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Assessment of GABA-B, metabotropic glutamate, and opioid receptor involvement in an animal model of binge drinking

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Abstract

Drinking to intoxication or binge drinking is a hallmark characteristic of alcohol abuse. Although hard to model in rodents, the scheduled high alcohol consumption (SHAC) procedure generates high, stable ethanol intake and blood ethanol concentrations in mice to levels consistent with definitions of binge drinking. The purpose of the present studies was to determine the effects of pharmacological manipulation of the opioidergic, glutamatergic, and γ-aminobutyric acid (GABA)ergic systems on binge drinking with the SHAC procedure. Parallel manipulations were conducted in mice trained in operant self-administration of either sucrose or ethanol. For the SHAC procedure, genetically heterogeneous Withdrawal Seizure Control mice were given varying periods of fluid access, with a 30-min ethanol session every third day (total of seven). Mice were pretreated intraperitoneally with naltrexone (0, 0.6, or 1.25 mg/kg), baclofen (0, 2.5, or 5.0 mg/kg), or 2-methyl-6-(phenylethynyl)-pyridine (MPEP; 0, 3.0, or 10.0 mg/kg) before each ethanol session. For the operant self-administration procedure, separate groups of C57BL/6 mice were trained to complete a single response requirement (16 presses on the active lever) to gain 30 min of access to an ethanol or a sucrose solution. Mice received pretreatments of the same doses of naltrexone, MPEP, or baclofen before the self-administration sessions, with saline injections on intervening days. Naltrexone produced a dose-dependent decrease in binge drinking, and the highest dose also significantly decreased operant self-administration of ethanol and sucrose. Both doses of baclofen significantly decreased binge alcohol consumption, but the higher dose also tended to decrease water intake. The highest dose of baclofen also significantly decreased operant self-administration of sucrose. MPEP (10 mg/kg) significantly decreased binge alcohol consumption and sucrose self-administration. These results indicate that manipulation of the opioidergic, glutamatergic, and GABAergic systems significantly decreased binge drinking.

Keywords: Mice; Alcohol; Operant; Naltrexone; Baclofen; MPEP

Introduction

Alcoholism is a complex disorder that is impossible to capture in its entirety within a single animal model. Therefore, multiple models are commonly used to increase our understanding of the mechanisms that underlie specific aspects of this disease, such as acquisition, maintenance of drinking behavior, dependence, and relapse (Rhodes et al., 2005; Rodd et al., 2004). Recent reports by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) indicate that 17.6 million people in the United States are alcohol dependent or abuse alcohol (NIAAA, 2007a). Additional epidemiological studies indicate that the percentage of individuals to engage in binge drinking ranged from 14 to 18% for adults or from 25 to 33% for adolescents (9th–12th grade), with even higher proportions in 12th graders alone (32–42%; Cozzoli et al., 2009, NIAAA, 2007b, 2007c). Binge drinking has been defined by NIAAA as five or more drinks (male) or four or more drinks (female) on at least one occasion in the past month or blood alcohol concentrations of ≥0.8 mg/mL within a 2-h drinking period (NIAAA, 2007a). With respect to binge drinking, it is often difficult to model either gross excess or obvious loss of control in a rodent model. Two contemporary methods that demonstrate animals drinking to the point of intoxication and achieving blood ethanol concentrations (BECs) consistent with that defined for binge drinking by NIAAA are the ''Drinking in the Dark'' (DID; details in Rhodes et al., 2005, 2007; Sharpe et al., 2005) and ''scheduled high alcohol consumption'' (SHAC; Cozzoli et al., 2009; Cronise et al., 2005; Finn et al., 2005)

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procedures. We chose to use the SHAC procedure as a model of binge drinking because recent work in our laboratory has shown that scheduling periods of fluid availability generated high and stable ethanol intake and a physiologically relevant BEC in both C57BL/6 and genetically heterogeneous (i.e., Withdrawal Seizure Control; WSC) mice (Finn et al., 2005). It is noteworthy that mouse genotypes with an innate high alcohol preference (C57BL/6) as well as a low alcohol preference (WSC) maintained elevated BECs (≥0.8 mg/mL) and ethanol intakes of ≥2.0 g/kg within the 30-min period of ethanol access. Animals under this procedure drink on a schedule that enables them to maintain high levels of ethanol consumption without forming a taste aversion (Finn et al., 2005; Szumlinski et al., 2007). An additional study established that the SHAC procedure produced quantifiable signs of intoxication in mice (Cronise et al., 2005).

An animal model that produces elevated BECs and generates behavioral intoxication possesses essential attributes for the examination of the neurochemical mechanisms that underlie binge-like intake and the development of pharmacological interventions for this drinking phenotype. Based on preclinical data and results with therapeutic drugs (i.e., naltrexone and acamprosate), a large body of evidence indicates that there are several different neurochemical systems that modulate alcohol's rewarding and reinforcing properties (reviewed in Koob and LeMoal, 2006). With this in mind, the present studies focused on the opioid, glutamate, and γ-aminobutyric acid (GABA) neurotransmitter systems.

The opioidergic system has been implicated as a major player in brain reward pathways, given that antagonists such as naltrexone reportedly reduce the reward value of abused drugs (Anton and Swift, 2003; Kiefer et al., 2003; Littleton and Zieglgänsberger, 2003; McCaul et al., 2000). Preclinical and clinical studies found that naltrexone reduced ethanol preference, consumption, and the risk for relapse (e.g., Heyser et al., 2003; Hölter and Spanagel, 1999; Stromberg et al., 1998, 2001, 2002). With regard to the DID model of binge drinking, naltrexone dose-dependently decreased ethanol intake at doses that did not influence water intake (Kamdar et al., 2007).

Baclofen is a $GABA_B$ receptor agonist that inhibits the acquisition of ethanol consumption, decreases alcohol-induced craving and withdrawal symptoms, and promotes abstinence (discussed in Heilig and Egli, 2006). Numerous preclinical and clinical studies have documented that $GABA_B$ receptor agonists suppress numerous alcohol-related behaviors, including reinforcement and conditioned place preference in rodents (Addolorato et al., 2002; Bechtholt and Cunningham, 2005; Colombo et al., 2000, 2002, 2003a, 2003b; Maccioni et al., 2008; Walker and Koob, 2007). $GABA_B$ receptor agonists also selectively alter binge drinking. Baclofen selectively increased ethanol intake with the DID procedure, whereas the $GABA_A$ receptor agonists muscimol and gaboxadol (4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol) reduced both ethanol and water intake (Moore et al., 2007).

Ethanol-induced alterations in glutamate neurotransmission within drug reward–related structures also are believed to contribute to the motivation to drink ethanol and to other behavioral effects of ethanol (reviewed in Gass and Olive, 2008; Szumlinski et al., 2008). Metabotropic glutamate receptor subtypes mGluR1 and mGluR5 have been studied extensively because they are localized in brain regions associated with drug reinforcement (Lu et al., 1999; Romano et al., 1995; Shigemoto et al., 1993). The mGluR5 antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP) reduces the rewarding effects of ethanol in various animal models of ethanol self-administration and reinstatement (Bäckström et al., 2004; Hodge et al., 2006; Lominac et al., 2006; Olive et al., 2005; Schroeder et al., 2005) and decreased ethanol intake with the DID procedure (Gupta et al., 2008). Additionally, microinjection of MPEP into the nucleus accumbens (NAC) significantly decreased alcohol consumption with the SHAC procedure at doses that had no effect on water consumption (Cozzoli et al., 2009).

The purpose of the present studies was to pharmacologically validate the SHAC procedure as a model of binge drinking by examining the effects of systemic drug injections of naltrexone, baclofen, and MPEP in this model. The overall goal was to determine whether the effects of pharmacological agents on binge ethanol intake were comparable to results achieved with a second model of limited access ethanol intake, namely, operant self-administration of ethanol with the ''sipper'' procedure. The advantages to the ''sipper'' procedure, over the traditional fixed ratio (FR) procedures, are that the appetitive and consummatory phases of ethanol self-administration can be procedurally separated (e.g., Samson et al., 1998, 2000) and that we had documented in C57BL/6 mice that phase separation yielded a heightened appetitive drive to acquire ethanol access and a twofold increase in ethanol consumption versus responding on an FR schedule (Ford et al., 2007a). In addition to determining the relative efficacy of naltrexone, baclofen, and MPEP in these two models of ethanol intake, a secondary goal was to determine the specificity of the drug effects by measuring water intake (SHAC procedure) and sucrose self-administration.

Methods

Animals

Two replicate lines of genetically heterogeneous WSC mice (i.e., WSC-1 and WSC-2) were kindly supplied by Dr. John C. Crabbe and were used in the studies with the SHAC procedure. These animals were bred in the Veterinary Medical Unit at the Veterans Affairs Medical Center (Portland, OR). Based on availability of the animals, studies were conducted on male WSC-1 ($n = 50$), male WSC-2 ($n = 51$), and female WSC-2 ($n = 20$) mice. These animals