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Effects of stress, acute alcohol treatment, or both on pre-pulse inhibition in high- and low-alcohol preferring mice

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ABSTRACT

Pre-pulse inhibition of the acoustic startle reflex (PPI) is a measure of sensorimotor gating frequently used to assess information processing in both humans and rodents. Both alcohol and stress exposure can modulate PPI, making it possible to assess how stress and alcohol interact to influence information processing. Humans with an increased genetic risk for alcoholism are more reactive to stressful situations compared to those without a family history, and alcohol may have stress-dampening effects for those with high genetic risk. The purpose of the present study was to examine the effects of stress, acute alcohol exposure, or both on PPI in male and female mice selectively bred for high- (HAP2) and low- (LAP2) alcohol preference. Experiment 1 assessed the effects of various doses of acute alcohol on PPI. Experiments 2 and 3 assessed the effect of 10 days of restraint stress on subsequent PPI tested at 30 min (Experiment 2) or 24 h (Experiment 3) following the termination of stress exposure. Experiment 3 also examined the effects of acute alcohol treatment (0.75 g/kg) on PPI in mice previously exposed to stress or no stress. Results indicate that 0.75 and 1.0 g/kg doses of alcohol increased PPI in HAP2 but not LAP2 mice. When PPI was tested 30 min after stress exposure, stressed HAP2 mice showed a trend toward decreased PPI and stressed LAP2 mice showed a trend toward increased PPI. The combination of stress and alcohol treatment did not alter PPI in either line 24 h following the termination of stress exposure, suggesting that alcohol does not ameliorate the effect of stress on PPI. Stressed LAP2 mice had increased basal circulating corticosterone on the final stress exposure day compared to non-stressed LAP2 mice, and no difference was found between stressed and non-stressed HAP2 mice. The results suggest that high genetic risk for alcoholism may be related to increased sensitivity to alcohol and stress effects on PPI, and this sensitivity could signify an endophenotype for increased genetic risk to develop alcoholism.

Introduction

Alcohol abuse and alcoholism represent major burdens to society with costs reaching $185 billion and 100,000 lives lost annually (Li, Hewitt, & Grant, 2004). Exposure to stress is an important variable that interacts with many environmental and biological factors to influence alcohol-drinking behavior in both humans and rodents (Sillaber & Henniger, 2004; Uhart & Wand, 2009). For example, rodents show stress-induced changes in alcohol consumption (e.g., Champagne & Kirouac, 1987; Chester, de Paula Barrenha, DeMaria, & Finegan, 2006; Lynch, Kushner, Rawleigh, Fiszdon, & Carroll, 1999), although the direction of effects are inconsistent and influenced by many factors like genetics, history of alcohol drinking, and type/history of stress exposure (Pohorecky, 1991). As well, interactions between these factors are important and likely contribute to the complex and often inconsistent findings in the literature.

Evidence suggests that humans with a family history of alcoholism are more reactive to stress compared to individuals without a family history of alcoholism. For example, adult sons of alcoholics (SOAs) display increased heart rates and greater vein constriction (classic cardiovascular stress responses) preceding an unavoidable electric shock compared to controls (Finn, Zeitouni, & Pihl, 1990), and adolescent SOAs display increased heart rates compared to non-SOAs while performing a mental arithmetic task (psychological stressor; Harden & Pihl, 1995). On the other hand, one study reported similar acoustic startle in response to threat of electric shock in SOAs compared to controls (Zimmermann, Spring, Wittchen, & Holsboer, 2004) and another study showed reduced skin conductance responses in anticipation of electric shock compared to controls (Finn, Kessler, & Hussong, 1994). These results may suggest that SOAs are more reactive to stressful stimuli under certain experimental conditions; however, more study is needed to clarify the basis of contradictory results. Animal models provide an opportunity to explore the influence of factors such as genetics and history of stress exposure under controlled experimental conditions.

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Rodents selectively bred for high- or low-alcohol drinking/preference have been a rich resource for investigators to assess how genetic influences on alcohol drinking behavior may also influence other behavioral traits (Crabbe, Phillips, & Belknap, 2010). With regard to stress reactivity, reports in selectively bred rat lines suggest that alcohol-preferring (P) rats may be more sensitive to stress-related effects on behavior compared to their non-preferring (NP) counterparts. For example, male P rats showed changes in stress-induced drinking while NP rats did not (Chester, Blose, & Froehlich, 2004). In another study that assessed foot shock effects on reinstatement of alcohol drinking in an alcohol deprivation model, Alcohol-Accepting (AA), High-Alcohol-Drinking (HAD), and P rats showed greater alcohol intake than Wistar rats following the foot shock exposure (Vengeliene et al., 2003). Foot shock stress has also been shown to reinstate alcohol responding to a greater degree in Marchigian Sardinian alcohol-preferring (msP) rats compared to Wistar rats (Hansson et al., 2006). Other reports also indicate that high-alcohol-preferring rodent lines are more susceptible to develop stress-induced, conditioned fear-related behavior than their low-alcohol-preferring counterparts are (Barrenha & Chester, 2007; Chester, Kirchhoff, & Barrenha, 2013; McKinzie et al., 2000).

In addition to being more reactive to stress, evidence from both humans and rodents indicates that individuals with an increased genetic risk for high alcohol drinking are more sensitive to alcohol's stress-dampening effects. For example, alcohol reduced the physiological stress response (i.e., heart rate and vein constriction) displayed by SOAs in anticipation of shock, but did not change response for those without a family history of alcoholism (Finn et al., 1990). Analogous results were found in high- (HAP) and low- (LAP) alcohol-preferring replicate mouse lines where alcohol reduced the expression of fear-potentiated startle (FPS) in HAP but not in LAP mice (Barrenha, Coon, & Chester, 2011). These results suggest that alcohol's stress-dampening effects on physiological and behavioral responding depend on genetic susceptibility for high- or low-alcohol-drinking behavior.

The mammalian acoustic startle response is an adaptive reflexive behavior in response to a loud acoustic stimulus and has served as a useful phenotype for emotion and cognition-related behavior (Grillon, Sinha, Ameli, & O'Malley, 2000). The startle response can also be decreased by presenting a relatively weaker stimulus directly (e.g., 100 ms) before a startle-inducing stimulus, termed pre-pulse inhibition (PPI). PPI is thought to reflect an inhibitory mechanism (or "gate") that protects the neural processing of the pre-pulse from interruption by the startle pulse (Graham, 1992; Norris & Blumenthal, 1996; Swerdlow, Geyer, Blumenthal, & Hartman, 1999), preventing cognitive overload (e.g., Braff & Geyer, 1990; Braff, Grillon, & Geyer, 1992). PPI is considered a general measure of information processing and has been utilized to study a range of neuropsychiatric disorders characterized by deficits in sensory and/or cognitive function (Braff, Geyer, & Swerdlow, 2001).

PPI is influenced by both genetic and environmental factors. For example, exposure to stress or stress hormones decreases PPI in rodents (Conti, Murry, Ruiz, & Printz, 2002; Risbrough, Hauger, Roberts, Vale, & Geyer, 2004; Sutherland, Burian, Covault, & Conti, 2010; Sutherland & Conti, 2011), although not all studies find disruptive effects of stress on PPI (Dubovicky, Paton, Morris, Mach, & Lucot, 2007; Faraday, O'Donoghue, & Grunberg, 1999; Pijlman, Herremans, van de Kieft, Kruse, & van Ree, 2003). Evidence of acute alcohol effects on PPI in rodents is sparse, but Jones et al. (2000) showed that alcohol disrupts PPI for female P rats but not NP rats, suggesting differential sensitivity to the effects of acute alcohol on PPI that is influenced by genetic susceptibility for high- or low-alcohol preference.

The purpose of the present study was to assess the effects of alcohol, stress, and their combination on PPI in mice that differ in genetic predisposition toward alcohol preference (HAP2/LAP2). We predict that repeated stress exposure will disrupt PPI in both HAP2 and LAP2 mice, based on the majority of evidence that stress exposure reduces PPI (e.g., Conti et al., 2002; Grillon & Davis, 1997; Richter et al., 2011; Risbrough et al., 2004; Sutherland et al., 2010; Sutherland & Conti, 2011). However, we further predict that HAP2 mice will show a greater stress-induced disruption of PPI than LAP2 mice and that alcohol will ameliorate the stress-induced disruption of PPI in HAP2 but not LAP2 mice. These predictions are based on the previously cited evidence that humans and animals with a genetic susceptibility toward high-alcohol preference may be more sensitive to stress-related effects on behavior (e.g., Chester et al., 2013; Hansson et al., 2006; Vengeliene et al., 2003) and to the stress-dampening effects of alcohol (Barrenha et al., 2011; Finn et al., 1990).

Materials and methods

Subjects

Subjects were alcohol-naïve replicate-line 2 HAP and LAP mice produced by mass selection from outbred HS/Ibg mice (Boulder, CO, USA) at the Indiana Alcohol Research Center (IARC) in Indianapolis, IN, USA (Grahame, Li, & Lumeng, 1999). Subjects in the current studies were generated at Purdue University from HAP2 and LAP2 breeders obtained from the IARC. Mice were housed in groups of 2–4 in 11.5 × 7.5 × 5.0 in. polycarbonate cages with aspen wood shavings for bedding. Food and water were available *ad libitum*, except during experimental procedures. Temperature in the colony room was maintained at 21 ± 2 °C. Experimental procedures were conducted during the light phase of the 12:12 light:dark cycle (lights on at 0700 h). Mice were from the 31st and 34th generations of selection for Experiment 1, the 34th and 35th generations of selection for Experiment 2, and the 39th generation of selection for Experiment 3. At the start of experimental procedures, mice were between 57 and 101 days old. All experimental procedures were approved by the Purdue Animal Care and Use Committee and were conducted in accordance with the principles of laboratory animal care.

Drugs

Alcohol was diluted from a 95% (v/v) solution to a concentration of 20% (v/v) with physiological saline (0.9%) and was administered as intraperitoneal (IP) injections at doses of 0.5, 0.75, and 1.0 g/kg of body weight in an injection volume of 3.17, 4.73, and 6.30 mL/kg, respectively.

Testing apparatus

PPI was assessed using a Coulbourn Instruments Animal Acoustic Startle System (Coulbourn Instruments, Allentown, PA). The startle chamber is sound-attenuated and contains 4 platforms equidistant from center speakers located in the floor and ceiling of the chamber. Each platform is weight-sensitive and records the amount of force in grams produced by the subject in the 200 ms after presentation of the startle stimuli. The force measurement does not include the subjects' body weight. All subjects were placed individually into open-air holders (8 × 8 × 16 cm) with metal rod floors (rod diameter 0.19 in. with each rod separated by 0.39 in.). The holders rest on top of the weight-sensitive platforms during the acoustic startle test sessions. A ventilating fan provided continuous 70–71 dB background noise.

PPI parameters

Each PPI session began with a 5-min habituation period (no stimuli) followed by 12 different trial types presented throughout