Ethanol exposure during either adolescence or adulthood alters the rewarding effects of cocaine in adult rats

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**Abstract**

Objectives: The present studies assessed the effects of adolescent and adult ethanol exposure on the rewarding effects of cocaine as measured with the conditioned place preference procedure.

Methods: Male rats were exposed to intraperitoneal (IP) injections of ethanol or vehicle for 10 days [postnatal days (PNDs) 30–39 or PNDs 70–79; 2 mg/kg]. Place preference conditioning began on PND 65 or PND 105, respectively, and consisted of a baseline test followed by four conditioning cycles with either 0, 5, 10 or 20 mg/kg cocaine. Following the fourth conditioning cycle a final preference test was performed. Changes in time on the drug-paired side between the baseline and final test were analyzed.

Results: Animals exposed to vehicle (during adolescence or adulthood) showed a significant place preference at 20 mg/kg cocaine. Animals exposed to ethanol (during adolescence or adulthood) showed a significant place preference at 10 mg/kg cocaine.

Conclusions: Exposure to ethanol (adolescents or adults) sensitized the rewarding effects of cocaine. This may indicate an increase in the abuse liability of cocaine following a history of ethanol exposure.

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1. Introduction

Alcohol is the most commonly used drug during adolescence, e.g., in 2010 65.2% of twelfth graders reported using alcohol in the past year (Johnston et al., 2011). In addition to being widely used by adolescents, early alcohol use is correlated with an increased likelihood to abuse alcohol and other drugs later in life (Cable and Sacker, 2008; Duncan et al., 1997; Grant and Dawson, 1997; Yu and Williford, 1992). Animal models of adolescent ethanol exposure have supported this human research by showing that early experience with ethanol alters the subsequent response to ethanol. For example, adolescent exposure to ethanol has been shown to produce tolerance to a number of ethanol-induced behavioral impairments in adulthood (see Matthews et al., 2008; Pascual et al., 2007; Slawekci, 2002; White et al., 2002). In addition to altering the intoxicating effects of ethanol, early exposure also alters the motivational properties of ethanol in adulthood. In one series of studies, researchers showed that exposure to ethanol vapor during adolescence subsequently attenuated ethanol-induced taste aversions (Diaz-Granados and Graham, 2007; Graham and Diaz-Granados, 2006). Interestingly, this effect was not seen when the initial exposure to ethanol occurred during adulthood (Diaz-Granados and Graham, 2007).

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Exposure to ethanol early in life also alters the rewarding effects of ethanol in adult rats. In one study, animals with a history of ethanol consumption during adolescence showed increased responding, slower extinction and enhanced reacquisition in an ethanol self-administration preparation (Rodd-Henricks et al., 2002). Similarly, other studies have found that early exposure to ethanol leads to increased ethanol consumption in adult rats (Pascual et al., 2009; Sherrill et al., 2011; Siciliano and Smith, 2001), although in one study this effect was only seen in female subjects (Sherrill et al., 2011).

Although work with animal models has shown that early ethanol exposure alters the response to ethanol administered later in life, surprisingly little work has been done to examine how such an ethanol history may subsequently impact the response to other drugs. Recent work has shown that exposure to ethanol during adolescence attenuates the aversive effects of cocaine (Hutchison et al., 2010) in adult rats. However, no work has been done to examine how early ethanol exposure may subsequently impact the rewarding effects of other drugs. In humans, adolescent alcohol use precedes the use of other drugs such as cocaine (Degenhardt et al., 2010; Kandel et al., 1992) and can be seen as a predictor for drug-related problems in adulthood (Johnson et al., 2000; Kandel et al., 1992; Yu and Williford, 1992). Given that in 2009, approximately 21.8 million Americans aged 12 or older reported using illicit drugs in the last month (Substance Abuse and Mental Health Services Administration, 2010), it is important to examine how adolescent exposure to alcohol may influence the abuse liability of other drugs. Therefore, the present study examined the effect of adolescent ethanol exposure on the rewarding...
properties of cocaine in adulthood. This was assessed using the conditioned place preference (CPP) design (see Bardo and Bevins, 2000; Sanchis-Segura and Spanagel, 2006; Tzschentke, 1998, 2007). To determine if any potential effects were age-related, ethanol was given during both the adolescent (Experiment 1) and adult (Experiment 2) developmental periods.

2. Experiment 1: adolescent ethanol exposure

2.1. Procedure

2.1.1. Subjects

Subjects (n = 67) were experimentally naïve male Sprague Dawley rats (Harlan Sprague Dawley Laboratories). The experiment was run in two replicates (n = 35 in the first replicate, n = 32 in the second) under identical parameters, and data were pooled for analysis. All groups were represented in each replicate. Animals arrived in the laboratory on postnatal day (PND) 25 and were housed in Plexiglas bins (26×48×21 cm) with three or four animals in each bin in a colony room maintained on a 12-h light/dark cycle (lights on at 0800 h) and at an ambient temperature of 23 °C. Training and testing took place during the light part of the cycle, with all procedures beginning at 1200 h. Food and water were available ad libitum for the entirety of the study. Animals were handled daily for 5 days prior to the start of the experiment to limit the effects of handling stress during the conduct of the research. Procedures recommended by the Guide for the Care and Use of Laboratory Animals (National Research Council, 1996), the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (National Research Council, 2003) and the Institutional Animal Care and Use Committee at American University were followed at all times. Food and water consumption and body weight were monitored daily to assess the health of the subjects.

2.1.2. Drugs and solutions

Ethanol (Sigma Aldrich Co., St. Louis, MO) was prepared as a 15% (v/v) solution in 0.9% saline. Cocaine hydrochloride (generously supplied by NIDA) was prepared as a 10 mg/ml solution in 0.9% saline. Doses of cocaine refer to the weight of the salt. Saline was used for vehicle injections.

2.1.3. Apparatus

All conditioning procedures were conducted using a 3-chambered automated apparatus (San Diego Instruments Place Preference System, San Diego, CA). The inner dimensions of each main conditioning chamber were 28 cm wide × 21 cm deep × 34.5 cm high; the two chambers were adjoined by a smaller middle chamber measuring 14 cm wide × 21 cm deep × 34.5 cm high. One of the main conditioning chambers featured a white aluminum diamond plate floor with white walls, the other conditioning chamber featured a haircell textured black plastic floor with black walls and the smaller middle chamber was outfitted with a steel rod floor and gray walls. Each individual chamber within each apparatus had two white LED lights set to minimal brightness within the otherwise unlit room. A total of eight identical apparatuses were used; each apparatus featured a 16 × 4 photobeam array for recording time (sec) spent in each chamber. The room in which the apparatuses were located was illuminated by an 85-watt red light mounted to the ceiling in the center of the room, and background noised was masked by a white noise generator located in the front of the room.

2.1.4. Ethanol preexposure

On PND 30, animals were divided into two groups and injected intraperitoneally (IP) with either ethanol (Group E; 2.0 g/kg; n = 35) or vehicle (Group V; n = 32). The time course, dose and route of administration of ethanol were chosen to match previous studies examining the effects of ethanol exposure on cocaine responsivity (Grakalic and Riley, 2002; Hutchison et al., 2010; Slawecki and Betancourt, 2002; Slawecki et al., 2001). Group assignments were made such that animals in each bin (see above) were administered the same compound. Injections were given daily for 10 consecutive days (PNDs 30–39). From PND 40 to PND 54, subjects were maintained in their home bins until place conditioning (see below).

2.1.5. Place preference conditioning

2.1.5.1. Baseline test

On PND 55, animals were individually housed in hanging wire cages (24.3 × 19 × 18 cm) and allowed 10 days to acclimate to this environment. This procedure was chosen to match previous work assessing the interaction of alcohol and cocaine (see Busse et al., 2004, 2005; Busse and Riley, 2002; Diaz-Granados and Graham, 2007; Graham and Diaz-Granados, 2006). On PND 65, baseline chamber preferences were determined by placing each animal in the center compartment of the CPP apparatus, then removing the barriers and allowing it free access to the entire apparatus for 15 min. A paired-samples t-test revealed that animals spent significantly less time in the white chamber than the black chamber (268 versus 354 s, t(66) = −5.1, p < 0.001), indicating a significant apparatus bias (Cunningham et al., 2003; Roma and Riley, 2005); there were no differences between preexposure groups in time spent in either the black or white chambers (ps > .05). Given that the animals showed an initial side preference in the apparatus, a biased conditioning design was used such that all subjects received drug in the white (least-preferred) chamber (see also Kelley and Rowan, 2004; Schramm-Sapyta et al., 2004).

2.1.5.2. Acquisition and final test

The CPP acquisition phase began on PND 66. Subjects in each of the two preexposure conditions, i.e., Groups V and E, were randomly assigned a conditioning dose of cocaine (5, 10 or 20 mg/kg) or vehicle (matched in volume to the 20 mg/kg dose of cocaine). This treatment resulted in eight groups designated as follows: V0 (n = 8), V5 (n = 8), V10 (n = 8), V20 (n = 8), E0 (n = 8), E5 (n = 9), E10 (n = 9) and E20 (n = 9). The first letter stands for the preexposure condition (ethanol or vehicle), and the second letter or number stands for the conditioning injection (vehicle or 5, 10 or 20 mg/kg cocaine). On Day 1 of the conditioning cycle, half of the animals were administered their conditioning injection (vehicle, 5, 10 or 20 mg/kg cocaine; IP) and confined to the white chamber for 30 min. The remaining animals received a saline injection and were confined to the black chamber for 30 min. On Day 2, animals experienced injections and chamber confinement opposite to those of Day 1. All groups were counterbalanced across conditioning days. This 2-day sequence constituted one conditioning cycle, and the acquisition phase consisted of four such cycles culminating in a final CPP test on PND 74. During the final CPP test, animals were placed in the center compartment and then allowed access to the entire apparatus for 15 min.

2.1.6. Data analysis

To assess the health of the subjects, body weights were analyzed during ethanol preexposure and place preference conditioning. For both the preexposure and conditioning phases, body weights were analyzed using repeated-measures ANOVAs. To assess the effects of ethanol preexposure on place preference conditioning, a 2 × 2 × 4 repeated-measures ANOVA with the within-subjects factor of Trial (baseline or final CPP test) and the between-group factors of Preexposure (vehicle or ethanol) and Dose (0, 5, 10 or 20 mg/kg cocaine) was performed with seconds spent in the drug-paired (white) chamber as the dependent variable. Following significant main effects, differences between time spent in the drug-paired chamber during baseline and final CPP tests were analyzed with one-way ANOVAs followed by Tukey’s post-hoc tests. To specifically examine changes in preference for the white (drug-paired) chamber
between the baseline and final CPP tests for each group, paired-samples t-tests were used. Statistical significance was set at $\alpha = .05$ for all analyses.

2.2. Results

2.2.1. Body weights

The 2 (Preexposure) $\times$ 10 (Day) repeated-measures ANOVA on body weight during the preexposure phase revealed significant effects of both Day [$F(9,585) = 2894.6, p < .001$] and Preexposure [$F(1,65) = 14492.8, p < .001$] as well as a significant Day $\times$ Preexposure interaction [$F(9,585) = 67.0, p < .005$]. Independent-samples t-tests on each day showed that on Days 4, 6, 7 and 8 animals that received ethanol injections weighed less than those that received saline during preexposure. Average body weights across these sessions were 0.141 kg for Group V and 0.130 kg for Group E. The 2 (Preexposure) $\times$ 4 (Dose) $\times$ 10 (Day) repeated-measures ANOVA on body weights during conditioning (including the baseline and final test session) revealed a significant effect of Preexposure, with no other factors reaching significance. When body weights were averaged across conditioning sessions, an independent-samples t-test revealed that the ethanol-preexposed animals weighed significantly less than the animals that received vehicle during adolescence ($p < .001$). Average weights during the conditioning sessions were 0.340 kg for vehicle-preexposed animals and 0.317 kg for ethanol-preexposed animals.

2.2.2. Place preference conditioning

The 2 (Trial) $\times$ 2 (Preexposure) $\times$ 4 (Dose) repeated-measures ANOVA on time in the drug-paired chamber revealed significant effects of Trial [$F(1,59) = 9.882, p < .01$], Preexposure [$F(1,59) = 5.100, p < .05$] and Dose [$F(3,59) = 5.388, p < .01$], as well as significant Preexposure $\times$ Dose [$F(3,59) = 4.452, p < .01$] and Trial $\times$ Preexposure $\times$ Dose [$F(3,59) = 3.605, p < .05$] interactions. Given the significant interaction of all three factors, further analyses were conducted to identify specific dose-response relationships within each preexposure condition on the baseline and final CPP test.

One-way ANOVAs on time in the drug-paired chamber followed by Tukey’s post-hoc tests were performed on each trial (baseline and final CPP test) to determine if there were any differences in time spent on the white (drug-paired) side between groups. Analysis of the baseline test (Fig. 1A) revealed significant differences between groups ($p < .05$). Specifically, Group V-10 spent significantly more time in the white chamber on this day than Group V-5. There were no other significant differences between groups on this trial. During the final CPP test (Fig. 1B), additional significant group differences within each preexposure condition emerged. For the vehicle-preexposed animals, the group exposed to the highest dose of cocaine (Group V-20) spent significantly more time in the drug-paired chamber than any of the other groups ($p < .05$). For animals exposed to ethanol during adolescence, subjects conditioned with 10 mg/kg cocaine spent significantly more time in the drug-paired chamber than their controls (Group E-0; $p < .05$). None of the other groups (vehicle- or ethanol-preexposed) differed from controls. In addition, there were no significant dose-dependent preexposure differences on either trial.

To more specifically assess the development of a preference for the drug-paired chamber, times spent in this compartment during the baseline and final CPP tests were compared using paired-samples t-tests for each group. A significant increase in time spent in the drug-paired chamber during the final test would indicate a significant preference for that compartment. For animals preexposed to saline (Fig. 2A), Group V-20 showed a significant increase in time spent on the drug-paired chamber from baseline to the final test ($p < .001$). No other vehicle-preexposed subjects showed a significant increase in time in the drug-paired chamber. In subjects preexposed to ethanol during adolescence (Fig. 2B), a significant increase in time spent in the drug-paired chamber was seen for the intermediate dose. Group E-10 ($p < .01$). None of the other ethanol-exposed groups showed a change in time spent in the drug-paired chamber over trials.

3. Experiment 2: adult ethanol exposure

3.1. Procedure

The procedures used for the assessment of the effects of ethanol exposure in adults were identical to those described for the adolescent subjects with the following exceptions. As in Experiment 1, Experiment 2 was run in two replicates ($n=32$ in the first replicate, $n=35$ in the second) under identical parameters and data was pooled for analysis. On PND 70, animals were divided into two groups and injected IP with either ethanol (Group E; 2.0 g/kg; $n=35$) or vehicle (Group V; $n=32$). Injections were given daily for 10 consecutive days (PNDs 70–79). From PND 80 to PND 84, subjects were maintained in their home bins until place conditioning (see below). On PND 85, animals were individually housed in hanging wire cages (24.3 x19 x18 cm) and allowed 10 days to acclimate to this environment. For Experiment 2, the baseline preference test took place on PND 105. Similar to Experiment 1, animals showed a significant preference for the black relative to the white side of the chamber during the baseline test (375 versus 283 s, paired-samples $t(66) = -5.7; p < .001$), with no differences between preexposure groups for time spent in either the black or white chambers ($p > .05$). Conditioning began on PND 106, and the final CPP test took place following four conditioning cycles (as above).
3.2. Results

3.2.1. Body weight

The 2 (Preexposure) x 10 (Day) repeated-measures ANOVA on body weight during the preexposure phase revealed a significant effect of Day \( [F(9, 585)=73.9; p < 0.001] \) and a significant Preexposure \( \times \) Day interaction \( [F(9, 585)=68.7; p < 0.001] \). Independent-samples t-tests on each day revealed that on Days 8–10 animals receiving ethanol injections weighed significantly less than those receiving vehicle injections \( (p < 0.05) \). Average weights across these 3 days were 0.354 kg for Group V and 0.340 kg for Group E. The 2 (Preexposure) x 4 (Dose) x 10 (Day) repeated-measures ANOVA during conditioning revealed a significant effect of Day \( [F(9, 531)=24.207; p < 0.001] \), as well as significant Preexposure \( \times \) Day \( \times \) Dose interaction \( [F(27, 531)=1.7; p < 0.05] \) interactions. However, one-way ANOVAs on each conditioning day did not reveal any additional significant differences between groups \( (p > 0.05) \).

3.2.2. Place preference conditioning

The 2 (Trial) x 2 (Preexposure) x 4 (Dose) repeated-measures ANOVA revealed a significant effect of Trial \( [F(1, 59)=10.335; p < 0.01] \) as well as a Trial \( \times \) Dose interaction \( [F(3, 59)=6.558; p < 0.001] \). None of the terms involving Preexposure reached significance. To explore the main effect of Trial, a paired-samples t-test revealed that time in the white chamber significantly increased between the baseline and final CPP tests \( (p < 0.01) \). The Trial \( \times \) Dose interaction was analyzed with one-way ANOVAs followed by Tukey’s post-hoc tests on each trial. During the baseline test \( (Fig. 3A) \), there was an effect revealed by the one-way ANOVA \( [F(3, 66)=2.819, p < 0.05] \). However, Tukey’s post-hoc tests did not reveal any significant differences between groups on this trial \( (ps > 0.05) \). Analysis on the final CPP test \( (Fig. 3B) \) also revealed a significant difference between doses \( [F(3, 66)=4.109, p = 0.01] \). Post-hoc analysis showed that groups conditioned with 10 and 20 mg/kg cocaine spent significantly more time in the white chamber than the saline-conditioned controls \( (p < 0.05) \). To examine the specific changes in time spent in the drug-paired chamber for each group, paired-samples t-tests were used to assess differences in time spent in the drug-paired chamber between the pretest and final CPP test. Group V-20 \( (Fig. 4A) \) and Group E-10 \( (Fig. 4B) \) showed a significant increase in time spent in the drug-paired chambers across trials \( (p < 0.05) \). There were no significant differences for any of the other groups.

4. Discussion

Experiment 1 was designed to assess the effects of ethanol exposure during adolescence on the rewarding effects of cocaine administered later in life. As described, a history of ethanol exposure produced a leftward shift of the cocaine dose–response curve. Specifically, animals preexposed to saline and conditioned with 20 mg/kg cocaine increased the time spent in the drug-paired chamber from baseline to the final test and spent more time in the drug-paired chamber following conditioning. These same effects were evident in the ethanol-preexposed subjects when conditioned at 10 mg/kg cocaine. In a similar assessment in adults, Experiment 2 found that animals preexposed to saline and conditioned with 20 mg/kg cocaine increased the time spent in the
drug-paired chamber from baseline to the final test while animals exposed to ethanol displayed this increase at 10 mg/kg cocaine. However, there was no effect of ethanol preexposure in adults when the more conservative measure of time in the drug-paired chamber was assessed. These results suggest that ethanol preexposure during both adolescence and adulthood sensitizes the rewarding effects of cocaine, although these sensitizing effects may be weaker with adult exposure.

Adolescent exposure to ethanol has been shown to produce a wide range of behavioral effects lasting into adulthood, including the production of lasting effects on drug-taking behaviors (Diaz-Granados and Graham, 2007; Duncan et al., 1997; Graham and Diaz-Granados, 2006; Hutchison et al., 2010; Matthews et al., 2008; Pascual et al., 2007; Pascual et al., 2009; Rodd-Henricks et al., 2002; Siciliano and Smith, 2001; Slaevecki, 2002; White et al., 2002). Interestingly, little work has been done to examine how early exposure to ethanol may impact the response to other drugs of abuse in adulthood. One such study examined the effect of adolescent ethanol exposure on cocaine-induced taste aversions in adult rats (Hutchison et al., 2010). In this study, ethanol exposure during adolescence resulted in an attenuation of cocaine-induced taste aversions in adult rats (Hutchison et al., 2010). Given that the abuse liability of a drug can be seen as a balance between its rewarding and aversive effects (Brockwell et al., 1991; Simpson and Riley, 2005; Wise et al., 1976), if a history of ethanol use attenuates the aversive effects of cocaine (Hutchison et al., 2010) while sensitizing the rewarding effects as seen in the present study, it would indicate an increase in the likelihood of cocaine abuse after ethanol exposure early in life. Such an effect would be consistent with the trends seen in human drug use, where alcohol use precedes the use of drugs such as cocaine (Degenhardt et al., 2010; Haertzen et al., 1983) and heavy use of alcohol in adolescence can be seen as a predictive factor for later drug abuse (Cable and Sacker, 2008; Duncan et al., 1997; Grant and Dawson, 1997; Yu and Williford, 1992).

The interaction between a history of ethanol exposure and subsequent cocaine-induced place preferences in adult rats has been explored in previous studies (Busse et al., 2005; Le Pen et al., 1998). Interestingly, in those reports adult ethanol exposure did not produce a sensitization to the rewarding effects of cocaine. Differences between the results reported here (Experiment 2) and this prior work may be due to a number of parametric variations. In terms of the ethanol preexposure procedure, one of the previous studies (Busse et al., 2005) used a series of five spaced injections of 1.5 g/kg ethanol, while the other study (Le Pen et al., 1998) administered ethanol over 14 days in a drug-taking preparation. In contrast, adult animals in Experiment 2 were exposed to 10 consecutive days of 2 g/kg ethanol injections. It should be noted that this preexposure procedure was chosen to match that of Experiment 1, which aimed to mimic ethanol exposure across the course of the adolescent developmental period. Given that adolescents tend to have higher levels of alcohol consumption than older adults (Substance Abuse and Mental Health Services Administration, 2010), it may be that the adolescent exposure procedure employed in the present series of experiments caused sensitization in the animals exposed as adults that would not be seen with a spaced preexposure regimen. One additional parameter that varied between prior work and Experiment 2 was the conditioning dose of cocaine. The present study used a dose–response approach to the place conditioning procedure and found a preexposure effect at the intermediate (10 mg/kg) dose of cocaine. In contrast, the previous studies each only used one dose of cocaine, which may not have detected all potential changes in the sensitivity to cocaine. Differences in these parameters may have resulted in the different results found between the present work with adult exposure and earlier work on ethanol's effects on conditioned place preferences in adult rats.

The fact that cocaine-induced place preferences were evident at lower doses in the ethanol-preexposed animals (when given during adolescence and adulthood) can be explained by a shift in the sensitivity to the rewarding effects of ethanol. An interesting feature of the current work, however, is that in both Experiments 1 and 2, ethanol-preexposed animals no longer displayed preferences at the 20 mg/kg dose of cocaine (whereas vehicle-exposed controls did). It is not clear why preferences were no longer evident at the higher dose in the ethanol-preexposed subjects. In studies using animals without a history of ethanol preexposure, place preferences have also been seen with 20 mg/kg cocaine (Busse et al., 2004; Durazzo et al., 1994). When ethanol and cocaine are given in combination during place preference conditioning, an attenuated preference is seen relative to subjects receiving cocaine alone (Busse et al., 2004; Busse and Riley, 2002), suggestive of the possibility that ethanol enhanced cocaine's aversive effects. In the present study a similar effect may have occurred, with the ethanol preexposure history enhancing the aversive effects of the highest dose of cocaine. Alternatively, given that animals in both experiments of the present manuscript were individually housed during CPP conditioning (see Busse et al., 2004, 2005; Busse and Riley, 2002; Diaz-Granados and Graham, 2007; Graham and Diaz-Granados, 2006; Hutchison et al., 2010), isolation stress may have affected place preference conditioning, interacting with cocaine to affect its aversive/rewarding properties at the higher dose in the ethanol-preexposed subjects (though see Gehrke et al., 2006; Smith et al., 2009; Solinas et al., 2008).
As noted, in comparison to adolescent ethanol exposure, similar but weaker results were seen when the preexposure was given during adulthood. Both adolescent (Experiment 1) and adult (Experiment 2) ethanol exposure produced an increased sensitivity to an intermediate (10 mg/kg) dose of cocaine as measured by a significant change in time spent in the drug-paired chamber between the baseline and final tests. The change in sensitivity was also seen in Experiment 1 when measured as time spent in the drug-paired chamber relative to controls during the final test; however, in Experiment 2, no preexposure effects were seen with this measure of place conditioning. Several previous studies have found long-lasting effects of ethanol following adolescent, but not adult, exposure (Bergstrom et al., 2006; Diaz-Granados and Graham, 2007; Graham and Diaz-Granados, 2006; Sircar and Sircar, 2005; White et al., 2000). However, other studies examining the long-term effects of adolescent and adult exposure to ethanol (Hutchison et al., 2010; Silveri and Spear, 2001) as well as similar exposure to other drugs such as cocaine (Schramm-Sapyta et al., 2004) have found no differences between age groups. These contrasting results across studies may indicate that differences between the long-term effects of adolescent and adult ethanol exposure might be dependent on the measures being tested. In addition to differences in place preference conditioning, age-related differences were also seen for ethanol’s effect on body weights. Ethanol-induced decreases in body weight were seen in the preexposure phase for both age groups. In Experiment 1, these effects persisted through the conditioning phase, with all ethanol-preexposed groups showing a decrease in average body weight later in life. In contrast, in Experiment 2, the body weight differences during the conditioning phase were dependent on conditioning dose and trial as well as preexposure condition, and no differences between individual groups reached significance. These results indicate that while ethanol preexposure effects may be seen following exposure during either adolescence or adulthood, exposure earlier in development may lead to stronger long-term physical and behavioral changes. Given that alcohol use is most commonly initiated during adolescence (Degenhardt et al., 2010; Johnston et al., 2011; Kandel et al., 1992; Substance Abuse and Mental Health Services Administration, 2010), adolescence should be viewed as a critical developmental period that may be involved in the later likelihood of drug misuse and abuse.

Because the rewarding effects of a drug play a strong role in its abuse potential (Bardo and Bevins, 2000), a sensitization of the rewarding effects of cocaine following adolescent ethanol exposure may indicate an increased likelihood of later cocaine abuse. To further clarify the role of ethanol in mediating cocaine’s abuse liability, it would be of interest to examine neural changes resulting from ethanol exposure early in life and how these changes may impact the biological response to cocaine. In addition, since adolescent ethanol exposure alters both the rewarding (as shown in the present study) and aversive (Hutchison et al., 2010) effects of cocaine, it would also be of interest to see how such exposure may alter cocaine self-administration. Since the rewarding and aversive effects of a drug play a role in its abuse liability (Brockwell et al., 1991; Simpson and Riley, 2005; Wise et al., 1976), the use of a self-administration procedure would help to clarify how these effects may translate to a model that more closely mimics human drug-taking behaviors. If early ethanol exposure reduces the aversive effect of cocaine (Hutchison et al., 2010) and also sensitizes its rewarding effects, it would be expected that adolescent ethanol exposure would increase cocaine self-administration later in life. This would parallel the drug-taking patterns seen in humans (Cable and Sacker, 2008; Degenhardt et al., 2010; Duncan et al., 1997; Grant and Dawson, 1997; Haertzen et al., 1983; Yu and Williford, 1992). A full understanding of how early ethanol exposure alters the response to cocaine on both the biological and behavioral level would be a large step towards understanding and potentially preventing such patterns seen in human drug abuse.

References
