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Impact of adolescent alcohol use across the lifespan: Long-lasting tolerance to high-dose alcohol coupled with potentiated spatial memory impairments to moderate-dose alcohol

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ABSTRACT

Understanding how alcohol exposure during adolescence affects aging is a critical but understudied area. In the present study, male rats were exposed to either alcohol or saline during adolescence, then tested every 4 months following either an ethanol or saline challenge; animals were tested until postnatal day (PD) 532. It was found that long-lasting tolerance to high-dose ethanol exists through the test period, as measured by loss of righting reflex, while tolerance to lower doses of ethanol is not found. In addition, alcohol exposure during adolescence facilitated spatial memory impairments to acute ethanol challenges later in life. The current work demonstrates that exposure to ethanol during adolescent development can produce long-lasting detrimental impairments.

Acute alcohol exposure in adult rodents produces a number of effects, including the production of cognitive impairments (Matthews, Ilgen, White, & Best, 1999; Matthews, Morrow, Tokunaga, & McDaniel, 2002; Matthews, Simson, & Best, 1995; see Chin, Van Skike, & Matthews, 2010 for review), motor impairments (Kamens, Phillips, Holstein, & Crabbe, 2005; Majchrowicz, 1975; White et al., 2002), decreases in anxiety (Criswell, Knapp, Overstreet, & Breese, 1994; Durcan & Lister, 1988; Sharko, Kaigler, Fadel, & Wison, 2015), and, at high doses, hypnosis (Matthews, Tinsley, Diaz-Granados, Tokunaga, & Silvers, 2008; Radcliffe et al., 2009; Silvers, Tokunaga, Mittleman, & Matthews, 2003). In the previous decade, rodent models of adolescent alcohol use have demonstrated that the effects of alcohol are age-dependent, in that adolescents often show greater or reduced effects of acute alcohol compared to adults. For example, adolescent animals consume more ethanol than adults (Brunell & Spear, 2005; Doremus, Brunell, Rajnedran, & Spear, 2005; Quoilin & Boehm, 2016), show less impairment in the loss of righting reflex (Silveri & Spear, 1998) and aerial righting reflex (Van Skike et al., 2010) compared to adults, and have less ethanol-induced hypothermia than adults (Ristuccia & Spear, 2004). Contrary to data from adolescent animals, it has recently been demonstrated that aged animals are often significantly more impaired than adults on many of alcohol's effects, including cognition and ataxia, as measured by either the aerial righting reflex or the accelerating rotarod (Novier, Ornelas, Diaz-Granados, & Matthews, 2016; Novier, Van Skike, Diaz-Granados, Mittleman, & Matthews, 2013; Ornelas, Novier, Van Skike, Diaz-Granados, & Matthews, 2015; see Novier, Diaz-Granados, & Matthews, 2015 for review).

A wealth of research has demonstrated that acute alcohol exposure produces less motor ataxia in adolescent animals compared to adults. For example, when behavior is measured by either the tilting plane test (Ramirez & Spear, 2010; White et al., 2002) or the aerial righting reflex (Van Skike et al., 2010), acute alcohol produces less motor ataxia in adolescents as compared to adults. Recently, we have shown that the increased sensitivity to the motor-impairing effects of alcohol continues to increase with age, as evidenced by greater sensitivity to alcohol-induced ataxia in 18-month-old rats compared to adult or adolescent rats (Novier et al., 2013; Ornelas et al, 2015). Importantly, these divergent effects are not driven by differential blood ethanol levels between animals of different ages (Novier et al., 2013). In agreement with the

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effect of aging on alcohol's ataxia effect, it has also been demonstrated that acute alcohol potentiates spatial memory deficits produced by normal aging (Novier et al., 2016).

While research demonstrating that the effect of acute alcohol exposure in aged rats is important for establishing the effect of aging on alcohol's effects, these data have limited generalizability to the human population because humans most often initiate alcohol consumption prior to old age. In fact, most people begin drinking alcohol during adolescence, often in dangerous patterns (Haighton, 2016). However, previous preclinical/animal research has focused on investigating the effect of alcohol in aging, where the animal first encounters alcohol during aging and not previously throughout its life. We believe this represents a significant limitation and therefore it is important to investigate the effect of alcohol exposure that occurs early in life, such as during adolescence, on later behavior of the subject, including behavior when the animal has reached old age.

A small set of studies has investigated the effect of long-term chronic alcohol exposure in rodents. Interestingly, data suggested that alcohol exposure during adolescence results in greater ethanol-induced spatial memory impairments when animals are tested as young adults (PD 90), compared to animals that were only treated with alcohol during young adulthood (White, Ghia, Levin, & Swartzwelder, 2000). This augmented effect produced by chronic ethanol during adolescence appears selective to cognition, in that chronic ethanol during adolescence produces tolerance to acute alcohol's motor incoordination effects (White et al., 2002) and loss of righting reflex (Matthews et al., 2008) when subjects are tested as adults. Recently, studies have investigated whether exposure to alcohol during adolescence alters behaviors later in life without further alcohol exposures. These studies have determined that chronic intermittent ethanol during adolescence alters BDNF expression in adulthood (PD ~ 135 when determined), without altering aggressive or anxiety-like behavior (Scheidt et al., 2015). Furthermore, chronic intermittent ethanol during adolescence impairs the hippocampal-dependent novel object recognition test when rats are tested at PD 165, and reduces hippocampal neurogenesis up to PD 220 (Vetreno & Crews, 2015; Vetreno, Yaxley, Paniagua, & Crews, 2015). It is apparent that alcohol exposure during adolescence can produce long-lasting alterations in many types of behaviors, with and without future alcohol exposure (see Novier et al., 2015; Van Skike, Zandy, & Matthews, 2016 for recent reviews).

These initial animal studies strongly suggest that chronic intermittent alcohol exposure during adolescence affects later behavior, neurobiology, and responsiveness to alcohol. Specifically, using rodents as model systems, it has been proposed that adolescent alcohol exposure might “stamp in” an altered response phenotype to later alcohol exposure in adulthood (Spear & Swartzwelder, 2014). However, it is yet to be determined whether alcohol exposure during adolescence affects general behavior and responsiveness to alcohol across the entire lifespan. To begin investigating this, we undertook a longitudinal study where animals were exposed to either ethanol or saline during adolescence and were then tested with ethanol or saline every 4 months until approximately 18 months of age on a variety of behavioral measures. We report data indicating that adolescent alcohol exposure produces effects that last throughout the lifespan.

Methods

Subjects

Seventy-seven male Sprague-Dawley rats (PD 28 upon arrival) were purchased from Harlan Laboratories (Indianapolis, IN) and pair-housed in an animal colony approved by the Institutional Animal Care and Use Committee at Baylor University. The animals were allowed 2 days to acclimate before the start of any experimental procedures. Thirty-two animals were randomly assigned to receive 4.0 g/kg chronic intermittent ethanol (CIE) via intraperitoneal (i.p.) injection of 20% ethanol every 48 h from PD 30 to PD 48, for a total of 10 injections (see Matthews et al., 2008 for a description of a similar protocol). The remaining animals (n = 45) were treated with equivalent amounts of saline (CIS). Food and water were available *ad libitum* throughout the study, and Clear H_20 DietGel Recovery was provided as needed for the animals to voluntarily consume after PD 290. Body weights were recorded during CIE treatment and once a month for the remainder of the study.

Beginning on PD 50, animals received either acute ethanol or acute saline and were tested in a series of behavioral tests occurring once every 120 days. Testing continued until PD 530 for a total of five testing sessions. Ethanol was administered in a 10% (w/v) concentration for Tests 1 and 2, but was increased to 20% (w/v) for the remaining test sessions to account for the growth in body weight of the animals. Five treatment conditions were formed:

1. A control group treated with CIS during adolescence and that received acute saline for all behavioral tests (CIS + Saline) (n = 14; two animals died throughout the course of the study).
2. A group treated with CIS during adolescence and that received acute ethanol for all behavioral tests (CIS + Ethanol) (n = 16; nine animals died throughout the course of the study).
3. A group treated with CIE during adolescence and that received acute saline for all behavioral tests (CIE + Saline) (n = 16; three animals died throughout the course of the study).
4. A group treated with CIE during adolescence and that received acute ethanol for all behavioral tests (CIE + Ethanol) (n = 16; eleven animals died throughout the course of the study).
5. A group treated with CIS during adolescence and that received acute saline for the first four behavioral test sessions, but received acute ethanol for the final test session at PD 530–532 (CIS + Saline + Ethanol) (n = 15; eight animals died throughout the course of the study).

The formation of five groups allowed us to examine the long-term effects of adolescent binge ethanol exposure and acute ethanol across the rat lifespan. The CIS + Saline group served as a control group and allowed us to observe the effects of the natural aging process on the performance variables. The CIS + Ethanol group received acute ethanol for the five test sessions but did not receive binge ethanol during adolescence. The CIE + Ethanol and CIE + Saline groups were used to examine the effects of CIE during adolescence with and without future ethanol exposure, respectively. Finally, the CIS + Saline + Ethanol group allowed us to examine the effects of an acute dose of ethanol in an ethanol-naïve aged rat. See Table 1A for the timeline of the various conditions and Table 1B for the timeline of various experiments (described below) for each test session.

Loss of righting reflex (LORR)

LORR was assessed in the acute ethanol-receiving groups (CIS + Ethanol, CIE + Ethanol, and CIS + Saline + Ethanol on PD 530) following an i.p. injection of 4.0 g/kg ethanol on PD 50, 170, and 290. The dose was lowered to 3.5 g/kg ethanol during the final two tests on PD 410 and PD 530 to reduce mortality. Each rat was placed in the supine position in the home cage and monitored for LORR. Recovery of righting reflex was defined as successfully righting three times in 1 min. Latency to recover the righting reflex (sleep time) was recorded.