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Acute alcohol intoxication decreases glucose metabolism but increases acetate uptake in the human brain

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ABSTRACT

Alcohol intoxication results in marked reductions in brain glucose metabolism, which we hypothesized reflect not just its GABAergic enhancing effects but also the metabolism of acetate as an alternative brain energy source. To test this hypothesis we separately assessed the effects of alcohol intoxication on brain glucose and acetate metabolism using Positron Emission Tomography (PET). We found that alcohol intoxication significantly decreased whole brain glucose metabolism (measured with FDG) with the largest decrements in cerebellum and occipital cortex and the smallest in the thalamus. In contrast, alcohol intoxication caused a significant increase in [1-^{11}C]acetate brain uptake (measured as standard uptake value, SUV), with the largest increases occurring in the cerebellum and the smallest in the thalamus. In heavy alcohol drinkers [1-^{11}C]acetate brain uptake during alcohol challenge tended to be higher than in occasional drinkers ($p<0.06$) and the increases in [1-^{11}C]acetate uptake in cerebellum with alcohol were positively associated with the reported amount of alcohol consumed ($r=0.66$, $p<0.01$). Our findings corroborate a reduction of brain glucose metabolism during intoxication and document an increase in brain acetate uptake. The opposite changes observed between regional brain metabolic decrements and regional increases in [1-^{11}C]acetate uptake support the hypothesis that during alcohol intoxication the brain may rely on acetate as an alternative brain energy source and provides preliminary evidence that heavy alcohol exposures may facilitate the use of acetate as an energy substrate. These findings raise the question of the potential therapeutic benefits that increasing plasma acetate concentration (i.e. ketogenic diets) may have in alcoholics undergoing alcohol detoxification.

Introduction

Low to moderate doses of alcohol (0.25–0.75 g/kg) result in significant reductions in glucose metabolism in the human brain (range 10–30%) that are not associated with the behavioral effects seen with intoxication (Volkow et al., 1990). Moreover, in alcoholics we showed much greater reduction in regional brain glucose metabolism during intoxication than in healthy controls despite the fact that the alcoholics in contrast to the controls showed no evidence of behavioral intoxication (Volkow et al., 1990). This led us to postulate that brain glucose metabolic decrements could reflect utilization of acetate as an alternative source of energy for the brain during alcohol intoxication (Volkow et al., 2006b). Acetate is an accepted marker of glial metabolism (Wyss et al., 2011) and it is readily taken up by the brain where it is predominantly metabolized by glia (Cruz et al., 2005). However, plasma acetate concentration is constitutively low (about 0.2 to 0.3 mM), whereas that of glucose is typically high (about 5 mM); so under normal physiological conditions acetate brain metabolism is one order of magnitude lower than glucose metabolism (Dienel et al., 2001; Kammula and Fong, 1973). In contrast, during alcohol intoxication the concentration of acetate in blood increases significantly (around 0.5–1 mM) (Korri et al., 1985; Orrego et al., 1988) to levels that could support 10–20% of the total brain metabolic rate (Waniewski and Martin, 1998). In this study we test the hypothesis that during alcohol intoxication there is an increase in acetate metabolism in the human brain using [1-^{11}C]acetate and Positron Emission Tomography (PET).

[1-^{11}C]Acetate has been proposed as a PET ligand to assess glial metabolism in brain (Lanz et al., 2012; Wyss et al., 2009). Indeed stimulation of the rodent and the human brain increases the brain uptake of [1-^{11}C] acetate (Wyss et al., 2009), consistent with autoradiographic studies showing increases in acetate metabolism in activated brain regions (Cruz et al., 2005; Dienel et al., 2007). The kinetics of [1-^{11}C] acetate in brain are confounded by the loss of ^{11}C as [^{11}C]CO2 when [1-^{11}C]acetate is oxidized through the tricarboxylic (TCA) cycle. Despite this confound,

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the initial uptake of [1-^{11}C]acetate (peaks ~20 min) appears to reflect acetate, such that higher uptake is associated with higher acetate metabolism (Wyss et al., 2009).

Here we used PET and [1-^{11}C]acetate to measure acetate metabolism after placebo and during alcohol intoxication both in occasional social drinkers (OSD) and in heavy drinkers (HD). As an indicator of acetate brain metabolism we quantified the standardized uptake values (SUV) of [1-^{11}C]acetate. In parallel we conducted a second study to assess the effects of acute alcohol intoxication on brain glucose metabolism using PET and 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}FDG) in occasional OSD to identify the brain regions that were most sensitive to alcohol's metabolic effects. We used a 0.75 g/kg alcohol dose, which is roughly equivalent to three drinks for a 50 kg person and are within the doses consumed socially (Stinson et al., 1998). We hypothesized that acetate metabolism (as measured by SUV of [1-^{11}C]acetate) in brain would be higher during acute alcohol intoxication and that the larger increases would occur in regions that showed the largest decreases in glucose metabolism. We also hypothesized that acetate metabolism would be associated with alcohol exposures and greater for HD than for OSD.

Material and methods

Subjects

The study on the effects of alcohol on brain glucose metabolism was done in 15 healthy OSD (12 males, 32 ± 7 years of age, BMI 25 ± 3, Education 14 ± 2 years) who were recruited to serve as comparison to the [1-^{11}C]acetate studies. The study on the effects of alcohol intoxication on acetate metabolism was done in 16 healthy male OSD (37 ± 7 years old, BMI 26 ± 4, Education 13 ± 2 years; 4 tobacco smokers) and 15 healthy male HD (37 ± 9 years old, BMI 28 4, Education 12 ± 1 years; 5 tobacco smokers). Inclusion criteria for all the subjects were: ability to understand and give informed consent and being 18–50 years of age. Inclusion criteria for OSD were having a prior experience with alcohol and regular use of no more than 1 drink per day. Inclusion criteria for HD were: history of 5+ drinks per day at least on 2 or more occasions per week. Exclusion criteria for subjects in both studies were: 1) urine positive for psychotropic drugs; 2) present or past history of dependence on alcohol or other drugs of abuse (except nicotine and allowed diagnosis of alcohol abuse though not dependence for HD); 3) present or past history of neurological or psychiatric disorder; 4) use of psychoactive medications in the past month (i.e., opiate analgesics, stimulants, sedatives); 5) use of prescription (non-psychiatric) medication(s), i.e., antihistamines; 6) medical conditions that may alter cerebral function; 7) cardiovascular and metabolic diseases and 8) history of head trauma with loss of consciousness of more than 30 min. We excluded subjects who had never been intoxicated since we did not want the experimental procedure to be their first exposure to alcohol intoxication. Subjects that met DSM IV diagnosis of alcohol dependence were excluded. Subjects were instructed to discontinue any over the counter medication two weeks prior to the PET scan, and were asked to abstain from alcohol for 48 h prior to the placebo and alcohol PET scanning session. Self-reports were used to determine if they had consumed any alcohol during the two days that preceded the study. Signed informed consents were obtained from the subjects prior to participation as approved by the Committee on Research in Human Subjects at Stony Brook University.

Alcohol and placebo administration

Subjects drank the alcohol (0.75 g/kg mixed in a caffeine-free diet soda) or the placebo (caffeine free diet soda) within a 20-minute period under blind conditions. For this purpose we used a specialized drinking container with an alcohol-containing lid that provided the smell of alcohol and delivered the same volume of liquid for both conditions. Participants were injected with the radiotracer 40 min after initiating alcohol consumption (20 min after completion of drinking). This timing was selected to correspond to the ascending limb of the blood alcohol curves and the time when peak concentration of alcohol is reached in the human brain after its oral administration (Hetherington et al., 1999).

Behavioral evaluation and measures of alcohol in plasma

Before placebo or alcohol, and at 10, 15, 30 and 85 min after placebo or alcohol administration, subjects were asked to evaluate on an analog scale (rated 1–10) their subjective sense of intoxication, high, sleepiness, and dizzy. At the end of the study subjects were asked to rate the effects of the drug for "liking" and "pleasant" (rated 1–10).

Blood alcohol concentrations were measured before and 20, 40, 60, 80, 90, and 120 min after the initiation of alcohol administration using the enzymatic assay described by Lloyd et al. (1978).

PET scans

PET scans were conducted with a whole-body, high-resolution positron emission tomograph (Siemens/CTI ECAT HR+, with 4.6 × 4.6 × 4.2 mm NEMA (National Electrical Manufacturers Association) collected on a 3D mode. Procedures for positioning of the subjects in the scanner, for transmission and emission scans for ^{18}FDG have been published (Wang et al., 1993) and for [1-^{11}C]acetate we used the same procedures that we have used for [^{11}C]raclopride scans (Volkow et al., 1993). For arterial sampling we used an automated device (Ole Dick, Denmark) that sampled every 2.5 s for the first 2 min and then every minute from 2 to 5 min and then at 10, 15, 20, 30, 45, and 60 min.

For the ^{18}FDG scans (study to measure brain glucose metabolism), subjects were injected with 4–6 mCi of ^{18}FDG and one 20-minute emission scan was started 35 min after injections. Subjects were scanned over a two day period tested with placebo on one day and with alcohol on the other with the order of the scans randomly assigned. Images were reconstructed using a filtered back projection (Hann filter with a 4.9 mm Kernel FWHM). The ^{18}FDG scans were transformed into metabolic images as previously described (Volkow et al., 1990) and metabolic rates were computed using an extension of Sokoloff's model (Phelps et al., 1979). In addition we also obtained regional SUV for FDG since that was the model we used to quantify the acetate measures.

For the [1-^{11}C]acetate scans, subjects were injected with 8–10 mCi of [1-^{11}C]acetate and dynamic emission scans were obtained immediately after radiotracer injection for a total of 60 min using the following time frames: 1 × 10 s; 12 × 5 s; 1 × 20 s; 1 × 30 s; 8 × 1 min; 4 × 5 min; 4 × 7.5 min. Each subject underwent two [1-^{11}C]acetate scans 2 h apart from each other; the first scan after placebo and the second after alcohol administration. To estimate brain acetate metabolism we used the SUV on the averaged images obtained between 3 and 20 min after injection. This initial uptake of acetate in brain has been shown to correspond with the initial metabolism of acetate through the TCA cycle (Wyss et al., 2009).

For all scans subjects were tested while lying in the supine position in a dimly lit room with noise kept to a minimum and the only intervention was the periodic assessment for self-report of drug effects. To ensure that subjects did not fall asleep they were monitored throughout the procedure and were asked to keep their eyes open.

Analysis

Regions of interest (ROI) were selected using a neuroanatomically template of 423 non-overlapping regions based on the Talairach and Tournoux's (1988) atlas. Values for the cortical, subcortical and cerebellar regions were computed using the weighted average from the different slices where the regions were obtained and grouped into 7 composite regions, which included frontal, parietal, temporal, occipital cortices, striatum, cerebellum and whole brain. An estimate of whole-brain metabolism was obtained by averaging the values from all of the regions of interest. For the ^{18}FDG scans these ROIs were delineated directly in the