Consumptive responses
Wistar rats

ABSTRACT

Binge drinking and the onset of alcohol-use disorders usually peak during the transition between late adolescence and early adulthood, and early adolescent onset of alcohol consumption has been demonstrated to increase the risk for alcohol dependence in adulthood. In the present study, we describe an animal model of early adolescent alcohol consumption where animals drink unsweetened and unflavored ethanol in high concentrations (20%). Using this model, we investigated the influence of drinking on alcohol-related appetitive behavior and alcohol consumption levels in early adulthood. Further, we also sought to investigate whether differences in alcohol-related drinking behaviors were specific to exposure in adolescence versus exposure in adulthood. Male Wistar rats were given a 2-bottle choice between 20% ethanol and water in one group and between two water bottles in another group during their adolescence (Postnatal Day [PD] 26–59) to model voluntary drinking in adolescent humans. As young adults (PD85), rats were trained in a paradigm that provided free access to 20% alcohol for 25 min after completing up to a fixed-ratio (FR) 16 lever press response. A set of young adult male Wistar rats was exposed to the same paradigm using the same time course, beginning at PD92. The results indicate that adolescent exposure to alcohol increased consumption of alcohol in adulthood. Furthermore, when investigating differences between adolescent high and low drinkers in adulthood, high consumers continued to drink more alcohol, had fewer FR failures, and faster completion of FR schedules in adulthood, whereas the low consumers were no different from controls. Rats exposed to ethanol in young adulthood also increased future intake, but there were no differences in any other components of drinking behavior. Both adolescent- and adult-exposed rats did not exhibit an increase in lever pressing during the appetitive challenge session. These data indicate that adolescent and early adult alcohol exposure can increase consumptive aspects of drinking but that adolescent exposure may preferentially influence the motivation to drink.

1. Introduction

Adolescence is a critical time period for brain development when emotional, cognitive, and social maturation occur (Dahl & Spear, 2004). The 2007 National Survey on Drug Abuse and Health has reported that approximately 16% of adolescents between the ages of 12 and 17 were current users of ethanol, with 10% of these teens classified as binge drinkers (U.S. Department of Health and Human Services, 2008). Data from the Monitoring the Future study show that 30-day prevalence and heavy drinking in men peaks at ages 21–22 and then declines linearly through adulthood (Bachman, Wadsworth, O'Malley, Johnston, & Schulenberg, 1997). In agreement with these findings, Grant et al. (2004) reported that individuals within the ages 18–29 exhibit the highest rates of previous-year ethanol abuse and dependence.

A number of epidemiological studies have clearly demonstrated that ethanol use during early adolescence is a risk factor for the later development of alcohol dependence (Ehlers, Slutske, Gilder, Lau, & Wilhelmsen, 2006; Ehlers et al., 2010; Grant & Dawson, 1997; Grant, 1998; Hicks, Iacono, & McGue, 2010; Hingson, Heeren, & Edwards, 2008). The mechanism by which early adolescent drinking leads to an increased risk for alcohol dependence in high-risk individuals is not known. One hypothesis suggests that early heavy drinking can interrupt the normal course of social and cognitive development, leading to an increased risk for a

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http://dx.doi.org/10.1016/j.alcohol.2016.12.002
0741-8329/

number of pathologies, including drug addictions (De Wit, Adlaf, Offord, & Ogborne, 2000; York, 1999). An alternate hypothesis is that teens that initiate drinking during early adolescence may have an underlying predisposition to disinhibitory behaviors that drives their early drinking as well as other risky actions (Iacono, Carlson, Malone, & McGue, 2002; Jessor & Jessor, 1977). These hypotheses are difficult to distinguish in human studies; however, the development of an animal model to study the effects of adolescent ethanol exposure on drinking behaviors in adulthood could ultimately prove useful in the understanding of the brain mechanisms underlying the effects of early adolescent drinking.

The adolescent period in rodents has a number of similarities with the human condition, making it a reasonable model to study the consequences of adolescent drinking (Spear & Varlinskaya, 2005; Spear, 2000a,b). Variables that have been used to investigate adolescent drinking patterns in animal models include: strain, sex, age, sweetened and/or flavored solutions, isolate-housing, investigator-administered alcohol, and different operant or free consumption paradigms with variable lengths of access to ethanol during the light or dark part of the circadian cycle (Bell et al., 2006; Brunell & Spear, 2005; Criado & Ehlers, 2013; Doremus, Brunell, Rajendran, & Spear, 2005; Ehlers, Walker, Pian, Roth, & Slawecki, 2007; Füllgrabe, Vengeliene, & Spanagel, 2007; Lancaster, Brown, Coker, Elliott, & Wren, 1996; Siciliano & Smith, 2001; Walker, Walker, & Ehlers, 2008). Studies investigating developmental differences in drinking patterns indicate that adolescent rats show greater levels of ethanol intake when compared to adult rats (Brunell & Spear, 2005; Doremus et al., 2005; Fabio, Nizhnikov, Spear, & Pautassi, 2014; Sarviharju, Jaatinen, Hyytiä, Hervonen, & Kiianmaa, 2001; Spear, 2004, 2007; Vetter, Doremus-Fitzwater, & Spear, 2007; Vetter-O'Hagen, Varlinskaya, & Spear, 2009).

Studies using animal models have also indicated that voluntary ethanol drinking during adolescence can, in some models, be shown to facilitate the acquisition of alcohol self-administration, increase craving behavior, and/or increase the probability of relapse in those animals in adulthood (Alaux-Cantin et al., 2013; Gilpin, Karanikas, & Richardson, 2012; Jeanblanc et al., 2015; McBride, Bell, Rodd, Strother, & Murphy, 2005; Serlin & Torregrossa, 2015; Spear, 2000c; Toalston et al., 2015). However, other studies have shown that ethanol exposure during adolescence has no effect on subsequent ethanol consumption in adulthood (Slawecki & Betancourt, 2002). For instance, Vetter et al. (2007) found that adult rats trained to drink ethanol during adolescence showed no differences in ethanol drinking when compared to a control group not exposed to ethanol during adolescence. Additionally, Siegmund, Vengeliene, Singer, and Spanagel (2005) have shown that Wistar rats that initiated alcohol consumption during adolescence, when not exposed to stress, actually consumed less alcohol and showed lower preference than rats that were initiated into drinking as adults. The reason that disparate findings have been obtained between studies is at this point not entirely clear. However, one reason may be the inclusion of sweeteners or flavorings into the ethanol solutions. In two recent studies, adolescent drinking of sucrose or sucrose/saccharin solutions with or without ethanol was found to increase the consumption of those sweetened solutions in adulthood but not the consumption of ethanol alone (Broadwater, Varlinskaya, & Spear, 2013; Pian, Criado, Walker, & Ehlers, 2009). This finding has been interpreted as suggesting that solution-specific increases in adulthood intake after adolescent exposure are most likely associated with solution "acceptance" due to familiarity (Broadwater et al., 2013). Thus, the drinking of ethanol in flavored or sweetened solutions during adolescence may confound the interpretation of potential increases in ethanol consumption in adulthood if the ethanol is presented in a sweet or flavored solution that the rat is familiar with.

The purpose of the present study was to develop a model of adolescent drinking of high concentrations of unsweetened and unflavored ethanol (20% ethanol in water) to test three specific aims: 1) to determine whether adolescent ethanol drinking affects future drinking in adulthood; 2) to test whether the amount of drinking during adolescence influences drinking in adulthood; and 3) to investigate whether adolescent alcohol drinking enhances appetitive (alcohol seeking or craving, as measured by increasing number of lever presses to drink) and/or consumptive (amount of alcohol consumed) components of alcohol drinking. Further, we sought to determine whether these behavioral differences were specific to adolescent exposure or were also seen in young adults exposed to the same drinking paradigm. Voluntary ethanol drinking using a 2-bottle choice paradigm was used to assess the effects of ethanol drinking in adolescence and young adulthood. In later adulthood in both groups of rats, the "sipper tube" model, developed by Samson and colleagues (Samson, Slawecki, Sharpe, & Chappell, 1998), was used to independently measure the number of lever presses, (to evaluate appetitive behaviors) and the amount of ethanol consumed (to measure consummatory behaviors).

2. Materials and methods

2.1. Animals

Fifty-three adolescent and 16 young-adult male Wistar rats were obtained from Charles River (USA). Adolescent rats were received and weaned on postnatal day (PD) 23, whereas adult rats were received at PD75. All animals were pair-housed in standard plastic cages and kept in a room with a light/dark cycle (12 h of light/12 h of dark, lights on at 8:00 a.m.) that was temperature controlled. Food and water were available *ad libitum* throughout the duration of the experiment. All experimental protocols were approved by the Institutional Animal Care and Use Committee of The Scripps Research Institute and were consistent with the guidelines of the NIH Guide for the Care and Use of Laboratory Animals.

2.2. Intermittent ethanol 2-bottle choice paradigm

To assess the effects of early ethanol drinking, adolescent rats and a comparison group of young adults were given the option to drink from two bottles. Experimental subjects (33 adolescents, 8 young adults) were given one bottle with 20% ethanol and one bottle with tap water. Control subjects (20 adolescents, 8 young adults) were provided with two bottles of tap water. At the start of each 2-bottle choice session, animals were divided from their cage mates by a Plexiglas® divider that separated the cage into two equal-sized compartments. Solutions were presented in 100-mL graduated cylinders that were fitted with ballpoint sipper tubes. The position of each bottle was alternated daily to avoid position preference. Animals were given 24-h access to the solutions, and food was available *ad libitum*. Two "leak" bottles, one for water and one for ethanol, were used to control for accidental sipper leakage during the experiment and were placed in an identical plastic cage with a wire top. Before each session, the amount of solution in each bottle was measured before presentation to the animal. During the session, each bottle was weighed after 30 min and 24 h of drinking. The amount consumed from each bottle was calculated by subtracting the amount removed from the corresponding leak bottle from the volume removed from each bottle by the animal's drinking. After each 24-h session, the pair-housed animals were placed back together in their home cage. Each week contained three sessions with a total of 15 sessions lasting 33 days (PD26–59 or