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Differential Effects of Acute Alcohol on Prepulse Inhibition and Event-Related Potentials in Adolescent and Adult Wistar Rats

Jerry P. Pian, PhD, Jose R. Criado, PhD, and Cindy L. Ehlers, PhD*

The Scripps Research Institute, Department of Molecular and Integrative Neurosciences, 10550 N. Torrey Pines Rd. SP30-1501, La Jolla, CA 92037, USA.

Abstract

Background—Previous studies have demonstrated that adolescent and adult rats show differential sensitivity to many of the acute effects of alcohol. We recently reported evidence of developmental differences in the effects of acute alcohol on the cortical electroencephalogram (EEG). However, it is unclear whether developmental differences are also observed in other neurophysiological and neurobehavioral measurements known to be sensitive to alcohol exposure. The present study determined the age-related effects of acute alcohol on behavioral and event-related potential (ERP) responses to acoustic startle (AS) and prepulse inhibition (PPI).

Methods—Male adolescent and adult Wistar rats were implanted with cortical recording electrodes. The effects of acute alcohol (0.0, 0.75, and 1.5 g/kg) on behavioral and ERP responses to AS and PPI were assessed.

Results—Acute alcohol (0.75 and 1.5 g/kg) significantly reduced the behavioral and electrophysiological response to AS in adolescent and adult rats. Both 0.75 and 1.5 g/kg alcohol significantly enhanced the behavioral response to PPI in adolescent, but not in adult rats. During prepulse+pulse trials, 1.5 g/kg alcohol significantly increased the N10 pulse response in the adolescent frontal cortex. Acute alcohol (0.75 and 1.5 g/kg) also increased the N1 ERP pulse response to prepulse stimuli in frontal and parietal cortices in adult rats, but not in adolescent rats.

Conclusions—These data suggest that alcohol's effect on behavioral and electrophysiological indices of AS do not differ between adults and adolescents whereas developmental stage does appear to significantly modify alcohol influenced response to PPI.

Keywords

Adolescence; Alcohol; ERP; Ethanol; PPI

Introduction

Ontogenetic differences in brain maturation have been shown to regulate the sensitivity and tolerance to alcohol and have been linked to the development of alcohol dependence (Ehlers et al., 2006; Grant et al., 2001; Spear, 2000). Moreover, during adolescence the brain undergoes extensive neural reorganization at the cellular level (Crews et al., 2007; Huttenlocher, 1979), which include synaptic pruning, changes in neurotransmitter levels and neural receptor sensitivity (Chugani et al., 1987; Huttenlocher, 1984; Teicher et al., 1995; Thatcher et al., 1987). These developmental changes in neural activity and plasticity may underlie the rapid changes that occur in cognitive function, as well as in social and

*Corresponding author. Cindy L. Ehlers, Ph.D. The Scripps Research Institute Molecular and Integrative Neurosciences Department, 10550 N. Torrey Pines Rd. SP30-1501, La Jolla, CA 92037, USA. Tel.: +1 858 784 7058; Fax: +1 858 784 7409. E-mail address: cindy@scripps.edu (C.L. Ehlers).

emotional behavior observed during adolescence (see Spear, 2000 for review and references).

Studies in animal models have contributed to our understanding of the differential sensitivity of adolescents and adults to the effects of alcohol. These studies have shown that adolescent rats are less sensitive than adult rats to the effects of acute alcohol on motor incoordination, sedation, and hypothermia (Hollstedt et al., 1980; Little et al., 1996; Moy et al., 1998; Pian et al., 2008; Silveri and Spear, 1998, 2000). Adolescent rats exhibit greater tolerance to the sedative effects of acute alcohol than adult rats while having higher blood alcohol levels (Pian et al., 2008; Silveri and Spear, 1998). Moreover, an increase in the sensitivity to alcohol-induced memory deficits following an alcohol challenge after an abstinence period is observed during adolescence, but not adulthood (White et al., 2000). To characterize further the neural substrates mediating the age-related differences to acute alcohol exposure, we recently studied the acute effects of alcohol on the electroencephalogram (EEG) of adolescent and adult Wistar rats. This study found that adolescent rats are more vulnerable than adult rats to the acute effects of alcohol on γ frequency band. In contrast to our finding with the γ band, we found that adult rats are more sensitive than adolescent rats to acute alcohol exposure on β band (Pian et al., 2008). The γ band has been associated with the integration of sensory and cognitive processes (Engel et al., 1992; Herrmann and Demiralp, 2005). It has also been shown that the γ band could be a marker in the development of alcoholism (Padmanabhapillai et al., 2006). Power in the β band has been correlated with arousal state (Merica and Fortune, 2004; Merica and Gaillard, 1992). These neurophysiological findings support previous results suggesting that alcohol exposure during adolescence has more severe consequences relative to comparable exposure during adulthood. In spite of these findings, the neurophysiological mechanisms mediating the behavioral and cognitive responses to acute alcohol in adolescent and adult rats remain unclear.

The assessment of the acoustic startle response (ASR) and prepulse inhibition (PPI) have been recently used to characterize the effects of alcohol on the adolescent brain (Brunell and Spear, 2006; Slawecki and Ehlers, 2005). ASR is an automatic and involuntary myogenic response to an unexpected intense auditory stimulus. ASR is mediated by neurons in the brainstem and attention processes are not involved in eliciting the reflex (Koch and Schnitzler, 1997). PPI measures the ability of low-intensity acoustic stimuli (prepulse), which precedes the startle-eliciting stimulus (pulse), to reduce the magnitude of the ASR. This neurobehavioral measure is considered an index of sensorimotor gating (Koch and Schnitzler, 1997; Swerdlow et al., 2001).

Deficiency in sensorimotor gating could represent a disruption of ongoing information processing and cognitive function (Koch and Schnitzler, 1997). The neural circuit regulating normal PPI function has been well characterized and consists of neurons from the pontine and brain stem regions as well as from several brain regions including the nucleus accumbens, medial septum, hippocampus, basolateral amygdala, ventral tegmental area, and prefrontal cortex (Davis et al., 1982; Koch and Schnitzler, 1997; Swerdlow et al., 2001). Previous studies have demonstrated that PPI is significantly reduced in adolescents compared to adults (Ellwanger et al., 2003; van den Buuse et al., 2003). These findings suggest that the neural circuit regulating PPI in the adolescent brain is still under development. Consistent with those reports, the highly alcohol-sensitive neurotransmitter systems that have been shown to modulate normal PPI function such as dopamine (DA), N-methyl-D-Aspartate (NMDA), and γ -aminobutyric acid (GABA) are still under maturational changes during adolescence (see Spear, 2000 for review). Based on these neural differences between adolescents and adults, we hypothesized that adolescent and adult Wistar rats under

the effects of an acute dose of alcohol could respond differently to presentation of acoustic stimuli in a PPI paradigm.

We have previously demonstrated that event-related potentials (ERPs) are effective in the neurophysiological assessment of developmental differences following alcohol exposure (Kaneko et al., 1993,1996;Slawecki et al., 2004). ERP paradigms have also been used to study the effects of acute alcohol administration on sensory and cognitive functioning (Jaaskelainen et al., 1995;Noldy and Carlen, 1990). The age-related effects of acute alcohol on sensorimotor gating and ERP responses are not well understood.

Previous reports have studied the relationship between PPI and suppression of several ERP-based gating measures, including the human P50, N100 and mismatch negativity component (Adler et al., 1982; Boutros et al., 2004; Light and Braff, 2005) and the auditory N40 component in rats (Swerdlow et al., 2006). Findings from those studies have provided insight into the relationship between PPI and ERP-based gating measures and the neurobiological mechanisms mediating these gating processes. Independent studies have shown that PPI and ERP-based gating measures are sensitive to acute alcohol administration (e.g., Brunell and Spear, 2006; Chester and Barrenha, 2007; Grillon et al., 1994; Hutchison et al., 1997; Jaaskelainen et al., 1995). However, contemporaneous assessments of these behavioral and electrophysiological gating measures within individual rats have not been previously used to study the acute effects of alcohol. Moreover, it is unclear whether the relationship between PPI and ERP-based gating measures are developmentally regulated.

The present study characterized the behavioral and ERP responses to AS and PPI following acute alcohol administration in adolescent and adult Wistar rats. This report is part of a larger study identifying endophenotypic markers for risk of alcohol dependence in humans and animal models. The present study used a clinical PPI paradigm that is currently implemented in our studies in humans. The objective of this approach is to facilitate the translation from animal to human studies. The following neurobehavioral and neurophysiological measures were characterized in adolescent and adult rats: a) ASR, which is mediated by a simple pathway in the lower brainstem involving sensory afferents and efferents modulating motor neuron activity (Koch, 1999; Wagner et al., 2000); b) PPI, which will provide a measure of preattentive sensorimotor gating; c) the N10 component, which is an early auditory evoked potential for indication of preattentive information processing; and d) the N1 component, which has been indicated as an index of attentional or arousal state (Gomez Gonzalez et al., 1994; Hansen and Hillyard, 1980). The objectives of the present study were to determine the relationship between PPI and the effects of the prepulse tone on the N10 and N1 ERPs and to assess: a) the consequences of acute alcohol exposure; and b) whether these measurements are developmentally regulated.

Materials and Methods

Subjects

Postnatal 29 days (P29) male adolescent Wistar rats (n=25) and postnatal 71 days (P71) male adult Wistar rats (n=25) were used in this study. Upon receipt, adolescent rats averaged 64±2 g and adult rats averaged 304±6 g. Rats were housed two/cage in standard plastic cages [25 (w) × 20 (h) × 45 cm (l)] during the experiment. For the duration of the experiment, a 12 h light/dark cycle (lights on at 6 am) was in effect and ad libitum food/water access was maintained. Temperature of the colony and experimental rooms were constantly maintained at 71 F. Animal care was in accordance with NIH and institutional guidelines.

Surgical Procedure

Rats were anesthetized with sodium pentobarbital (50 mg/kg, intraperitoneally). Atropine (24 µg, subcutaneously) co-administration minimized respiratory suppression. Surgical coordinates were obtained from the Paxinos and Watson, (1986) atlas. For the purpose of comparison with our previous studies in cortical ERPs (Slawecki et al., 2000a), screw electrodes were placed in the skull overlying the frontal cortex (AP: +1.5 mm, ML: ±3.0 mm) and parietal cortex (AP: -4.5mm, ML: ±4.5 mm) in adult rats and the frontal cortex (AP: +1.5mm, ML: ±2.0mm) and parietal cortex (AP: -4.0mm, ML: ±3.5mm) in adolescent rats. The stereotaxic coordinates for adolescent rats were based on our previous studies which resulted in placement overlaying the same cortical areas, i.e, FR1/FR2 and PAR1 (Slawecki et al., 2006). A midline screw electrode was placed posterior to lambda in the skull overlying the cerebellum. The tooth bar was set at -3.3 mm. Electrode connections were made to an Amphenol five-pin connector, and the assembly was anchored to the skull with dental acrylic and anchor screws. A one-week recovery period was provided before the effects of alcohol were assessed.

Acoustic Startle Response (ASR)/Prepulse Inhibition (PPI)

ASR and PPI were assessed in SR LAB Startle chambers (San Diego Instruments, San Diego, CA). A speaker mounted in the ceiling of the chamber produced background noise and acoustic stimuli. Within each test chamber, a single Plexiglas cylinder (9 cm diameter × 16 cm length) was housed. A piezoelectric accelerometer mounted on the bottom of each cylinder detected movement and transduced this movement into a voltage signal. The voltage signal was collected and analyzed using software developed for the laboratory by Dr. James Havstad. This software also controlled the timing and generation of auditory stimuli.

Before ASR and PPI assessments were started, rats were injected 0, 0.75, or 1.5 g/kg alcohol and left in the home cages for 5 min, and were transferred to the SR LAB Startle chambers for 10 min habituation. After recording was started, each session contained 45 trials and consisted of randomly presented pulse trials (115 dB auditory pulse burst for 40 msec) or prepulse+pulse trials (115 dB auditory pulse burst with preceded 85 dB auditory prepulse burst for 20 msec duration). The Plexiglas cylinders were cleansed with alcohol and water between each test. The variables assessed included: ASR magnitude on prepulse+pulse and pulse trials. Percent PPI was calculated using the following formula: $[(\text{ASR magnitude on pulse trials} - \text{ASR magnitude on prepulse+pulse trials}) / \text{ASR magnitude on pulse trials}] \times 100$. The order of assessment on the test day was counterbalanced across age and treatment groups to minimize any potential influence of time of day during testing.

Electrophysiological Recording Procedures

Adolescent (P25) and adult (P67) rats were underwent surgery 1 to 3 days after arrival. The acute effects of alcohol on cortical ERPs were tested on P36, P38 and P40 in adolescent rats (average adolescence period in rat is P28-P60 and after P60 is considered as adulthood in rat) (Spear, 2000) and P78, P80 and P82 in adult rats. Each rat was tested with only one dose each day. Ten minutes after alcohol administration, the rat was transferred to the recording chamber from the home cage.

Recordings were conducted in SR LAB chambers (San Diego Instrument: San Diego, CA). Each chamber contained a 9 cm (diameter) × 16 cm (length) Plexiglas tube which was equipped with moving sensor. The chamber was designed for EEG, ERP (event-related potentials) recordings and motor response. ERPs and motor recordings were collected between 8 AM and 4 PM.

ERPs were recorded approximately 15 min following treatments. ERPs were elicited using a modified form of an established method to assess PPI developed by Swerdlow and colleagues (Hsieh et al., 2006), which is currently used in our clinical research studies. Auditory stimuli were presented from a speaker attached to the top of the recording chamber (45 cm above the subjects). Two tones were presented with 60 dB background noise: a prepulse tones (85 dB, 33% probability), and a pulse tones (115 dB, 67% probability). Prepulse tone was presented for 20 msec and pulse tone was presented for 40 msec with rise and fall times of 1 msec. Interval of 100 msec between prepulse and pulse tones. Individual trials were 1000 msec in duration (150 msec pre-stimulus + 850 msec post-stimulus) and were separated by constant interval of 15000 msec. Each session consisted of 45 individual tone presentations (i.e. 45 trials).

ERPs were digitized at a rate of 256 Hz. Each wave component was quantified on the basis of latency to peak amplitude from stimulus onset, peak amplitude, and polarity. Pre-stimulus baseline activity was determined from average EEG activity 150 msec prior to stimulus onset. Each component was identified with an automated peak detection program and confirmed by visual inspection. Movement artifact (i.e. voltages exceeding $\pm 400 \mu\text{V}$) was assessed with an automated computer detection program and eliminated following confirmation by visual analysis. Trials for each tone type were then averaged. ERP components were identified based on the largest amplitude peak within a specified latency range, as previously described (Ehlers et al., 1991). Latency windows used to identify ERP components were as follows: Fctx: N10=10-50 msec, N1=40-100 msec; Pctx: N10=10-50 msec, N1=40-100 msec. To characterize the effect of alcohol on PPI and its relationship to cortical N10 and N1 ERP components, we measured average ERP responses to the prepulse +pulse and pulse tones. Percent (%) N10 and N1 pulse responses were calculated as the amplitude of the ERP (N10 or N1) generated by the pulse tone during prepulse+pulse trials/ amplitude of the ERP (N10 or N1) generated by the pulse tone during pulse trials $\times 100$.

Alcohol Administration

All subjects were alcohol-naïve before acute alcohol administration (i.p.) prior to ASR, PPI, and ERP recordings. Based on our previous studies, the 0.75 and 1.5 g/kg alcohol doses were used to test the low and moderate effects of alcohol on cortical ERPs (Ehlers et al., 1992, 1998b; Rodd et al., 2004). 10 % and 20 % alcohol were used for 0.75 g/kg and 1.5 g/kg i.p. injection respectively. Injection volumes ranged from 1 to 4 mL based on the subjects' free-moving body weight (range, 108-450 g). For vehicle injections, volumes were randomized within each group so that vehicle injections were equal in volume to one of the alcohol doses in each group of subjects. Alcohol and vehicle injections were administered according to a pseudorandom design in their home cage.

Statistical Analysis

Two-way mixed analysis of variance (ANOVA) was used to assess the effects of alcohol on the ASR and PPI (group $\times$ dose). The observed significant interactions between adolescent and adult in dose (0, 0.75, and 1.5 g/kg of alcohol) were further analyzed by one-way ANOVA with post hoc analyses separately. One-way ANOVA was used to assess baseline (with no alcohol administration) differences between adolescents and adults. Nonparametric analysis was used to determine the effects of the prepulse tone on N10 and N1 ERP responses generated by the pulse tone. To determine the levels of statistical significance, significance level was set at $p < 0.05$.

Results

Behavioral State Assessment

Subjective visual inspection of adolescent and adult rats preceding alcohol administration showed normal exploratory and grooming behaviors in both groups. Acute administration of alcohol produced dose-dependent effects on behavioral responses in adolescent and adult rats. Consistent with previous studies (e.g., Slawecki, 2002), administration of 0.75 g/kg alcohol decreased motor activity and body tone during handling, whereas administration of 1.5 g/kg alcohol impaired gait with rats often falling to one side. Significant main effects of alcohol, and age $\times$ alcohol interactions observed on the amplitudes of ASR, PPI and ERPs in frontal and parietal cortices of adolescent and adult rats are described below.

Acoustic Startle Response (ASR) and Prepulse Inhibition (PPI) Assessment

Acoustic startle response (ASR)—One-way ANOVA revealed that the ASR to the pulse tone was significantly greater in alcohol-naïve adult than in adolescent rats [$F(1,37)=21.37$, $p<0.05$] (Fig.1a).

Effect of acute alcohol on ASR—Two-way (age $\times$ alcohol dose) ANOVA suggested a main acute effect of alcohol dose [$F(2,70)=32.77$, $p<0.05$], and an age $\times$ alcohol dose interaction [$F(2,70)=8.04$, $p<0.05$] (Fig. 1a and 1b). One-way ANOVA across age indicated that 0.75 g/kg and 1.5 g/kg alcohol significantly suppressed ASR in adolescents [$F(2,36)=23.19$, $p<0.05$] and adults [$F(2,34)=19.14$, $p<0.05$] on pulse trials (Fig. 1a).

Baseline and acute effects of alcohol on prepulse inhibition (PPI)—One-way ANOVA demonstrated that adolescents have significantly less PPI than the adults [$F(1,36)=47.45$, $p<0.05$] (Fig. 1c). Two-way (age $\times$ alcohol dose) ANOVA of the PPI data suggested a main acute effect of alcohol dose [$F(2,70)=35.10$, $p<0.05$], and an age $\times$ alcohol dose interaction [$F(2,70)=19.73$, $p<0.05$]. One-way ANOVA revealed that 0.75 g/kg and 1.5 g/kg alcohol significantly enhanced PPI in adolescents [$F(2,36)=43.42$, $p<0.05$], whereas alcohol (0.75 and 1.5 g/kg) had no effect on PPI in adult rats [$F(2,34)=5.04$, $p<0.05$; pairwise comparisons, not significant (NS)] (Fig. 1c).

ERP Assessment

Significant main effects of acute alcohol, and age $\times$ alcohol, on the ERPs in frontal and parietal cortices of adolescent and adult rats were found. The responses to the auditory stimuli in frontal and parietal cortices of adolescent and adult rats consisted of an early negative, N10, and a late negative, N1, component. The N10 occurred between 10-50 msec after the onset of auditory stimulus. The N1 occurred between 50-100 msec after the onset of auditory stimulus. Grand averages from cortical regions are shown in Fig. 2a and 2b.

N10 Pulse Response and Prepulse Modulation of the N10 Response (% N10 pulse) in Frontal and Parietal Cortices of Adolescent and Adult Rats

One-way ANOVA showed no significant difference between adolescent and adult rats in baseline levels of the N10 pulse response in the frontal [$F(1,37)=0.92$, NS] and parietal cortices [$F(1,37)=3.40$, NS] (Fig. 3a). Two-way (age $\times$ alcohol dose) ANOVA suggested a main acute effect of alcohol on the N10 pulse response in the frontal [$F(2,70)=68.49$, $p<0.05$] and parietal [$F(2,70)=49.34$, $p<0.05$] cortices of adolescent and adult rats. One-way ANOVA also suggested that 0.75 g/kg and 1.5 g/kg alcohol administration significantly suppressed the N10 pulse response in the frontal [$F(2,36)=28.64$, $p<0.05$] and parietal [$F(2,36)=20.59$, $p<0.05$] cortices of adolescent rats (Fig. 3a). Similarly, 0.75 g/kg and 1.5 g/

kg alcohol administration significantly suppressed the N10 pulse response in the frontal [$F(2,34)=54.50$, $p<0.05$] and parietal [$F(2,34)=20.59$, $p<0.05$] cortices of adult rats (Fig.3a).

Acute administration of 1.5 g/kg alcohol increased prepulse facilitation of the N10 response in frontal cortex of adolescent rats [$\chi^2=8.32$; $df=2$, $p<0.05$] (Fig.3b) and in the parietal cortex of adult rats [$\chi^2=8.44$; $df=2$, $p<0.05$] (Fig.3b).

N1 Pulse Response and Prepulse Modulation of the N1 Response (% N1 pulse) in Frontal and Parietal Cortices of Adolescent and Adult Rats

One-way ANOVA showed no significant difference between adolescent and adult rats in baseline levels of the N1 pulse response in the frontal [$F(1,37)=0.54$, NS] and parietal cortices [$F(1,37)=0.16$, NS] (Fig. 4a). Two-way (age $\times$ alcohol dose) ANOVA suggested a main acute effect of alcohol on the N1 pulse response in the frontal [$F(2,70)=36.03$, $p<0.05$] and parietal [$F(2,70)=31.82$, $p<0.05$] cortices of adolescent and adult rats. One-way ANOVA between adolescent and adult rats indicated that 0.75 g/kg and 1.5 g/kg alcohol significantly suppressed the N1 pulse response in the frontal [$F(2,36)=13.48$, $p<0.05$] and parietal [$F(2,36)=13.46$, $p<0.05$] cortices of adolescent rats (Fig.4a). Similarly, 0.75 g/kg and 1.5 g/kg alcohol significantly suppressed the N1 pulse response in the frontal [$F(2,34)=22.29$, $p<0.05$] and parietal [$F(2,34)=18.40$, $p<0.05$] cortices of adult rats (Fig.4a).

Prepulse facilitation of the N1 response in the frontal [$\chi^2=6.78$; $df=2$, $p<0.05$] and parietal [$\chi^2=13.00$; $df=2$, $p<0.05$] cortices of adult rats were significantly increased by administration of 0.75 g/kg and 1.5 g/kg alcohol. (Fig.4b). In contrast, the prepulse tone had no effect on the N1 pulse response after administration of 0.75 g/kg and 1.5 g/kg alcohol on either frontal or parietal cortices of adolescent rats (Fig.4b).

Discussion

We recently reported that chronic alcohol exposure during adolescence, but not during adulthood, significantly enhanced the behavioral response to PPI in rats after one week of alcohol withdrawal (Slawecki and Ehlers, 2005). To further understand the mechanisms mediating the neurobehavioral consequences of adolescent alcohol exposure, we investigated the effects of acute alcohol on behavioral and electrophysiological responses to AS and PPI in adolescent and adult rats. Our findings show that adult rats exhibit greater basal ASR amplitudes than adolescent rats in response to the pulse tone. In contrast, ASR amplitudes in adult and adolescent rats in response to the prepulse+pulse tone were not significantly different. Results from the present study also showed that acute alcohol inhibited the behavioral response to AS in both adolescent and adult rats in a dose-dependent manner. These findings are consistent with previous studies in animal models (Brunell and Spear, 2006; Jones et al., 2000; Pohorecky et al., 1976) and humans (Curtin et al., 1998).

Our findings are not consistent with previous studies showing that adolescent are less sensitive than adult rats to the sedative effects of alcohol (Jones et al., 2000; Pian et al., 2008; Silveri and Spear, 1998). While attenuation of ASR has been positively correlated with the sedative effects of alcohol (Slawecki and Ehlers, 2005), findings from the present study suggest that adolescent rats do not show resistance to the sedative effects of alcohol. Brunell and Spear (2006) have also reported a similar result and they concluded that alcohol-induced sedative effects on ASR might reflect qualitatively different phenomena as compared to indices of alcohol-induced anxiolysis or sedation.

Findings from the present study are consistent with previous studies showing that PPI is significantly lower in adolescent, compared to adult rats (Ellwanger et al., 2003; van den

Buuse et al., 2003). The fact that adolescent rats showed less PPI suggests an age-related developmental delay in the brain circuit regulating PPI, which is still under synaptic pruning and reconnecting processes during adolescence. We also found that alcohol (0.75 g/kg and 1.5 g/kg) significantly increased PPI in adolescent, but not in adult rats, in a dose-dependent manner. However, our data also show high basal PPI levels in adult rats. Therefore, we cannot exclude the possibility that the behavioral effects of acute alcohol on PPI that were not observed in adult rats could be due to a ceiling effect.

It was recently demonstrated that acute alcohol administration had no effect on PPI in either adolescent or adult Sprague-Dawley rats (Brunell and Spear, 2006). Those findings do not support previous studies suggesting that acute alcohol administration reduces PPI in adult alcohol-preferring P rats (Jones et al., 2000). While it is still unclear whether these conflicting results are dependent on the strain of the rat, there is evidence to suggest that strain differences influence PPI responses under basal (Palmer et al., 2000; van den Buuse, 2003) and drug-treated conditions (Kinney et al., 1999; Rigdon, 1990; Swerdlow et al., 1998; Weber and Swerdlow, 2008). Alcohol-preferring P rats were originally derived from an out-bred Wistar rat strain to develop a genetic animal model of alcoholism (Cicero, 1979; Lumeng et al., 1977). Evidence of differences in the ASR and PPI between Wistar and Sprague-Dawley rats has been conflicting (Farid et al., 2000; Ouagazzal et al., 2001; Varty et al., 1999). However, a recent study using a method of PPI standardization showed that the ASR and PPI are different in these two strains (Hince and Martin-Iverson, 2005). This study found that whereas Wistar rats exhibited greater ASR and prepulse-mediated increase in response threshold, Sprague-Dawley rats showed greater PPI in response capacity (Hince and Martin-Iverson, 2005). Consistent with those findings, Martin-Iverson and Stevenson (2005) proposed a relationship between stimulus intensity and response magnitude. Findings from their study revealed that stimulus intensity and response magnitude is different across strains and species. For instance, under the no prepulse condition, adult Sprague-Dawley rats showed an increased response threshold and lower response capacity than adult Wistar rats. Sprague-Dawley rats also demonstrated higher sensitivity in response to a prepulse+pulse tone across a wider range of time-intervals between stimuli than Wistar rats. These findings suggest that the dynamics of PPI regulatory systems are different between Sprague-Dawley and Wistar rats. Other studies also have shown that strains exhibit different profiles of PPI under baseline and drug treatments (Swerdlow et al., 2004). As a result, genetic variability and PPI parameters could modulate the mechanisms that regulate ASR and PPI under baseline and acute alcohol administration.

PPI is regulated by a hierarchical organization of several neurotransmitter systems (Koch and Schnitzler, 1997; Swerdlow et al., 2001, 2004). The dopaminergic D1 and D2 receptors are known to regulate PPI (Chester et al., 2006; Hoffman and Donovan, 1994; Wan et al., 1996). D2 receptors expressed in the mesoaccumbens DA projection have been shown to be part of the circuitry that reduces PPI (Swerdlow et al., 2001). However, PPI is also regulated by several neurotransmitter systems, including glutamate, GABA, and serotonin (Kodsi and Swerdlow, 1995; Sipes and Geyer, 1995; Wan et al., 1995). While these neurotransmitter systems have been shown to be sensitive to alcohol (Bowirrat and Oscar-Berman, 2005; Lovinger and Homanics, 2007), the mechanisms mediating the acute effects of alcohol on ASR and PPI remain unclear.

In the present study, we combined behavioral and electrophysiological techniques to characterize the acute effects of alcohol on ASR, PPI and ERPs. Larger numbers of stimulus trials are required to elicit reliable ERPs than to elicit reliable neurobehavioral responses. In addition, the time window allotted to complete the experiment following acute alcohol administration was limited. Moreover, since ERP amplitudes are a function of the startle stimulus intensity, using different startle parameters to generate comparable basal levels of

PPI in young and old animals would be a confounding variable preventing ERP comparisons between age groups. As a result, we used PPI parameters with a single 85 dB prepulse tone that is currently implemented in our human studies. Some studies have suggested that the prepulse+pulse stimulus used to study PPI could activate the release of inhibitory neurotransmitters such as GABA and glycine (Brenowitz et al., 1998; Koch and Friauf, 1995). The single or multiple intensity of the prepulse tone could produce different levels of activation of the neural circuit regulating PPI. Therefore, strain differences combined with different parameters could generate and lead to different PPI profiles.

ERPs have been used to study sensory input to the cortex and how the cortex processes incoming sensory information (Ehlers et al., 1991, 1997; Picton and Taylor, 2007). The present study evaluated two components of the auditory ERPs (i.e. N10 and N1) to determine the relationship between the effects of acute alcohol on sensorimotor gating and on neurophysiological markers associated with sensory and cognitive processing. Here we demonstrate that acute alcohol administration significantly reduced N10 amplitude on pulse trials in both frontal and parietal cortices of adolescent and adult rats. Our data also showed that the prepulse tone significantly increased the amplitude of the N10 pulse response after acute alcohol administration in the frontal cortex of adolescent rats, but not in adult rats. These data suggest that acute alcohol altered the processing of sensory information that inhibits effects of ensuing pulse stimuli in the frontal cortex of adolescent rats. As we have previously shown, alcohol increases ERP amplitudes (e.g. N1) in P rats, but not in NP rats. It is postulated that inhibitory neural circuits in P rats could be disinhibited by alcohol, suggesting a frontal activating effect of alcohol (Ehlers et al., 1991). Interestingly, we also found a similar frontal activating effect of alcohol in adolescent rats. These findings suggest that P rats and adolescent rats may share a similar neural mechanism in response to alcohol. These findings also suggest that neural circuits in the adolescent frontal cortex mediating sensory processing are not fully developed and are more sensitive to the effects of acute ethanol than the adult brain.

The N1 component in humans has been called an attention-related component as suggested by the fact that its amplitude increases when the subject attends to a tone as opposed to when the subject does not attend to it (Hillyard and Hansen, 1986). The N1 component has also been associated with arousal and attention (Ehlers, 1988; Herrmann and Knight, 2001; Hillyard and Kutas, 1983; Slawewski et al., 2004) and stimulus salience (Ehlers et al., 1998a, 1998b) in animal models. Similar to N10, alcohol produced a dose-dependent decrease in the amplitude of the N1 component during pulse trials in both frontal and parietal cortices of adolescent and adult rats. The decrease in the N1 component seen following acute alcohol exposure during pulse trials has been consistently observed in previous studies in adult humans and animal models (Ehlers et al., 1988, 1992; Perrin et al., 1974; Salamy and Williams, 1973; Slawewski et al., 2000b). However, during prepulse+pulse trials, the prepulse tone significantly increased the amplitude of the N1 pulse response after acute alcohol administration in both the adult frontal and parietal cortices, but not in adolescent rats. Consistent with these findings, we recently reported evidence that EEG frequencies in the β -band, which have been also implicated with attention and arousal (Merica and Fortune, 2004; Merica and Gaillard, 1992), are more sensitive to the acute effects of alcohol in adult than in adolescent rats (Pian et al., 2008). These findings suggest that acute alcohol administration produced an inhibitory effect on neural circuits mediating attention and arousal processes in both adolescent and adult rats. Results from the present study also suggest that activation of pathways modulating attention and arousal processes are more sensitive to the acute effects of alcohol in adult than in adolescent rats. However, whether the lack of an alcohol effect on the amplitude of the N1 pulse response during prepulse+pulse trials in adolescent rats is due to compensatory changes associated with this developmental stage remains unclear and needs to be addressed in future studies.

The contemporaneous assessment of PPI and ERP measures performed in the present study allowed direct comparisons of the effects of alcohol on these two variables within individual rats. Our results in adolescent rats showed that while acute alcohol significantly enhanced PPI, it only increased the amplitude of the frontal N10 pulse response during prepulse+pulse trials. In contrast, findings in adult rats indicated that alcohol had no effect on PPI, while increasing the amplitude of the parietal N10 pulse response and the parietal and frontal N1 responses during prepulse+pulse trials. It is important to point out that acute alcohol significantly decreased the amplitude of the N10 and N1 ERP components during pulse trials in both frontal and parietal cortices of adolescent and adult rats. These data suggest that the doses of alcohol tested in the present study produced clear inhibitory effects on electrophysiological correlates of indices of preattentive information processing, attention and arousal in both adolescent and adult rats. However, age-related differences were observed on the effects of alcohol on neural modulators of the N10 and N1 pulse response that are recruited during the prepulse+pulse trials.

One theoretical interpretation of these results is that subcortical circuits responsible for the generation of the N10 to PPI are more sensitive to the effects of alcohol in adolescent rats whereas cortical circuits responsible for the generation of the N1 to PPI are more sensitive to the effects of alcohol in adult rats. Further research is needed to characterize how the brain areas that modulate sensory and cognitive processing, and their sensitivity to the acute effects of alcohol, are developmentally regulated.

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Figure 1.

(a) Effects of acute alcohol administration (0, 0.75, and 1.5g/kg) on startle amplitude during prepulse+pulse tone and pulse tone in adolescent and adult rats. **(b)** Vehicle in each group is converted to 0 % as compared to alcohol-treated groups (0.75 and 1.5g/kg) on ASR during prepulse+pulse tone and pulse tone in adolescent and adult rats. Above 0 % indicate % alcohol-mediated inhibition on ASR response as compared to vehicle. **(c)** Effects of acute alcohol administration (0, 0.75, and 1.5g/kg) on prepulse-inhibition (PPI) in adolescent and adult rats. Data are the mean $\pm$ standard error of the mean. **a** indicates significant different from adolescents. * $p < 0.05$ or ** $p < 0.01$ indicates significant different from vehicle. **b** indicates different from 0.75 g/kg alcohol, pairwise comparisons, $p < 0.05$.

Figure 2a

Adolescent

Figure 2b

Figure 2. Grand average of auditory event-related potentials (ERPs) (a) adolescent (n=20) and (b) adult (n=18) Wistar rats in the frontal cortex (Fctx) and parietal cortex (Pctx) during prepulse+pulse and pulse trials at 0 (solid line), 0.75 (dashed line), and 1.5 (dot line) g/kg alcohol. Labeled peaks are as indicated (i.e., N10, N1).

Figure 3a

Figure 3b

Figure 3.

(a) Effects of acute alcohol administration (0, 0.75, and 1.5g/kg) on frontal (FCTX) and parietal (PCTX) cortical N10 amplitudes in adolescent and adult rats during pulse tone. **(b)** Effects of acute alcohol administration (0, 0.75, and 1.5g/kg) on prepulse modulation of the N10 response (% N10 pulse response) in adolescent and adult rats. Dash line indicates 100 % pulse response. Data are the mean $\pm$ standard error of the mean. * $p<0.05$ or ** $p<0.01$ indicates significant different from vehicle.

Figure 4.

(a) Effects of acute alcohol administration (0, 0.75, and 1.5g/kg) on frontal (FCTX) and parietal (PCTX) cortical N1 amplitudes in adolescent and adult rats during pulse tone. **(b)** Effects of acute alcohol administration (0, 0.75, and 1.5g/kg) on prepulse modulation of the N1 response (% N1 pulse response) in adolescent and adult rats. Dash line indicates 100 % pulse response. Data are the mean $\pm$ standard error of the mean. * $p < 0.05$ or ** $p < 0.01$ indicates significant different from vehicle.