

In vivo alcohol uptake kinetics in rat brain

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Introduction

Individual differences in alcohol uptake kinetics may contribute to the development of problem drinking. The animal model of alcohol preferring (P) and non-preferring (NP) Wistar rats offers an opportunity to study alcohol uptake kinetics in vivo under controlled conditions. Here we report the feasibility of monitoring brain ethanol uptake and kinetics in the native P/NP Wistar stock.

Methods

Each of 4 adult Wistar rats (~7 months old, 573 -616g) was scanned in a 2-hour session before and after ethanol infusion. Data were acquired on a clinical 3T GE Signa human MRI scanner equipped with maximum gradients amplitude and slew rate of 40mT/m and 150 T/m/s. An 8-rung birdcage transmit/receive coil was constructed on clear plexiglass tubes, 4.8cm long by 4.4cm (inner diameter). Given the low RF requirement of this coil, the transmitter RF power was attenuated by 15dB, allowing the use of automated scanner software. Animals were placed on a tray, supporting the RF coil and a nose cone for delivery of oxygen (~2 liters/min) plus 1-4% isoflurane anesthesia. After sedation, a flexible catheter was inserted in the intraperitoneal (ip) cavity. Prior to MRS acquisition, T1-weighted multislice whole-body images were acquire before and after injection of 1cc, 1% Gd-DTPA to ensure proper catheter placement. Rectal temperature and oxygen saturation were monitored throughout the experiment. Heat was maintained by warm water bags and a temperature-controlled water-heating blanket tented above the animal.

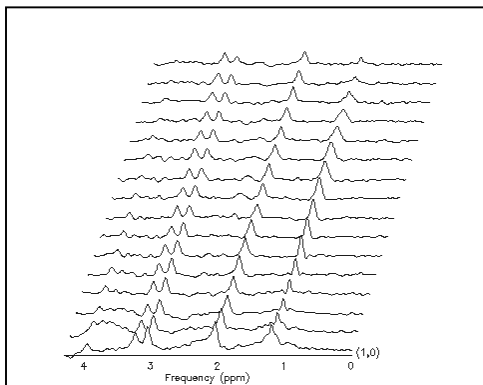


Fig. 1: 16 spectra in one 2D J-resolved acquisition.

Each study was processed using SAGE™ (GE Medical Systems, Milwaukee, WI) and IDL. All data were phase and frequency corrected, using the internal water of each TE frame as its own reference. Pure water subtraction (3) was used to reduce residual water and water sidebands from each suppressed frame. Data were then apodized with a 6 Hz Gaussian filter, zero filled, and Fourier transformed in the chemical shift dimension. Each frame was further referenced to the NAA peak at 2.02ppm, to compensate for small temperature variations during the exams. The spectra for TE=55-185ms were averaged and used for signal estimation. For a given rat, all spectra across all time points were used to make a grand average spectrum. Six peak frequencies were identified (Cr2, Cho, Cr, Glu, NAA, ethanol), each fit individually to a Gaussian using data points within a 0.143 ppm range around the identified frequency. These values served as starting points for a multi-parametric, least squares fit to the grand average spectrum. The solutions for the NAA and ethanol peaks were used as basis functions for a linear, least-squares fit to obtain amplitude estimates for these signals for each time point.

RESULTS AND DISCUSSION

Fig. 2 shows the time course of the ethanol signal amplitude, normalized to NAA, for each rat. Three rats were sampled with 4-min acquisitions; one rat was sampled at higher rate of 2-min intervals, with a corresponding sacrifice of SNR for each observation. All rats achieved maximum MRS visible ethanol concentration within 4-8 min of injection, followed by a gradual decline over 1 hr (rate ~40%/hour). Assuming a rat brain NAA concentration of 10 mM, two animals achieved approximately 90 mg/dl and two 70 mg/dl. The expected maximum at this dose with full absorption, instantaneous uptake, no metabolism, and full MRS visibility would be 100 mg/dl. The expected brain concentration of alcohol after ip injection is governed primarily by absorption in first 5-10 minutes, followed by a combination of absorption, metabolism and elimination, and after 30 minutes, primarily elimination and water/fat equilibration. The time course data obtained suggest the ability to quantify the stages of alcohol kinetics in vivo.

CONCLUSION

The data demonstrate the feasibility of measuring in vivo brain alcohol kinetics in small animals. Concentrations measured suggest sensitivity to the majority of the injected dose. Differences among animals suggest individual variability in uptake, distribution or metabolism of alcohol.

SUPPORT: AA13521, AA05965

REFERENCES 1. Dreher W et al, MRM, 34, 331, 1995; 2. Hurd R et al, MRM, 40, 343, 1998; 3. Hurd R et al, JMR, 93, 666, 1991.

A series of single-voxel, 2D J-resolved spectra (1,2) were acquired before and after bolus injection of 1 g/kg ethanol ip in approximately 5cc volume. A 3-plane localizer scan (TE = 2.1ms, TR = 54ms, FOV = 80mm, 256x128 pixels, 5mm thick, 10 slices/plane) was used for prescription of coronal fast spin-echo (FSE) images (TE₁ = 18ms, TE₂ = 90ms, TR = 2.2 s, echo-train length = 8, FOV=40mm, 256 x 256 pixels, 2.5mm thick, 12 slices). The FSE image that fit the largest rectangular spectroscopic brain voxel was the center slice for a graphical prescription of a PRESS volume, a rectangular solid of ~5 mm thickness, and in-plane dimensions of ~10mm (L/R) and 5mm (S/I), for a voxel volume ~0.25cc.

Three very selective saturation (VSS) pulses were prescribed around the voxel to minimize out-of-voxel signal contamination. Two saturation bands were placed in a V-like configuration at the bottom of the volume (viewed in a coronal section); one was positioned horizontally at the top of the voxel. Following manual shimming with linear terms, 3 J-resolved spectra were acquired, each 4:40 min long (TE₁ = 35ms, ΔTE = 10ms, 16 t1 steps, TR = 2s, Fig. 1). In two of three pre-injection spectra, the water resonance was suppressed with CHES; one baseline spectrum was acquired in without water suppression for use in post-processing quantitation.

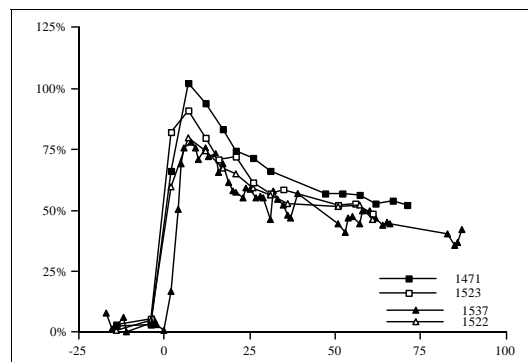


Fig. 2. Ethanol as % of NAA, as a function of time (min).