Published in final edited form as:

Psychopharmacology (Berl). 2006 July ; 186(4): 579–586. doi:10.1007/s00213-006-0380-9.

Effects of acute ethanol or amphetamine administration on the acoustic startle response and prepulse inhibition in adolescent and adult rats

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Abstract

Rationale—Adolescents differ from adults in their sensitivity to a variety of psychoactive drugs. For example, adolescent rats are less sensitive to locomotor stimulant and stereotypic effects of amphetamine as well as to motor-impairing and hypnotic effects of ethanol while more sensitive to ethanol-induced disruption of brain plasticity.

Objective—The current study further explored age differences in psychopharmacological sensitivity by examining the effects of *d*-amphetamine (1.0 and 4.0 mg/kg) or ethanol (0.5, 1.0 and 1.5 g/kg) given interperitoneally on the acoustic startle response (ASR) and prepulse inhibition (PPI) in male adolescent and adult Sprague-Dawley rats.

Materials and methods—The animals were given five startle trials (120 dB for 40 ms) before semi-randomized presentation of 12 startle trials interspersed with ten trials at each prepulse intensity (40 ms pulse of 5, 10, or 20 dB above background; 100 ms before the startle stimulus).

Results—Adolescent controls showed significantly less PPI than adults, replicating previous ontogenetic findings. The higher dose of amphetamine disrupted PPI in adult but not in adolescent insensitivity to amphetamine to include this measure of sensorimotor gating. Ethanol exposure failed to alter PPI at either age, although both the 1.0 and 1.5 g/kg doses of ethanol significantly suppressed the magnitude of the ASR at both ages, potentially reflecting sedative or anxiolytic effects.

Conclusion—These data provide further evidence of the relative insensitivity of adolescent animals to amphetamine, although no age effects were found in terms of ethanol sensitivity using these measures of startle and sensorimotor gating.

Keywords

Adolescence; Development; Ethanol; Amphetamine; Prepulse inhibition; Acoustic startle response; Rats

Introduction

Adolescents differ from adults in their sensitivity to a variety of drugs of abuse, including ethanol. For example, studies using a rodent model have shown adolescents to be less sensitive than mature animals to many consequences of ethanol, including its hypnotic (Silveri and Spear 1998), anxiolytic (Varlinskaya and Spear 2002) and motorimpairing (White et al. 2002; Silveri and Spear 2001) effects. To the extent that some of these consequences of ethanol use serve as feedback cues to limit the amount consumed during a drinking session, the reduced sensitivity of adolescents to these ethanol effects may serve as permissive factors allowing greater ethanol intake among adolescents. The results from our laboratory have indeed shown that adolescent animals voluntarily drink more ethanol than the adults under a variety of experimental situations (e.g., Brunell and Spear 2005; Doremus et al. 2005). High ethanol consumption is also evident among human adolescents, as shown by the widespread occurrence of binge drinking in this population (e.g., see "Monitoring the future" survey data summarized in Johnston et al. 2002). The pervasiveness of binge drinking among adolescents is especially troubling considering that they may be especially vulnerable to ethanol-induced disruption of brain plasticity and memory (Markwiese et al. 1998; Swartzwelder et al. 1995a,b). The purpose of the current study was to determine whether adolescents are likewise more sensitive to ethanol-induced cognitive disruption on a task involving sensorimotor gating via the assessment of prepulse inhibition (PPI) using an acoustic startle response (ASR).

The ASR is an involuntary contraction of body and facial muscles after the presentation of a loud acoustic stimulus (Koch 1999). A number of manipulations have been shown to modulate the ASR, for example, it can be potentiated by a fearful state (e.g., Walker et al. 1997) or decreased by positive affect (Schmid et al. 1995). Pharmacological treatments also affect the ASR, with depressant drugs that generally decrease overall neural activity typically decreasing the ASR whereas an increase is often evident after administration of agents which increase overall neural activity (see Koch 1999, for a discussion). For example, ethanol has been shown to decrease the ASR in both rats (Pohorecky et al. 1976) and humans (Grillon et al. 1994), while the stimulant amphetamine often increases the ASR (Bell et al. 2003; although see also Varty et al. 2001).

PPI involves the presentation of a non-startling acoustic stimulus just before the startle stimulus, generally resulting in an attenuation of the ASR (see Van den Buuse et al. 2003, for a review). PPI is used as an index of sensorimotor gating, i.e., the ability of the brain to filter irrelevant stimuli (Koch 1999). Persons with psychiatric disorders such as schizophrenia (Braff and Geyer 1990) and obsessive compulsive disorder (Swerdlow et al. 1993) have demonstrable deficits in PPI. There is some experimental evidence that this filter may be less pronounced in younger animals, with adolescents showing less PPI than adults [e.g., see Ellwanger et al. 2003; van den Buuse et al. 2003; Elmer et al. 2004; Martinez et al. 2002 (based on visual inspection of the data); although, also see Bakshi and Geyer 1999]. This ontogenetic deficit is possibly due to the relative immaturity of some of the brain regions that modulate PPI, brain regions that include the amygdala, nucleus accumbens, hippocampus, ventral tegmental area, and prefrontal cortex (see Spear 2000 and Koch and Schnitzler 1997, for reviews).

A number of pharmacological manipulations have been shown to modulate PPI, including drugs affecting the dopamine, serotonin, and *N*-methyl-D-aspartate (NMDA) systems (Geyer et al. 2001). Ethanol affects some of the same neurotransmitter systems involved in the regulation of PPI (Geyer et al. 2001; see Koch 1999, for a review) and, hence, ethanol administration might be expected to disrupt PPI. There are several reports of ethanol effects on PPI, particularly in populations vulnerable to elevated ethanol consumption or at high risk for ethanol abuse. For instance, ethanol administration was observed to disrupt PPI in ethanol-preferring (P) but not in non-preferring (NP) rats (Jones et al. 2000). In humans, ethanol has

been reported to be associated with a disruption of PPI (Hutchison et al. 2003; Grillon et al. 2000), an effect found by the Grillon et al. (2000) group only among children of alcoholics and not among control subjects. Given the age-related vulnerability of adolescents to high levels of ethanol consumption, the present study was designed to test the hypothesis that adolescent animals might be more sensitive to ethanol-induced disruption of PPI than adult animals.

Amphetamine was included in the current experiment as a positive control. In contrast to relatively limited research literature regarding ethanol effects on PPI amphetamine has been reported to reliably disrupt PPI (e.g., Martin et al. 2004; Sills 1999), although one study by Bell et al. (2003) that examined amphetamine-induced PPI disruption in female adolescent and adult P and NP rats found this disruption only in P rats at both ages. In addition to the reliable disruption of PPI by amphetamine, age differences in amphetamine effects on PPI might also be expected, given prior evidence for attenuated sensitivity of adolescent animals to at least the locomotor-stimulating effects of amphetamine (e.g., Spear and Brake 1983; Bolanos et al. 1998).

Materials and method

Animals

Male offspring of Sprague-Dawley rats (Taconic Farms) bred in our vivarium were used in this experiment. On postnatal day 1 (P1), litters were culled to seven to ten subjects, with six males and four females retained whenever possible (and the females used in other projects in the laboratory). The animals were weaned on P21, housed in same-sex pairs, and maintained on a 14/10-h light/dark cycle (lights on at 07:00 hours) with food and water available ad libitum. All experimental procedures were approved by the university's Institutional Animal Care and Use Committee.

Drug challenge

Ethanol doses (0.5, 1.0, and 1.5 g/kg) were delivered as a 12.6% (v/v) solution diluted in 0.9% saline. The two doses (1.0 and 4.0 mg/kg) of *d*-amphetamine sulfate (Sigma, St. Louis, MO, USA) were dissolved in 0.9% saline and injected in a volume of 1 ml/kg. Saline control animals received a dose of 0.9% saline in a volume of 1 ml/kg.

Apparatus

Testing was conducted using a commercially available startle system (S-R Lab, San Diego, CA, USA). Sound-attenuated chambers (35×33×38.5 cm, length×width×height) each housed a cylindrical Plexiglas compartment (8.9 cm in diameter×20.3 cm in length for adults, 5.7×15.3 cm for adolescents) where the animals were contained during testing. Each cylinder contained a piezoelectric accelerometer that transduced the movement of the animals to the attached PC computer using S-R Lab software (version 5.0 for Windows). Within the ceiling of each chamber was a houselight (3 lx) and a speaker which generated the prepulse (PP) and startle stimuli as well as a 70-dB white noise background that remained on throughout the habituation and testing phases. Data were sampled at 1-ms intervals within a 100-ms response window which began at the time of onset of the startle stimulus. Chambers were calibrated weekly to equivalent sensitivities using a San Diego Instruments calibration device.

Procedure

The design of the project was a 2 age (adolescent and adult) × 6 injection (saline, 1.0 or 4.0 mg/kg *d*-amphetamine, 0.5, 1.0, and 1.5 g/kg ethanol) factorial. Seven to nine animals, each from a different litter, were randomly assigned to each of the experimental groups. On P30–31 for the adolescents and P69–71 for the adults, the animals were re-housed in standard clear

plastic breeder tubs containing pine shavings, with the animals remaining with their original cage-mates.

To habituate the animals to the testing procedure, beginning on the first day and for the following 3 days, the cages were placed on a cart and wheeled a short distance down the hallway. The animals were then returned to the colony room and injected with a 1-ml/kg dose of saline and handled for approximately 1 min.

On a test day, the cages were placed on a cart and wheeled to the testing room. The animals were injected intraperitoneally 20 min (*d*-amphetamine) or 30 min (ethanol and saline) before testing and placed back into their cages; these injection test intervals were chosen based on prior ASR research with ethanol (Pohorecky et al. 1976) and amphetamine (Bell et al. 2003). Five minutes before the onset of the test session, each animal was placed inside the startle apparatus for a 5-min habituation period. After the habituation period, five startle-alone trials were given (120 dB of white noise for 40 ms), each separated by an intertrial interval that varied randomly from 7 to 21 s. Animals then were administered semi-randomized (no consecutive delivery of identical trials) presentations of 12 startle alone trials (120 dB for 40 ms) and 10 prepulse trials at each of the three prepulse stimulus intensities: 5, 10, and 20 dB of white noise above background. Each prepulse stimulus had a duration of 40 ms and was initiated 100 ms before the standard startle stimulus. Startle and prepulse trials were separated by a variable intertrial interval ranging from 7 to 21 s.

Data analysis

The ASR for each animal was calculated as the mean peak startle amplitude of the 12 startle-alone trials. Percent PPI was calculated as the percent decrease in the startle amplitude at each prepulse intensity relative to the startle-alone trials. Data were analyzed using analysis of variance (ANOVA) separately for the ethanol and amphetamine groups, using the same saline control group in both sets of analyses. Prepulse intensity was treated as a within-subjects variable, with dose and age considered as between-subjects variables. All post hoc tests were conducted using Fisher's least-significant difference tests, with differences between groups considered significant at $p < 0.05$.

Results

ASR

To determine whether the two ages differed in baseline ASR, a 2 (age) one-way ANOVA was conducted on the average ASR for each saline-treated control animal on the 12 startle-alone trials. This ANOVA failed to reach significance, suggesting no age differences in baseline ASR. Because of similar baseline ASR scores, all ASR analyses included animals of both ages.

Amphetamine effect on ASR—A 2 (age) $\times$ 3 (dose) factorial ANOVA conducted on the ASR data revealed a main effect of dose [$F(2,54)=3.52$, $p < 0.05$], an effect that did not interact with age. Post hoc analysis of this effect showed that the ASR of the animals, collapsed across age, in the 4.0-mg/kg group were significantly higher than in the 1.0-mg/kg group, with neither group differing significantly from the saline controls (see Fig. 1a).

Ethanol effect on ASR—A 2 (age) $\times$ 4 (dose) factorial ANOVA of ASR data revealed a main effect of dose [$F(3,59)=3.51$, $p < 0.05$], with no main effect or interaction involving age. Post hoc analysis of data collapsed across age revealed that the animals that received the 1.0- and 1.5-g/kg doses of ethanol had a significantly lower ASR than the saline-injected controls (see Fig. 1b).

PPI

A 2 (age) $\times$ 3 (PP intensity) ANOVA conducted on percent PPI in the control animals revealed significant main effects of age [$F(1,18)=7.47$, $p<0.05$] and PP intensity [$F(2,36)=19.88$, $p<0.0001$], with no interaction of these variables. As would be expected, the percent inhibition of the ASR increased significantly from the pre-pulse intensity of 5 dB (26.62 ± 8.10) to 10 dB (47.21 ± 7.36) and 20 dB (56.29 ± 6.66). Adolescent animals showed significantly less PPI (28.66 ± 7.25) than the adults (61.35 ± 9.88). Because of these age differences in baseline PPI, drug effects on PPI were analyzed separately at each age.

Amphetamine effect on PPI—The 3 (dose) $\times$ 3 (PP intensity) ANOVA performed on PPI in the adults revealed main effects of dose [$F(2,26)=5.10$, $p<0.05$] and PP intensity [$F(2,52)=41.44$, $p<0.0001$], both of which were tempered by a dose $\times$ PP intensity interaction [$F(4,52)=2.65$, $p<0.05$]. Post hoc analyses of this interaction revealed that, whereas increases in PP intensity were generally associated with increases in PPI in all groups, the amount of PPI induced in response to the 5-dB prepulse stimulus was significantly less in adults given the 4.0-mg/kg dose than in the control and 1-mg/kg groups (see Fig. 2b). The ANOVA conducted on the adolescent PPI data revealed only a main effect of PP intensity [$F(2,56)=84.05$, $p<0.0001$]. Unlike the adults, neither dose of amphetamine was associated with a significant disruption of PPI among the adolescents (see Fig. 2a).

Ethanol effect on PPI—The 4 (dose) $\times$ 3 (PP intensity) ANOVA of the adult PPI data revealed a main effect of PP intensity [$F(2,56)=20.77$, $p<0.0001$], as did the analysis of the adolescent data [$F(2,62)=24.20$, $p<0.0001$], with PPI increasing with each elevation in intensity, as would be expected. Neither analysis revealed a significant main effect or interaction involving dose; hence, ethanol administration was not associated with the disruption of PPI at any intensity at either age (see Fig. 3a,b).

Discussion

Confirming prior ontogenetic studies (e.g., van den Buusc 2003; Ellwanger et al. 2003), saline-exposed adolescent animals in the present study showed less PPI than like-exposed adults. An age effect also emerged in terms of PPI disruption after amphetamine administration, with the 4.0 mg/kg dose of amphetamine significantly disrupting PPI in adults but not adolescents. However, this index of sensorimotor gating failed to reveal any ethanol-related age differences; ethanol indeed failed to affect PPI at any dose regardless of age. Ethanol did have an effect on the ASR, with animals of both ages showing an attenuation of the ASR at the 1.0- and 1.5-g/kg doses.

The finding of an ethanol-induced decrease in the ASR in rats replicates previous reports by Pohorecky et al. (1976) and Jones et al. (2000) and is an effect that has also been observed in humans (Stritzke et al. 1995; Curtin et al. 1998). However, the lack of an age difference, in the magnitude of the ethanol-induced decrease in startle was surprising given previous ontogenetic findings that adolescents are less sensitive than mature animals to several relevant ethanol effects. For example, adolescents are less sensitive to the anxiolytic effects of ethanol than adults in a social interaction test (Varlinskaya and Spear 2002). In addition, Silveri and Spear (1998) found that adult animals take significantly longer to recover their righting reflex after challenge with a sedative dose of ethanol than adolescents, suggesting an attenuated sensitivity to ethanol's hypnotic effects among the younger animals. Previous researchers have suggested that attenuation of the ASR reflects the sedative and "anxiolytic" effects of ethanol (e.g., Jones et al. 2000). However, the result of the current study suggest that the ASR may reflect qualitatively different components of the ethanol response from indices of ethanol-induced

anxiolysis and sedation as measured in the social interaction test and time to recover the righting reflex, at least with respect to ontogenetic sensitivities.

ASR was also affected by amphetamine, with the high 4.0-mg/kg dose tending to increase startle, although the comparisons revealed a significant increase only relative to animals receiving 1.0 mg/kg. While this trend for startle facilitation did not interact with age, visual inspection of the data suggests that the adult animals primarily drove this effect, with little increase evident among the adolescents. Marable and Maurissen (2004) did indeed report a significant age-related difference in amphetamine-augmented ASR, with young adult Sprague–Dawley rats (P63) showing this increase whereas post-weanling (P22) animals did not.

In terms of ethanol effects on PPI, given the results of Jones et al. (2000) of an ethanol-induced disruption of PPI in P rats but not in NP rats, it was hypothesized that high-ethanol-consuming adolescents would show an ethanol-related disruption of this index of sensory-motor gating, whereas relatively low-drinking adults would not. Additional support for this hypothesis was provided by demonstrations that NMDA antagonists and dopamine reuptake inhibitors have been associated with PPI disruption (see Koch 1999, for a review), given that ethanol both increases dopamine release and acts as an NMDA antagonist (see Nevo and Hamon 1995 and Geyer et al. 2001, for reviews). This hypothesis, however, was not supported, with no effect of ethanol on PPI emerging at either age. The lack of an ethanol-induced disruption of PPI in the current study may have been due to methodological differences between the current study and that of Jones et al. (2000), such as the use of a longer prepulse presented immediately before the startle stimulus in the latter. However, a lack of an ethanol-induced decrease in PPI is not without precedent, with, for instance, Rassnick et al. (1992) reporting no deficit in PPI among animals given chronic ethanol treatment via an ethanol-containing liquid diet (although this procedure may have been sufficiently stressful to have affected PPI results). In contrast to these results, Grillon et al. (2000) did observe an ethanol-induced disruption of PPI among humans.

The mechanisms underlying the resistance of PPI to disruption by ethanol in animals of both ages in the present study are not clear. However, it has been demonstrated that both augmenting serotonin transmission via selective serotonin reuptake inhibitors and depleting serotonin with *p*-chlorophenylalanine are associated with disruptions of PPI (see Fletcher et al. 2001, for a discussion), suggesting that levels of serotonin tone may be critical for the modulation of PPI. Given that ethanol is associated with the release of serotonin (e.g., see Langen et al. 2002), it is possible that the ethanol-induced release of serotonin may be sufficient to suppress the otherwise PPI-disrupting effects of ethanol, including its NMDA-antagonistic and dopamine-faciliatory actions (again, see Nevo and Hamon 1995 and Geyer et al. 2001 for reviews). Ethanol also has GABA-potentiating properties (e.g., see Celentano et al. 1988) which may alternatively have served as a protective influence on PPI. The PPI-induced disruption associated with administration of dopamine agonists has indeed been reported to be reversed by the administration of a GABA_A agonist (Swerdlow et al. 1990). Thus, known effects of ethanol on various neurotransmitter systems include both systems facilitating PPI disruption and those protective against such disruptions. In the case of the current study, these opposing influences may have countered each other. If opposing factors were responsible for the lack of an ethanol-induced decrease, it is interesting that it occurred in animals of both ages, in spite of developmental differences in neural systems underlying various ethanol effects between adolescents and adults (see Spear 2000, for a review). For example, there is evidence that immaturity in the GABA_A receptor system may contribute to the attenuated sensitivity of adolescents to ethanol sedation (Silveri and Spear 2002) whereas developmental over-expressed NMDA receptors may contribute to the greater sensitivity of adolescents to ethanol-induced disruption of neural plasticity (Swartzwelder et al. 1995a,b).

It is alternatively possible that the nature of our PPI test circumstances were not conducive to detection of pharmacological-induced PPI disruptions. This possibility does not appear to be the case, however, given that PPI was sensitive to disruption by the 4.0-mg/kg dose of amphetamine in adult animals, despite considerable differences in the methodology of the current experiment from typical parameters used to investigate the effects of amphetamine on PPI. For example, subcutaneous injection of amphetamine is often employed (e.g., Feifel et al. 1997) and prepulses are often shorter in duration and of lower intensity (e.g., Sills 1999). The insensitivity of adolescent animals to the PPI-disrupting effects of amphetamine observed in the present study is reminiscent of other reports of an attenuated sensitivity of adolescents to other effects of amphetamine and other catecholamine agonists when compared with adults (e.g., Laviola et al. 1995; Tirelli et al. 2003; see Laviola et al. 1999, for a review; although see also Caster et al. 2005; Niculescu et al. 2005). The insensitivity of adolescent animals to the PPI-disrupting effects of amphetamine could alternatively potentially reflect lower brain concentrations of the drug in the younger animals, given findings of a trend for lower brain levels of amphetamine 15 min after a 5.0-mg/kg injection among adolescents when compared with adult animals (Spear and Brake 1983). While amphetamine did not disrupt PPI among adolescents in the current study, it is not simply the case that animals of this age are insensitive to pharmacologically induced reductions in PPI. For example, Lipska et al. (1995) found that the dopamine agonist apomorphine disrupted PPI in adolescent animals. Apomorphine is a direct dopamine receptor agonist, however, whereas the indirect agonist amphetamine affects not only dopaminergic but also norepinephrine and serotonergic systems. These different pharmacologies could well induce different ontogenetic patterns.

Further research is needed to determine why ethanol does not reliably disrupt PPI. Pretest circumstances, ethanol dose, and test timing influence the mosaic of neurotransmitter/neuromodulator alterations induced by ethanol (Eckardt et al. 1998), some of which are protective and others disruptive of PPI (e.g., Swerdlow et al. 1990; Koch 1999). As one example, Sills (1999) found that amphetamine-induced PPI disruption was only evident when measured 10 min (and not 40 or 60 min) after administration. It is possible that ethanol may disrupt PPI if testing occurs while blood ethanol levels are rising, rather than testing near peak levels as was done in the current experiment. Experimental parameters such as background noise level, prepulse duration, and latency between the prepulse and the startle stimulus (e.g., see Canal et al. 2001 and Hsieh et al. 2006, for discussions) likewise have been shown to affect PPI. Systematic manipulation of these experimental parameters may reveal ethanol-associated disruption of PPI. If adolescent animals were included in these experiments, developmental differences in reactivity to these manipulations described above may emerge as well as possible differential sensitivity to ethanol-induced disruptions of PPI.

Acknowledgements

This research was supported by grants R37 AA12525 and R01 DA019071.

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Fig. 1.

a Mean acoustic startle response ($\pm$ SEM) for adolescents and adults after amphetamine administration. *a* Significant increase relative to 1.0 mg/kg dose (when collapsed across non-significant variable of age). **b** Mean ASR ($\pm$ SEM) for adolescents and adults after ethanol administration. *b* Significant decrease from controls (when collapsed across age)

Fig. 2. Mean prepulse inhibition ($\pm$ SEM) after amphetamine administration in adolescent (**a**) and adult (**b**) animals. *a* Significant increase compared with the 5-dB intensity, *b* significant increase compared with the 10-dB intensity, *c* significant decrease compared with saline-exposed age-matched controls

Fig. 3. Mean prepulse inhibition ($\pm$ SEM) after ethanol administration in adolescent (**a**) and adult (**b**) animals