ELSEVIER

Alcohol 35 (2005) 119–128

ALCOHOL

Effects of acute administration of ethanol on cerebral glucose utilization in adult alcohol-preferring and alcohol-nonpreferring rats

Wendy N. Strother[a,b,*], William J. McBride[a,b,c], Lawrence Lumeng[c,d], Ting-Kai Li[c,d,1]

[a]*Institute of Psychiatric Research, Indiana University School of Medicine, Indianapolis, IN 46202-4887, USA*
[b]*Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN 46202-4887, USA*
[c]*Department of Biochemistry, Indiana University School of Medicine, Indianapolis, IN 46202-4887, USA*
[d]*Department of Medicine, Indiana University School of Medicine, Indianapolis, IN 46202-4887, USA*

Received 13 August 2004; received in revised form 27 December 2004; accepted 10 February 2005

Abstract

Local cerebral glucose utilization (LCGU) rates, as determined by the [^{14}C]-2-deoxyglucose (2-DG) technique, were examined after acute ethanol administration within selected brain regions of alcohol-preferring (P) and alcohol-nonpreferring (NP) rats. Adult male P and NP rats were injected with saline, 0.25 g/kg, or 1.0 g/kg ethanol, intraperitoneally (ip), 10 min before an intravenous bolus of [^{14}C]2-DG (125 μCi/kg). Timed arterial blood samples were collected over 45 min and assayed for plasma glucose, ethanol, and [^{14}C]2-DG levels. Image densities were determined using quantitative autoradiography and LCGU values calculated. Data were collected from several key limbic, basal ganglionic, cortical, and subcortical structures. Low-dose ethanol (0.25 g/kg) significantly decreased LCGU rates in several brain regions including the medial prefrontal cortex, olfactory tubercles, and the CA1 subregion of the hippocampus of P rats. Low-dose ethanol had no significant effects on LCGU rates in the NP rats. Moderate-dose ethanol (1.0 g/kg) also significantly lowered LCGU rates in many brain regions of P rats, including key limbic structures, such as the medial prefrontal cortex, olfactory tubercles, ventral tegmental area, basolateral nucleus of the amygdala, lateral septum, and ventral pallidum. Moderate-dose ethanol also significantly lowered LCGU rates in the medial prefrontal cortex as well as in the habenula of NP rats. All other regions were unaffected in the NP rats. These findings support the suggestion that certain central nervous system regions of P rats may be more sensitive than those of NP rats to the effects of low to intermediate doses of ethanol.

Keywords: Local cerebral glucose utilization; Alcohol-preferring rats; Ethanol effects; Alcohol-nonpreferring rats

1. Introduction

Quantitative modern brain mapping methodologies, such as the [^{14}C]-2-deoxyglucose (2-DG) technique, provide powerful tools to help define the neuroanatomical structures mediating the effects of ethanol within the brain. Selective breeding for alcohol preference has yielded rat lines, which exhibit divergent ethanol drinking behaviors, including the alcohol-preferring (P) and alcohol-nonpreferring (NP) rat lines. The P rat line satisfies the proposed criteria for an animal model of alcoholism (Cicero, 1979; McMillen, 1997). These selected rat lines exhibit numerous neuroanatomical, neurochemical, and electrophysiological differences in key limbic brain regions (for review, see McBride & Li, 1998; Murphy et al., 2002). The quantification of neuronal activity changes after ethanol administration in selectively bred animals, particularly in brain regions implicated in ethanol reward, offers great potential for understanding the neuroanatomical substrates that underlie the genetic basis of alcoholism.

Several laboratories, including ours, have successfully used the 2-DG technique to examine the effects of acute ethanol on functional neural activity. Previous results, using unrestrained, nonselected rats, tested during the light portion of the light–dark cycle, have demonstrated that local cerebral glucose utilization (LCGU) rates increased in several mesocorticolimbic and nigrostriatal regions after a low dose of ethanol [0.25 g/kg, intraperitoneal (ip)], whereas, in contrast, a moderate dose of ethanol (1.0 g/kg, ip) resulted in significant decreases in LCGU values within sensory and motor areas (Williams-Hemby & Porrino, 1994).

* Corresponding author. Tel.: +1-317-274-2333; fax: +1-317-274-1365.
E-mail address: wstrothe@iupui.edu (W.N. Strother).
[1] Present address: NIAAA, 5635 Fishers Lane, MSC 9304, Bethesda, MD 20892-9304, USA.

0741-8329/05/$ – see front matter
doi: 10.1016/j.alcohol.2005.03.003

Additionally, an intermediate dose of ethanol (0.5 g/kg) resulted in a mixed response between the other two doses tested, with some brain regions exhibiting decreased LCGU rates similar to the 1.0 g/kg ethanol dose and other regions exhibiting higher LCGU rates similar to the 0.25 g/kg ethanol dose (Williams-Hemby & Porrino, 1994). Recently, Learn et al. (2003), from our laboratory using the selectively bred high-alcohol-drinking (HAD) and low-alcohol-drinking (LAD) rat lines (replicate 2), tested during the dark portion of the light–dark cycle, found that a low dose of ethanol (0.25 g/kg, ip) significantly decreased LCGU rates in several brain regions in the LAD-2 rats but not in the HAD-2 rats. This study also found that a moderate dose of ethanol (1.0 g/kg, ip) further reduced LCGU rates in the LAD-2 rats and in many more regions than in the HAD-2 line (Learn et al., 2003). This study hypothesized that the LAD-2 rats were more sensitive to the acute effects of ethanol, or conversely that the HAD-2 rats were less sensitive to the acute effects of low- and moderate-dose ethanol as measured by LCGU. Differences between the findings in the Learn et al. (2003) study and those of the Williams-Hemby and Porrino (1994) study may be due to several factors. First, 2-DG testing occurred at different phases of the light–dark cycle between the two studies. Second, the reported mean blood ethanol concentrations (BEC) were different between the two studies, particularly at the 1.0 g/kg ethanol dose. And finally, strain differences between the rats used in each study may account for some of the disparate findings.

In a previous 2-DG report by Learn et al. (2001), alcohol-naïve HAD and LAD rats did not differ in their basal LCGU rates in any region examined. This is in contrast to basal LCGU values obtained for alcohol-naïve P and NP rats that showed significant differences, with P rats displaying higher innate basal LCGU rates in numerous regions, including several limbic regions (Smith et al., 2001a). These differences in basal LCGU rates between the two pairs of selectively bred rat lines indicate that selective breeding for a high alcohol drinking trait is not necessarily associated with altered basal central nervous system (CNS) functional activity as revealed by the 2-DG method. This difference between the line pairs is one of several different behavioral and neurochemical–pharmacological characteristics that are demonstrated between the P and NP lines, but are not found between the HAD and LAD lines (for review, see McBride & Li, 1998; Murphy et al., 2002). It should be noted again here that only the P line of rats has been found to fulfill all of the proposed criteria of an animal model of alcoholism (Cicero, 1979; McMillen, 1997), whereas the HAD line of rats has not been fully characterized in terms of the animal model criteria (reviewed in Murphy et al., 2002).

The ability to compare animal imaging work with human clinical studies is one of the advantages of the 2-DG technique. Clinical studies using 2-deoxy-2-[^{18}F]-fluoro-D-glucose or ^{11}C-glucose, analyzed by positron emission tomography, and human beings with and without histories of alcohol use and abuse have been done to study the effects of acute ethanol on brain glucose metabolism. Acute administration of a moderate dose of ethanol (0.8–1.0 g/kg) in normal human beings has been shown to significantly decrease cerebral metabolic rates in numerous cortical and subcortical brain regions (Volkow et al., 1990; Wang et al., 2000; Wik et al., 1988). In previously alcohol-dependent individuals, acute moderate dose ethanol administration resulted in greater metabolic decreases than in normal control subjects (Wik et al., 1988). Additionally, acute ethanol administration resulted in greater metabolic decreases in alcohol-dependent individuals with a positive family history for alcoholism than in control subjects with a negative family history (Volkow et al., 1990). These results support the suggestion that individuals at a greater risk for the development of alcohol abuse and/or dependence are more sensitive to the effects of acute ethanol.

This study was undertaken to determine the effects of low and moderate doses of ethanol on LCGU rates in the selectively bred alcohol-naïve P and NP rats. The hypothesis to be tested is that rats bred for high alcohol drinking preference will be more sensitive to the effects of acute ethanol administration than their nonpreferring counterparts.

2. Methods

2.1. Animals

Adult, male, ethanol-naïve P and NP rats were randomly assigned to one of three dose groups: saline, 0.25 g/kg ethanol, or 1.0 g/kg ethanol ($N = 6$–7 rats per dose group per line). Rats weighed approximately 300–375 g at the time of [^{14}C]2-DG injection. The P and NP rats had been selectively bred for over 45 generations at the initiation of this study. All rats were individually housed in plastic tubs on a reversed 12:12 light cycle (lights off at 0900 h) with food and water available ad libitum. One week before catheterization surgery, animals were habituated daily to test cages in a separate room maintained on the same 12:12 light schedule. Test cages were made of clear Plexiglas ($22 \times 45 \times 39$ cm) and were equipped with water bottles. Animals were moved to the test cages before lights out and kept for a period of 4 h with ad-lib access to water only. Food was removed during this period to control for the effects of differential feeding upon blood glucose levels. Postsurgery, and for an additional 2 days, animals were returned to the test cages for the 4-h acclimation period. The animals used in these experiments were maintained in facilities fully accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care. All experimental protocols were approved by the Institutional Animal Care and Use Committee of the Indiana University School of Medicine and are in accordance with the guidelines of the Institutional Care and Use Committee of the National Institute on Drug Abuse, National Institutes of Health, and the *Guide for the Care and Use of Laboratory Animals*