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The reinforcing properties of ethanol are quantitatively enhanced in adulthood by peri-adolescent ethanol, but not saccharin, consumption in female alcohol-preferring (P) rats

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ABSTRACT

Alcohol drinking during adolescence is associated in adulthood with heavier alcohol drinking and an increased rate of alcohol dependence. Past research in our laboratory has indicated that peri-adolescent ethanol consumption can enhance the acquisition and reduce the rate of extinction of ethanol self-administration in adulthood. Caveats of the past research include reinforcer specificity, increased oral consumption during peri-adolescence, and a lack of quantitative assessment of the reinforcing properties of ethanol. The current experiments were designed to determine the effects of peri-adolescent ethanol or saccharin drinking on acquisition and extinction of oral ethanol self-administration and ethanol seeking, and to quantitatively assess the reinforcing properties of ethanol (progressive ratio). Ethanol or saccharin access by alcohol-preferring (P) rats occurred during postnatal day (PND) 30–60. Animals began operant self-administration of ethanol or saccharin after PND 85. After 10 weeks of daily operant self-administration, rats were tested in a progressive ratio paradigm. Two weeks later, self-administration was extinguished in all rats. Peri-adolescent ethanol consumption specifically enhanced the acquisition of ethanol self-administration, reduced the rate of extinction for ethanol self-administration, and quantitatively increased the reinforcing properties of ethanol during adulthood. Peri-adolescent saccharin consumption was without effect. The data indicate that ethanol consumption during peri-adolescence results in neuroadaptations that may specifically enhance the reinforcing properties of ethanol during adulthood. This increase in the reinforcing properties of ethanol could be a part of biological sequelae that are the basis for the effects of adolescent alcohol consumption on the increase in the rate of alcoholism during adulthood.

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Introduction

For the vast majority of Americans, the initiation of alcohol use begins during adolescence. A high percentage (12%) of adolescents begin using alcohol during middle school (8th grade), and prior to high school graduation the vast majority of Americans (80–90%) have consumed alcohol (Johnston, O'Malley, Bachman, & Schulenberg, 2004). In combination with moderate alcohol consumption, adolescents engage in binge drinking episodes in a U-shape pattern related to age. Self-reports have indicated that 22 and 28% of 10th and 12th grade students, respectively, reported an incident of binge drinking within the previous 2 weeks (Johnston et al., 2004). College students report a previous high level of binge drinking during high school (70%) and frequent on-going episodes of binge drinking during college (44%). A subset of college students are frequent binge drinkers (19–25% report more than 3 episodes of binge drinking per week; SAMHSA, 2008; Wechsler, Dowdall, Davenport, & Castillo, 1995; Wechsler, Lee, Kuo, & Lee, 2000).

Alcohol consumption during adolescence is associated with a number of deleterious consequences. Age of first drink and the propensity to have binge ethanol-drinking episodes during adolescence is associated with increased alcohol involvement, heavier drinking bouts, arrests for driving with ability impaired, and an increased rate of alcohol dependence during adulthood (Chou & Pickering, 1992; Hingson, Heeren, & Edwards, 2006;

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Hingson, Hereen, & Winter, 2008). Epidemiological studies have indicated a 1.3 to 1.6 times increased rate of alcohol dependence in individuals who initiate alcohol use prior to the age of 15 (Dawson, Goldstein, Chou, Ruan, & Grant, 2008). The deleterious effects of adolescent ethanol consumption on adult alcohol dependence are compounded in individuals with a family history of alcoholism (Agrawal et al., 2009; Jacobus et al., 2009).

The neurological remodeling of the adolescent brain is extensive and includes cortical and limbic regions (Spear, 2000). It is the interaction between adolescent ethanol drinking and the neurological flux of adolescence that is thought to produce the enduring deleterious consequences observed in adult alcoholics. Peri-adolescent ethanol intake in male alcohol-preferring (P) rats produces persistent neuroadaptations in the posterior ventral tegmental area (pVTA) that enhance the sensitivity, and prolong the response, to ethanol (Toalston et al., 2014). Repeated alcohol administration during adolescence alters the expression of histones in the nucleus accumbens (Pascual, Boix, Felipo, & Guerri, 2009). Recent electrophysiological data have indicated that adolescent ethanol intake has a tendency to affix a portion of the hippocampus in the adolescent state (Spear & Swartzwelder, 2014). Specifically, adolescent ethanol intake has been shown to produce persistent alterations in $GABA_A$ receptors in the dentate granule cells that result in a maintained higher sensitivity to ethanol (Fleming, Acheson, Moore, Wilson, & Swartzwelder, 2012). Adolescent ethanol intake, but not comparable adult exposure, results in long-term alterations in inactivating potassium channels in interneurons in the hippocampus that may be the basis of memory-related impairment produced by adolescent ethanol intake (Li et al., 2013). The neuroadaptations produced by adolescent ethanol intake are likely the biological components that mediate the alteration in behavior observed in these organisms.

Peri-adolescent alcohol drinking by P rats has been reported to produce long-lasting alterations in the reinforcing effects of ethanol, as indicated by P rats with access to ethanol, compared to the water control group, acquiring acquisition of ethanol operant responding sooner, showing a greater resistance to extinguishing of responding, and having a more prolonged elevated level of relapse responding for ethanol (Rodd-Henricks et al., 2002a). Adult ethanol intake for a comparable time period did not result in these effects (Rodd-Henricks et al., 2002b). In Sprague-Dawley rats, adolescent consumption of a sweetened ethanol solution increased adult consumption of the same solution, but not unsweetened ethanol (Broadwater, Varlinskaya, & Spear, 2013). Adolescent consumption of a sweetened solution increased intake of the sweetened solution, but not ethanol or a sweetened ethanol solution (Broadwater et al., 2013). In mice, adolescent ethanol intake can enhance adult ethanol consumption, but this is influenced by gender and genotype (Moore, Mariani, Linsenbardt, Melón, & Boehm, 2010; Strong et al., 2010).

The current experiments were designed to determine the effects of peri-adolescent ethanol and saccharin (SACC) consumption on the acquisition and extinction of ethanol self-administration, and to quantifiably assess the reinforcing properties of oral ethanol self-administration (progressive ratio). The overall hypothesis to be tested was that peri-adolescent ethanol consumption would enhance acquisition of ethanol self-administration, retard extinction training, and enhance the reinforcing properties of ethanol during adulthood.

Methods

Subjects

Female pups ($n = 61$) from the 60th and 61st generations of the selectively bred alcohol-preferring P line were weaned at 21 days of age and housed with littermates until the beginning of the experiment. At 28–29 days of age, subjects were transferred to and maintained in individual hanging wire mesh cages with access to *ad libitum* water and food. Body weights increased normally during the course of the experiment for all groups. Female subjects were chosen over male subjects due to general weight consistency desired over the long length of time used for operant testing. Subjects used in these experiments were maintained in facilities fully accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care. All research protocols were approved by the Institutional Care and Use Committee of the Indiana University School of Medicine (Indianapolis, IN), in accordance with guidelines of the Institutional Care and Use Committee of the National Institute on Drug Abuse, the NIH, and the Guide for the Care and Use of Laboratory Animals (2011).

Peri-adolescent ethanol or saccharin exposure procedure

Pups were single-housed in hanging stainless-steel cages (Allentown Caging Equipment Co., Allentown, New Jersey) on PND 28. Subjects were initially maintained on a 12-h light/dark cycle, with lights on at 9:00 AM. There were 3 adolescent exposure groups (water, ethanol, and SACC). On PND 30, subjects received either *ad libitum* water or continuous access to 15% v/v ethanol and water, or 0.0125% w/v SACC and water until PND 60 as previously described (Rodd-Henricks et al., 2002a). The concentrations of ethanol and SACC used were determined by previous research that indicated that under operant conditions, P rats self-administered these concentrations at equivalent levels (Nowak, McKinzie, McBride, & Murphy, 1999). Food was available *ad libitum*. Bottle and body weights for all subjects were recorded every other day.

On PND 60, ethanol or SACC access ceased, and subjects were pair-housed in standard shoebox cages, within the same treatment condition. Subjects were also immediately transferred to a 12-h reverse dark/light cycle, lights off at 10:00 AM, to optimize rats' nocturnal activity levels for later procedures. After PND 60, subjects received no further oral ethanol or SACC intake experience in their home cage.

Adult operant self-administration procedure

Self-administration experiments were conducted in standard two-lever operant chambers (25 × 28 × 30 cm, Coulbourn Instruments, Allentown, PA), within ventilated sound-attenuated enclosures. Two levers, located on the same wall, were placed 15 cm above a grid floor and 13 cm apart. Directly beneath each lever was a trough from which a 0.1-mL dipper cup could rise (response-contingently, controlled by a desktop computer) to deliver fluid. When a reinforced response was reached and the dipper cup would rise, a small cue light illuminated the dipper cup (4 s). Arrangement of water and reinforcement levers to the left or right position were counterbalanced among subjects, but levers remained the same for each subject throughout all experimental sessions. Chambers were illuminated by house lights during experimental sessions. Sessions (except the Progressive Ratio tests) were 60 min in duration, occurring daily.

Operant self-administration testing started on PND 75. Rats were allowed to self-administer water, and 15% ethanol or 0.0125% SACC (6 total groups: naïve in adolescence, ethanol operant; naïve in adolescence, SACC operant; ethanol in adolescence, ethanol operant; ethanol in adolescence, SACC operant; SACC in adolescence, ethanol operant; and SACC in adolescence, SACC operant). Rats were only tested for either ethanol or SACC self-administration during adulthood. Therefore, there were two separate groups of rats that were tested for ethanol or SACC self-administration during