First direct ^{13}C detection of glucose metabolism in the mouse brain at 9.4T using a ^{13}C-cryo-coil

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Introduction

MRS studies typically require a high signal-to-noise ratio (SNR), especially for ^{13}C spectroscopy where the low natural abundance of ^{13}C (1.1%) is a problem. Additionally, the relative low frequency of ^{13}C increases this limitation for ^{13}C in comparison with ^{1}H MRS. The approach of dynamic ^{13}C MRS in mice is even more challenging due to the small brain size. We present in vivo data from one of the first ^{13}C-cryo-coils for mouse brain imaging using an ISISDEPT sequence and [1-^{13}C]-enriched glucose on a 9.4T scanner (Bruker, Ettlingen, Germany) obtained from a single animal.

Fig. 1: Image of the ^{13}C-cryo-coil; anatomically shaped and additional ^{1}H saddle coil.

Methods

The ^{13}C-cryo-coil (Bruker, Ettlingen, Germany) consists of an anatomically-shaped ^{13}C element and a ^{1}H saddle coil for decoupling. Due to its geometry only small animals like mice can be scanned (Fig. 1). The ^{13}C element as well as the narrow band pre-amplifier are encapsulated in an insulated vacuum chamber and are helium cooled to lower their operating temperature down to approximately 30K. To avoid injuries the contact area of the coil is heated.

The freely breathing mouse was anesthetized with isoflurane (1 - 1.5%) and the 99%-enriched [1-^{13}C] glucose (1.075M solution) was administered through the tail vein. We used a similar infusion protocol as in [1] (bolus of 130mg/kg in 20s followed by continuous infusion of 0.97g/h/kg over 3.75h), which keeps the plasma glucose concentration above the euglycemic level.

To measure the turnover curves of metabolites in mouse brain, we combined the localization sequence ISIS with distortionless enhanced polarization transfer (DEPT). Based on ^{1}H spin echo images the voxel (5.5 x 3.5 x 7 mm³ = 134.75 µl) was placed within the mouse brain (Fig 2a). After localized shimming with fastmap (cube size 6 x 6 x 6 mm³) a full-width at half-maximum of 27Hz for the water signal was obtained. The ^{1}H ISIS consisted of adiabatic inversion pulses with a bandwidth (BW) of 7.3ppm and a 90° rectangular pulse (BW_{90}=15.9ppm), which represents also the first pulse of the DEPT sequence. All other pulses used in the polarization transfer sequence were sinc-shaped pulses except for the last ^{1}H rectangular pulse (theta-pulse). In detail, ^{13}C: inversion BW_{180}=77ppm, excitation BW_{90}=123.5ppm; ^{1}H: inversion BW_{180}=10ppm. The last ^{1}H pulse (BW_{theta}=31.9ppm) had a flip angle of 45° to detect signals from CH, CH_2 and CH_3 groups and an interpulse delay of 3.45ms was chosen to optimize for a coupling constant J_{CH} of 145Hz [1]. Decoupled (MLEV16, 500µs elements, center frequency at 2.6ppm) spectra were acquired with 256 averages and TR = 1.7s resulting in a time resolution of 7.5min per spectrum (including one dummy cycle) over 225 minutes.

Results

The spectrum of the summed last three measurements can be seen in figure 2a. Despite the small voxel size and the relatively short measurement time of 22.5 minutes the spectrum shows an excellent SNR of 22.7 for the GluC4 peak (noise calculated by the last 200 points of the FID). Figure 2b and 3 show the time course and turnover curves of different metabolites, respectively (please note that there are spikes near 54ppm, which influenced the quantitation of GlnC2, NAAC2 and AspC2). All spectra were fitted using AMARES (jMRUI software v4.0).

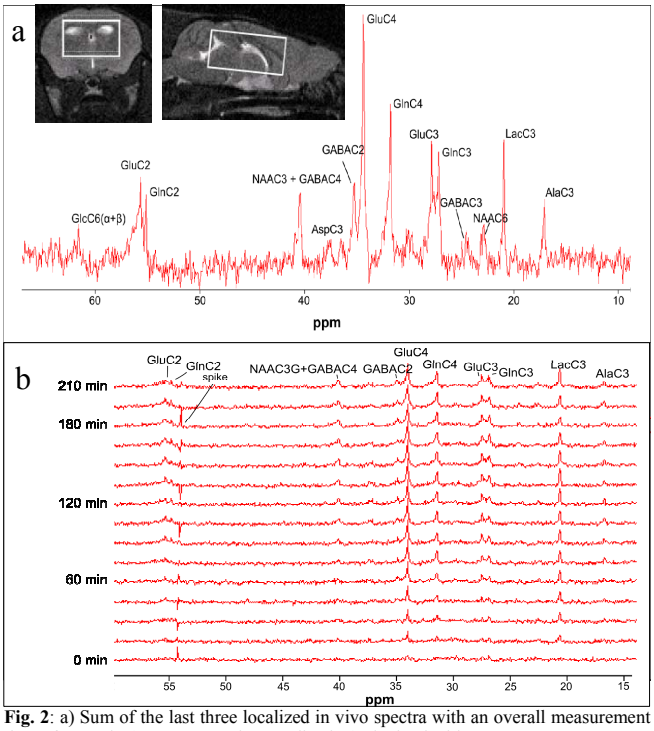

Fig. 2: a) Sum of the last three localized in vivo spectra with an overall measurement time of 22.5min (10Hz Lorentzian apodization) obtained with an ISISDEPT sequence. On the left: Position of the 134.75µl voxel in the mouse brain. b) Time course of ^{13}C label incorporation. Each spectrum represents the sum of two measurements resulting in 15min spectra.

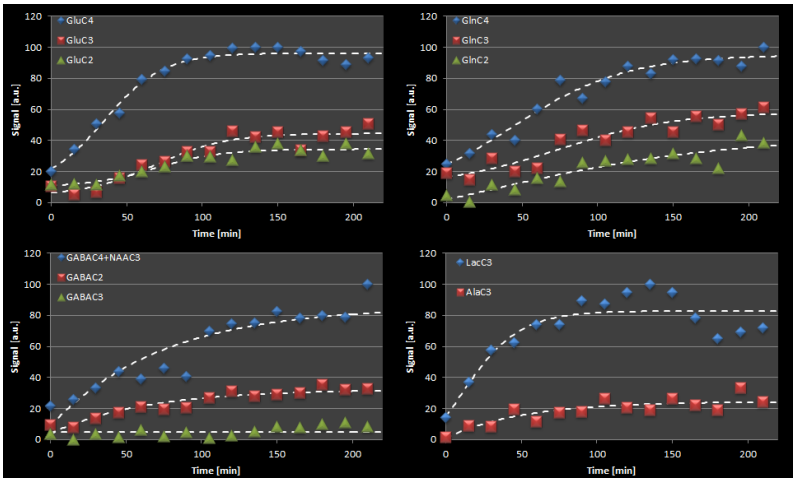

Fig. 3: Turnover curves of metabolites in mouse brain with a 15min time resolution of glutamate, glutamine, GABA (C4, C3, C2 position), alanine and lactate (C3 position). Dashed lines represent Boltzmann sigmoidal fits. Note that lactate begins to decrease at the end of the measurement time implicating a potentially instable plasma glucose concentration and resulting in a poor fit.

Discussion

The results show that the use of a cryo-coil makes ^{13}C MRS feasible for in vivo mouse brain experiments and offers the possibility to investigate disorders which are related to a changed brain metabolism in mouse models. Phantom measurements showed that an SNR increase of 5.3 can be achieved compared to geometrical similar room temperature coils [2]. Further investigations will be made to decide whether a higher time resolution of metabolites turnover curves or a smaller voxel size, possibly down to the order of mouse brain areas, will lead to reliable metabolic flux rates.

References:

1. Nabuurs C., Klomp D., Veltien A., et al. (2008). *Localized sensitivity enhanced in vivo ^{13}C MRS to detect glucose metabolism in the mouse brain.* Magnetic Resonance in Medicine **59**, 626 - 630.

2. Sack M., Wetterling F., Ende G., et al. (2011). *SNR improvement of a ^{13}C-cryo-coil in comparison with room-temperature coils*. In: Proceedings of the 19th Scientific Meeting of ISMRM, #2257