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Sex and age differences in heavy binge drinking and its effects on alcohol responsivity following abstinence

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ABSTRACT

Binge drinking during adolescence may perturb the maturing neuroenvironment and increase susceptibility of developing an alcohol use disorder later in life. In the present series of experiments, we utilized a modified version of the drinking in the dark-multiple scheduled access (DID-MSA) procedure to study how heavy binge drinking during adolescence alters responsivity to ethanol later in adulthood. Adult and adolescent C57BL/6J (B6) and DBA/2J (D2) males and females were given access to a 20% ethanol solution for 3 hourly periods, each separated by 2 h of free water access. B6 adults and adolescents consumed 2 to 3.5 g/kg ethanol an hour and displayed significant intoxication and binge-like blood ethanol concentrations. There was an interaction of sex and age, however, driven by high intakes in adult B6 females, who peaked at 11.01 g/kg. Adolescents of both sexes and adult males never consumed more than 9.3 g/kg. D2 mice consumed negligible amounts of alcohol and showed no evidence of intoxication. B6 mice were abstinent for one month and were retested on the balance beam 10 min following 1.75 g/kg ethanol challenge (20%v/v; i.p). They were also tested for changes in home cage locomotion immediately following the 1.75 g/kg dose (for 10 min prior to balance beam). Although there was no effect of age of exposure, all mice with a binge drinking history demonstrated a significantly dampened ataxic response to an ethanol challenge. Female mice that binge drank during adulthood showed a significantly augmented locomotor response to ethanol when compared to their water drinking controls. This alteration was not noted for males or for females that binge drank during adolescence. These results highlight the importance of biological sex, and its interaction with age, in the development of behavioral adaptation following binge drinking.

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1. Introduction

Adolescence is a major stepping-stone in mammalian development. It is a period characterized by substantial changes in brain structure, systems and connectivity, and includes reorganization of neurochemical networks, and increases in synaptic pruning and myelination (Bava and Tapert, 2010; Giedd, 2004; Spear and Brake, 1983; Tamnes et al., 2011). The dramatic brain changes that occur at this time period may leave the central nervous system especially vulnerable to adulteration by drugs and alcohol. Consequently, the high rate of binge alcohol consumption in this age group elicits concern (Johnston et al., 2007). Alcohol use during this time period may not only perturb the neuroenvironment, but may also stunt maturation and increase susceptibility to the development of dependence and abuse (Crews et al., 2007; Witt, 2010). Indeed, there is a strong relationship between age of first drink and rate of alcohol dependence (Dawson et al., 2008; Hingson et al., 2006; Pitkänen et al., 2005). Our research team has previously shown a positive relationship between binge alcohol consumption during adolescence and higher than average consumption of the drug during adulthood (Moore et al., 2010). Interestingly, we have also shown that both sensitivity to alcohol during adolescence, and the effects of adolescent alcohol exposure on adult receptivity to the drug, may be modulated by genetic background (Melón and Boehm, 2011; Moore et al., 2010). This is not surprising, as a substantial body of literature supports a role for genetic background in the progression from recreational drug use or social drinking to abuse and addiction. Furthermore, though most alcohol consumers initiate use prior to the end of adolescence, only a small percentage of those go on to develop an alcohol use disorder. However, little is known about how the interaction between genetics and ontogeny alters the effect of adolescent exposure on the risk of developing addiction during adulthood.

Given the ethical limitations of human research, animal models are crucial to our ability to clarify the independent and/or synergistic roles of genetics and ontogeny with respect to the vulnerability to develop alcohol use problems (Zucker et al., 2008). Unfortunately, many animal models of voluntary alcohol consumption yield higher alcohol intake among adolescents than adults (Doremus et al., 2005;

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García-Burgos et al., 2009; Maldonado et al., 2008; Moore et al., 2010; Vetter et al., 2007). Although this highlights the face and ecological validity of these animal models in representing alcohol related behaviors seen in human adolescents, it makes it difficult to isolate the importance of age of exposure from the general pathological effects of high alcohol intake. Put another way, in experimental models where adolescent rodents actually consume more alcohol than their adult conspecifics, it is impossible to infer whether the effects seen following this early pre-exposure were due to the age at which the animals were drinking, or to the amount of alcohol to which the animals were exposed. With this in mind, we adapted the recently characterized drinking in the dark-multiple scheduled access (DID-MSA) paradigm (Bell et al., 2006, 2011) in order to induce home cage binge drinking in mice. Like the drinking-in-the-dark (DID) paradigm (Rhodes et al., 2005, 2007), this procedure is an oral self-administration protocol that takes place in the animal's home environment. Although the original DID-MSA protocol has been shown to induce age-dependent binge drinking behavior in rats (Bell et al., 2011), preliminary evidence from our laboratory suggested that this adapted access schedule could produce similar alcohol consumption across adolescent and adult mice.

The goals of the present series of experiments were threefold: 1) to characterize the level of consumption and intoxication achieved using the DID-MSA procedure in adolescent and adult C57Bl/6J (B6) mice; 2) to assess whether age of exposure moderates the development of functional tolerance to intoxication following multiple binge sessions and 3) to evaluate whether age of exposure affects later sensitivity to alcohol. We hypothesized that this modified DID-MSA protocol would initiate high but comparable levels of intake in B6 adults and adolescents and that later sensitivity to alcohol would be affected by age of exposure in this strain. Given our ultimate interest in exploring the interaction of ontogeny and genetics in moderating the effects of alcohol exposure, we also included the alcohol non-preferring, DBA/2J inbred mouse strain to see whether this type of scheduled drinking procedure could induce any level of relevant alcohol intake in these mice.

2. Methods

2.1. Subjects

Male and female DBA/2J (D2) and C57BL/6J (B6) adult (PD 60 ± 3) and adolescent (PD 30 ± 3) mice were purchased from Jackson Laboratory (N = 251 mice). Animals arrived at the Indiana University-Purdue University Indianapolis School of Science animal facility at PD 21 ± 3 or PD 56 ± 3. Animals were singly housed in standard shoebox cages and were habituated to the facility for seven days. Mice were maintained across two holding rooms, each kept at 21 ± 1 °C and approximately 50% humidity. An anteroom, where all mice were moved for daily weights, separated the holding rooms. Behavioral testing and blood retrieval also occurred in this anteroom. Food and water were available ad libitum, except during alcohol access periods. All procedures were approved by the Indiana University-Purdue University Indianapolis School of Science Institutional Animal Care and Use Committee and were consistent with the Guide for the Care and Use of Mammals in Neuroscience and Behavioral Research (National Research Council (US) Committee for the Update of the Guide for the Care and Use of Laboratory Animals, 2011).

2.2. Drugs and drinking solution

For drinking, 95% ethanol (Ethanol; Pharmco Products Inc., Brookfield, CT) was diluted with tap water to a 20% v/v solution. For intraperitoneal injections, 95% ethanol was diluted with 0.9% physiological saline to a 20% v/v solution and administered by varying injection volume for a 1.75 g/kg dose.

2.3. Experiment 1: alcohol pre-exposure using the "drinking in the dark-multiple scheduled access" (DID-MSA) protocol

The drinking protocol was adapted from Bell et al. (2011) and is outlined in Table 1. Each day, mice received access to water or a 20% unsweetened ethanol solution during three, 1-hour access periods. Each access period was separated by 2 h, during which all mice had ad libitum access to water. Immediately following lights-out, regular water bottles were removed from all cages and replaced with a 10 mL plastic Mohr pipette affixed to a ball bearing sipper. This modified drinking tube contained either water or the ethanol solution and volumes were recorded before and after each hourly access period. The regular heavy duty glass water bottles (16 mL) were placed atop the modified tubes. This helped to reduced leakage by keeping the modified tubes in place. Additionally, two leak cages (one with a modified tube containing water, and one with a modified tube containing the ethanol solution) were maintained on each animal rack, and were read at the end of each access period. An average hourly leak was calculated for each solution (water or 20% ethanol), for the entire experiment. These constants were subtracted from all respective intake values.

2.4. Experiment 2: assessment of intoxication and blood ethanol concentration during DID-MSA

We were interested in evaluating the level of intoxication achieved using this DID-MSA procedure with B6 and D2 mice. Additionally, we wanted to assess the degree of functional tolerance seen following multiple binges using this DID-MSA procedure. Therefore, mice were assessed for signs of motor incoordination immediately following either the first (1H), second (2H) or third (3H) hour of access to ethanol (or water) on days 7 and 14 of drinking. Mice were pseudorandomly assigned to either group 1H, 2H or 3H. Motor incoordination was measured using the balance beam apparatus. Given the potential confound due to size differences between the adults and adolescents (Doremus et al., 2006; Moore et al., 2011; Linsenbardt et al., 2009) we used one hardwood balance beam for adults (122 cm long × 2 cm wide × 4 cm tall) and a second hardwood balance beam for adolescents, scaled to 3/4 the size of the adult beam (91.5 cm long × 1.5 cm wide × 3 cm tall). Each beam was affixed atop two 48 cm tall ring stands. Approximately 2 h before lights out on days 7 and 14, adolescents and adults were trained on their respective balance beam apparatus. During this training, a mouse was placed onto the starting edge of the balance beam to traverse the length of the beam, to and fro. The eraser end of a pencil was used to nudge mice that paused, or attempted to turn prematurely, along the beam. During the balance beam test, hind foot-slips were counted by the same experimenter that performed the training earlier that morning. Immediately after the mouse traversed the balance beam, a retro-orbital sinus blood sample was collected (25 μL).

2.5. Experiment 3: effect of alcohol intake during adolescence on alcohol-induced motor in-coordination and stimulation during adulthood in B6 mice

Only B6 mice were maintained for this portion of the study. Exactly one month following the fourteen days of DID-MSA ethanol access, the same B6 mice from Experiments 1 and 2 were intraperitoneally administered a 1.75 g/kg dose of ethanol (20% v/v). Animals who formerly consumed ethanol as adolescents were PD 73 ± 3 and those who consumed ethanol as adults were PD 102 ± 3. Prior to lights out on this test day, all mice were trained on the adult sized balance beam. Training proceeded as described earlier. Immediately following the 1.75 g/kg ethanol administration, mice were returned to their home cages. The home cages were placed onto a rack containing home cage activity monitoring systems (Columbus Instruments, Columbus, OH) in order to assess locomotor activity following the 1.75 g/kg ethanol administration. The activity monitor sampled activity in ten

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