Preliminary Evidence of Increased Brain Acetate Uptake and Oxidation in Heavy Drinkers Probed by $^{13}$C-MRS

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Introduction
Ethanol is a widely used and abused drug that can cause changes in brain metabolism and function. Understanding brain alcohol metabolism may help to find new approaches to relieve alcohol detoxification and treat alcohol abuse. Alcohol metabolism begins with two steps: first, alcohol is converted to acetaldehyde via alcohol dehydrogenase, and then acetaldehyde is changed to acetate by aldehyde dehydrogenase. Astrocytes consume fuel through oxidation in the Krebs cycle via acetyl-CoA. Drinking alcohol increases blood acetate, and beyond 1-2 drinks the level plateaus at 1-2 mM [1]. The objective of the present study is to test whether heavy alcohol use can affect brain choice of energy sources, thereby providing insight into alcohol addiction and abuse. [2-$^{13}$C]Acetate can be used to track brain metabolism of acetate, using $^{13}$C magnetic resonance spectroscopy [2-5]. Here, we observed the rise of $^{13}$C-labeled glutamine, glutamate, and GABA in the brain during the infusions of [2-$^{13}$C]acetate in heavy and light drinkers.

Materials and methods
Three heavy drinkers who regularly consumed at least 8 drinks per week and four light drinkers who drank only occasionally and less than 2 drinks per week have been recruited for this study. All subjects underwent a telephone interview, physical exam, and blood chemistry and toxicology tests to ensure there was no substance abuse that could affect brain metabolism, besides alcohol. Subjects abstained from alcohol for 48 hours and fasted overnight before the study. In the morning, breath alcohol levels were measured, and two intravenous lines were inserted in the left and right antecubital veins for infusion of $^{13}$C-acetate and periodic blood draws. Subjects were placed supine in a 4T imaging spectrometer (Bruker Instruments). The back of the head lay against a radio-frequency probe consisting of one 8.5 cm diameter circular $^{13}$C surface coil and two quadrature $^1$H coils for $^1$H acquisition and decoupling. Magnetic resonance spectra were acquired using an adiabatic $^{13}$C-$^1$H polarization transfer sequence optimized for detection of glutamine and glutamate in the C4 position, with ISIS localization. The spectroscopic voxel was located in the occipital-parietal lobe, with dimensions of 5×4×4.5 cm$^3$. After acquisition of the baseline $^{13}$C-spectr, [2-$^{13}$C]acetate (350 mM) was infused at rate of 3 mg/min per kg body weight for two hours. $^{13}$C-magnetic resonance spectra were acquired continuously throughout the study. The FIDs after reaching steady state (typically after 45-60 minutes) were added and the spectral data were prepared for analysis using 2Hz Lorentzian/6 Hz Gaussian and Fourier transformation. An LCModel approach was used to fit the spectra from 20 to 43 ppm, deriving the scaling factors for glutamate, glutamine, and GABA. Plasma acetate concentrations and enrichments were measured using $^1$H-$^{13}$C spectroscopy on 500MHz high resolution NMR spectrometer (Bruker Instruments).

Results
The pre-infusion plasma acetate in heavy drinkers was higher (0.18±0.02 mM) than in the light drinkers (0.09±0.02 mM), even though the drinkers had abstained for more than 48 hours and had breath alcohol concentrations of zero on the day of the infusion. Infusion of [2-$^{13}$C]acetate yielded plasma acetate levels that were similar between light and heavy drinkers, ranging from 1.6-2.2 mM in both groups. In spite of the similar plasma acetate levels, the steady-state brain acetate levels also in the brain were higher in the heavy drinkers (Figure 1A). Steady-state GABA C2 and glutamate C4 labeling were greater in heavy drinkers (Figures 1 B and C). Glutamine C4 showed no significant differences between light and heavy drinkers, because one light drinker had a level of glutamine labeling that was unusually high among any healthy controls run in any acetate-labeling studies at Yale. These results suggest that heavy drinking is associated with an enhanced ability to import and oxidize acetate. Systemically available acetate may provide a metabolic reward for drinking.

References

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