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Differential effects of ethanol on motor coordination in adolescent and adult rats

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Abstract

Recent evidence suggests that adolescence represents a unique period of sensitivity to the effects of ethanol. Adolescent animals are more sensitive than adults to many of the effects of ethanol, including ethanol-induced learning and memory impairments, while being less sensitive to others, including ethanol-induced sedation. It is well known that ethanol produces dramatic impairments in balance and motor coordination. While previous research suggests that adolescents and adults do not differ in their sensitivity to the effects of relatively low doses of ethanol on motor coordination, it is not known whether differences in performance would emerge at higher doses. The present study compared the impact of a range of ethanol doses (1.0, 2.0 and 3.0 g/kg) on motor coordination in adolescent [postnatal day (PD) 35–40] and adult (PD 70–75) rats. Motor coordination was assessed using the tilting plane test before ethanol administration (baseline) and at 15, 30, 60, 120 and 180 min after ethanol administration. Performance was not affected by 1.0 g/kg ethanol in either age group. However, adults were more impaired than adolescents at nearly every time point following administration of both 2.0 and 3.0 g/kg ethanol. The results provide further evidence that adolescents and adults are differentially sensitive to the behavioral effects of ethanol. Given the critical role of motor coordination in the ability to operate motor vehicles and the central role of balance and coordination in field sobriety tests, these data could have important implications if extended to human subjects.

Keywords: Adolescent; Motor coordination; Ataxia; Balance; Tilting plane

1. Introduction

Recent research suggests that adolescence represents a unique period of sensitivity to the effects of ethanol. Adolescent subjects appear to be more sensitive than adults to some of the effects of ethanol while being less sensitive to others. For instance, adolescent rats are more sensitive than adults to the acute effects of ethanol on spatial learning (Markwiese et al., 1998), and preliminary evidence suggests that ethanol exposure during adolescence enhances vulnerability to ethanol-induced spatial memory impairments later in life (White et al., 2000). Ethanol also inhibits the induction of long-term potentiation (LTP) (Swartzwelder et al., 1995a; Pyapali et al., 1999) and NMDA receptor-mediated synaptic potentials (Swartzwelder et al., 1995b) more potently in hippocampal slices from adolescent rats than in those from adults. Conversely, the onset of sedation following ethanol administration is slower, and the magnitude of sedation smaller, in adolescent rats than in adult rats (Little et al., 1996; Swartzwelder et al., 1998; Silveri and Spear, 1998). In addition, adolescent animals develop tolerance to the thermoregulatory effects of ethanol more rapidly than adults (Swartzwelder et al., 1998) and are less vulnerable to chemoconvulsant-induced seizures following cessation of chronic treatment (Acheson et al., 1999).

Among the multitude of behavioral changes produced by ethanol, perhaps the most salient are the effects of ethanol

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on motor activity. Ethanol disrupts the ability to perform tasks that require balance and motor coordination, such as driving an automobile, walking and even standing stationary in an upright position (Nieschalk et al., 1999; Liguori et al., 1999). Indeed, the assessment of ethanol-induced motor impairments serves as the basis of standard field sobriety tests used by law enforcement agencies (Cole and Nowaczyk, 1994). In laboratory experiments with humans, the assessment of ethanol-induced motor impairments often includes a measure of body sway, the side-to-side and back-and-forth movements that occur as a subject attempts to stand stationary (e.g., Nieschalk et al., 1999). In rodents, motor coordination is often assessed using the tilting plane test, a task that measures the ability of a rat to maintain its balance as the angle of a horizontal plane is gradually increased (Arvola et al., 1958; Siegel and Larson, 1996; White et al., 2002).

It is currently unclear whether the effects of ethanol on motor coordination differ between adolescents and adults. One might expect this to be the case, given that brain regions involved in motor coordination, such as the cerebellum, continue to develop during adolescence (Mueller et al., 1998; Luna et al., 2001). Hollstedt et al. (1980) examined the impact of ethanol on motor coordination in rats of different ages, including some that were roughly 40 and 60 days of age. Postnatal days (PD) 40 and 60 fall within the windows of adolescence and young adulthood, respectively (Spear, 2000). Motor coordination was assessed beginning 30 min after the injection of 1.25 g/kg ethanol. The effects of ethanol on performance in the two groups did not appear to differ, though the results of this comparison were not reported. While such findings might suggest that adolescents and adults do not differ in their sensitivity to ethanol-induced motor impairments, it is not known whether differences in performance between the two age groups would emerge at higher doses.

The purpose of the current study was to investigate further the impact of ethanol on motor coordination in adolescent and adult subjects. Motor coordination was assessed using the tilting plane test before (baseline) and 15, 30, 60, 120 and 180 min after the administration of three doses of ethanol (1.0, 2.0 and 3.0 g/kg ip) in adolescent (PD 35–40) and adult (PD 70–75) rats.

2. Methods

2.1. Subjects

Sixty male Sprague–Dawley rats were group housed (four per cage) in a temperature- and humidity-controlled vivarium with a 12-h light/dark cycle (06:00 h light/18:00 h dark) and were given ad libitum access to food and water. Half of the rats were adolescents (PD 35–40) (average weight±S.D. 113.6±13.1 g) and the other half were adults (PD 70–75) (average weight±S.D. 303.1±11.3 g) (Spear, 2000).

2.2. Apparatus

Motor coordination was assessed using a tilting plane apparatus (Arvola et al., 1958; White et al., 2002). The apparatus consisted of a clear Plexiglas box (61×24×20 cm) with a hinge at one end. A 1/8-in. thick sheet of glass covered the floor of the box. The box was tilted via a wooden arm protruding from the nonhinged end. A meter stick, located at the end of the box lifted by the wooden arm, was used to measure the height at which subjects began to slide down the floor of the box.

2.3. Procedures

Baseline data were collected from each subject. The subject was placed in the apparatus facing towards the end of the box from which the wooden arm protruded. The wooden arm was then lifted slowly until the subject began to slide down the floor of the apparatus. The height at which the subject began to slide was measured and the procedure was repeated. Five measurements were taken for each subject. Sliding angles were calculated using the length of the apparatus and the height at which subjects began to slide.

Following baseline measurements, subjects were injected intraperitoneally with either 1.0, 2.0 or 3.0 g/kg ethanol (16% v/v). Motor coordination was assessed 15, 30, 60, 120 and 180 min after ethanol administration employing the procedures used for baseline measurements.

The weight of a subject can influence the angle at which the subject slides in the tilting plane (Hollstedt et al., 1980). In order to assess the impact of ethanol on performance unconfounded by weight, it is necessary to know the sliding angles of subjects in the total absence of motor coordination (Quintanilla and Tampier, 2000). Thus, after testing under ethanol, all subjects were anesthetized with halothane and five sliding angle measurements were taken using the procedures detailed above. These values were then used to adjust for the influence of weight on performance during testing under ethanol (see below).

2.4. Statistical analyses

For each subject, average sliding angle scores were calculated from the five measurements taken during baseline (i.e., pre-ethanol injection), the five measurements taken at each testing point after ethanol administration (i.e., 15, 30, 60, 120 and 180 min postinjection) and the five measurements taken under halothane anesthesia. As anticipated, adult subjects slid sooner than adolescent subjects under halothane anesthesia [$t(58)=2.56$, $P<.025$], highlighting the need to adjust for the influence of weight on performance during testing under ethanol. To adjust for the influence of weight, the following strategy was implemented. For each subject, the difference between baseline performance and performance while anesthetized was calculated (baseline

deviation). Next, the difference between performance at each time point after ethanol administration and performance while anesthetized was calculated (ethanol deviations). The change in performance relative to baseline at each of the testing points after ethanol administration was then calculated using the following formula: [(ethanol deviation/baseline deviation−1)×100].

To assess the impact of ethanol on motor coordination and to determine whether the age of subjects influenced the effect, changes in performance relative to baseline were analyzed using a three-way, mixed-design ANOVA [Age×Dose×Testing point]. Additional ANOVA and Student *t* tests were performed to determine sources of significance in the larger analysis.

3. Results

Ethanol produced a dose-dependent impairment in motor coordination [$F(5,270)=60.24$, $P<.001$], the nature of which differed between adolescents and adults [$F(2,54)=4.30$, $P<.025$] (see Fig. 1). Overall, performance was not impaired under 1.0 g/kg ethanol [$F(5,90)=1.26$, $P>.25$] but was impaired under both 2.0 and 3.0 g/kg [$F(5,90)=22.81$, $P<.001$ and $F(5,90)=58.37$, $P<.001$, respectively].

Both adolescents and adults were impaired following 2.0 g/kg ethanol [$F(5,45)=8.62$, $P<.001$ and $F(5,45)=15.56$, $P<.001$, respectively]. Overall, adolescents were less impaired than adults [$F(5,90)=22.81$, $P<.001$]. There were no differences in baseline performance between adolescents and adults [$t(18)=0.65$, $P>.50$]. However, age-related differences in performance were observed at every time point following ethanol administration [$t(18)$, all P's<.05]. Relative to baseline scores, adolescents were significantly impaired at 15, 30, 60 and 180 min postinjection [$t(9)$, all P's<.05] and marginally impaired at 120 min postinjection [$t(9)=2.26$, $P=.05$]. Adults were impaired at every time point following ethanol administration [$t(9)$, all P's<.05].

Similarly, both adolescents and adults were impaired following 3.0 g/kg ethanol [$F(5,45)=19.66$, $P<.001$ and $F(5,45)=47.95$, $P<.001$, respectively]. Overall, adolescents were less impaired than adults [$F(5,90)=22.81$, $P<.001$]. There were no differences in baseline performance between adolescents and adults [$t(18)=1.63$, $P>.10$]. However, age-dependent differences in performance were observed 15, 30, 60 and 120 min after ethanol administration [$t(18)$, all P's<.05]. Performances did not differ 180 min postinjection [$t(9)=1.96$, $P>.05$]. In both groups, performance was impaired relative to baseline at every time point following ethanol administration [$t(9)$, all P's<.05].

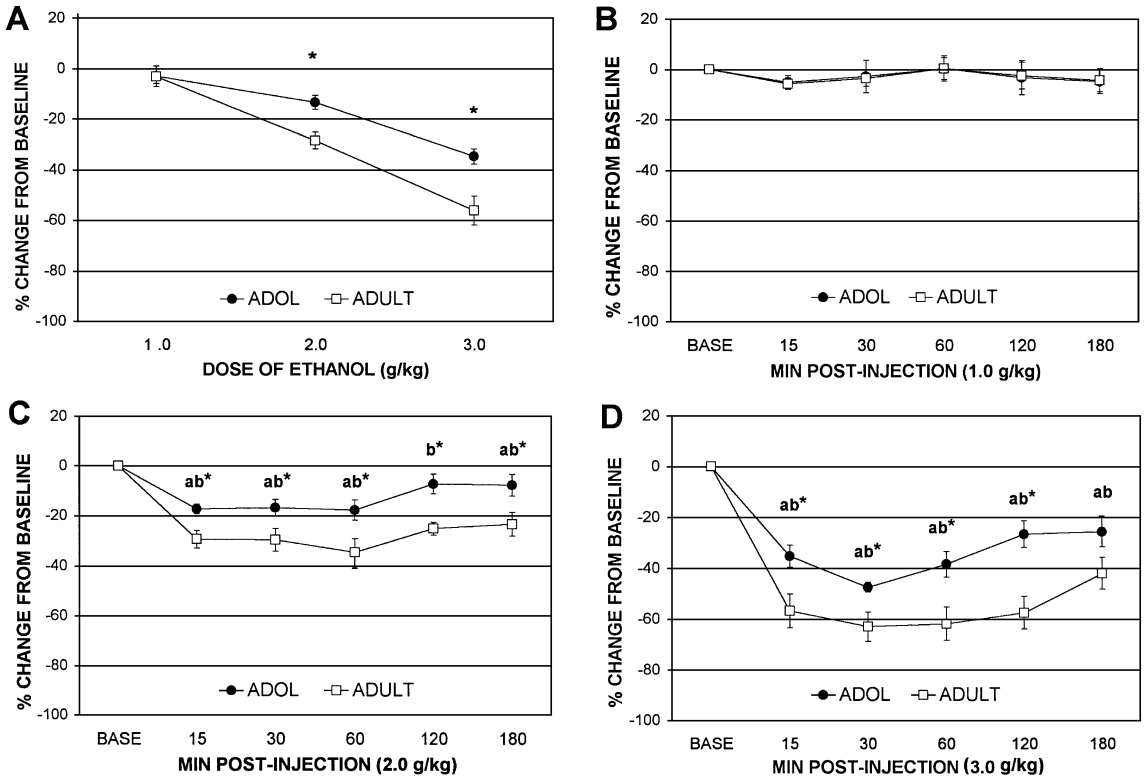

Fig. 1. Impact of ethanol (1.0, 2.0 and 3.0 g/kg) on motor coordination in adolescent (PD 35–40) and adult (PD 70–75) rats. The overall change in performance was greater in adults than adolescents following 2.0 and 3.0 g/kg ethanol (A). Performance was not impaired in either age group under 1.0 g/kg ethanol (B). Adolescents were less affected than adults at nearly every time point following both 2.0 g/kg (C) and 3.0 g/kg (D) ethanol. ([a]Difference relative to baseline for adolescent subjects, [b]Difference relative to baseline for adult subjects, *Between-group difference. All P's<.05).

4. Discussion

Adolescent animals were less sensitive than adults to the motor impairing effects of ethanol. Performance was not affected by 1.0 g/kg ethanol in either age group. However, younger subjects were less impaired than adults at nearly every time point when the dose was raised to both 2.0 and 3.0 g/kg ethanol.

The observation that adolescent subjects were less sensitive than adults to the motor impairing effects of ethanol adds to a growing body of evidence that adolescents and adults are differentially affected by ethanol. Previous research indicates that adolescent rats are less vulnerable to both the sedative (Little et al., 1996; Swartzwelder et al., 1998; Silveri and Spear, 1998) and the lethal (Hollstedt and Rydberg, 1985) effects of ethanol. In contrast, adolescent animals are more sensitive to the acute effects of ethanol on spatial learning (Markwiese et al., 1998) and ethanol exposure during adolescence, but not adulthood, appears to enhance vulnerability to ethanol-induced spatial memory impairments later in life (White et al., 2000). Ethanol also suppresses NMDA-mediated currents (Swartzwelder et al., 1995b) and disrupts LTP (Swartzwelder et al., 1995a; Pyapali et al., 1999) more potently in hippocampal slices from adolescent rats than adult rats. Finally, there is evidence that binge exposure to ethanol produces more widespread brain damage in adolescent than adult subjects (Crews et al., 2000).

The explanation for the age-dependent difference in ethanol potency observed in the present study is unclear. Ethanol produces ataxia in part by altering neuronal activity in the cerebellum (Dar, 1995), a brain region that continues to develop during adolescence (Mueller et al., 1998). Systemic administration of ethanol increases (Sinclair et al., 1980), while local administration decreases (Palmer et al., 1988), the firing of cerebellar Purkinje cells. Intracerebellar infusion of the $GABA_A$ inverse agonist, Ro15-4513, partially reverses ethanol-induced ataxia (Dar, 1995) and changes in Purkinje cell firing (Palmer et al., 1988), strongly suggesting GABAergic involvement in these effects. It is currently unknown whether the adolescent cerebellum is less sensitive to the effects of ethanol, but this could be a mechanism underlying the behavioral data observed here.

Previous research suggests that adolescents achieve higher peak brain ethanol levels than adults following ethanol administration (Silveri and Spear, 2000). Such evidence makes the large age-related differences in sensitivity to ethanol-induced motor impairments observed in the present study even more striking. Specifically, on the basis of brain ethanol levels alone, one might expect adolescents to be more vulnerable than adults to the effects of ethanol on motor coordination. In contrast, adolescents were considerably less impaired than adults following both 2.0 and 3.0 g/kg ethanol.

The findings of the present study appear, at least on the surface, to be somewhat inconsistent with the findings of a previous report regarding ethanol-induced motor impairments in the developing rat. Hollstedt et al. (1980) examined the impact of a single dose of ethanol (1.25 g/kg) on motor coordination in 25, 50, 100, 150, 200 and 250 g rats. Ages were not provided for all groups, but the ages of 50, 150 and 250 g subjects were reported as roughly 20, 40 and 60 days, respectively. PD 40 and 60 fall within the windows of adolescence and young adulthood, respectively (Spear, 2000). Subjects tested at PD 20 were less affected than subjects tested at PD 40 or 60, indicating an age-dependent difference in sensitivity to ethanol-induced motor impairments. Subjects tested at PD 40 did not appear to differ from those tested at PD 60, though the results of this comparison were not stated. Based upon the data reported by Hollstedt et al., one might conclude that adolescent and adult rats do not differ in their sensitivity to ethanol-induced motor impairments. However, the present study reveals that clear differences in sensitivity between adolescents and adults emerge when higher doses of ethanol are used.

It is currently not known if adolescent humans are less sensitive than adults to ethanol-induced disruptions in balance and motor coordination. Jones and Neri (1994) examined the impact of a moderate dose of ethanol (0.68 g/kg) on a variety of measures of motor activity, including body sway, eye movement and other overt signs of intoxication, in adult males representing four groups: 20–29, 30–39, 40–49 and 50–59. In general, age did not play a role in the impact of ethanol on the variables assessed in the experiment. Thus, following a mildly intoxicating dose of ethanol, young adults are not affected differently than older adults on standard tests of motor activity. It is not known if younger, adolescent-aged subjects would perform differently than older subjects nor is it known whether the performances of young adults and older adults would separate at higher doses of ethanol.

In summary, adolescent subjects were less sensitive than adults to ethanol-induced motor impairments following administration of both 2.0 and 3.0 g/kg ethanol. These data add to a growing body of evidence that adolescent and adult subjects are differentially affected by ethanol. Given the critical role of motor coordination in the ability to operate motor vehicles and the central role of balance and coordination in field sobriety tests, these data could have important implications if extended to human subjects.

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