In Vivo Application of 3D Deuterium (^{2}H) CSI for Quantitative Imaging of Cerebral Glucose Metabolism at Ultrahigh Field

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Introduction

Cerebral glucose metabolism is of importance for brain function and maintaining electrophysiological activity including neuronal firing and signaling. Simultaneous assessment of cerebral glucose consumption rate (CMR_{glc}) and associated major metabolic fluxes, such as TCA cycle (V_{TCA}) and oxygen consumption rates, is crucial to understanding neuroenergetics under physiological and pathological conditions. Recently, we developed a novel *in vivo* Deuterium (^{2}H) MR (DMR) approach for noninvasively assessing glucose metabolisms in global rat brain with superior sensitivity at ultrahigh field (1). As for the CMR_{glc} measurement, this new approach has the advantage of eliminating the usage of radioactive tracer commonly employed by traditional ^{18}FDG-PET imaging. Also when comparing with the classic ^{13}C MRS method for V_{TCA} quantification (2), the much shorter T_1 relaxation time of deuterated glucose (~0.05 s) allows more signal averaging, thus, provides a substantial sensitivity gain for DMR detection, which could make the *in vivo* application of localized DMR possible. Therefore, this study is aiming to evaluate the feasibility and reliability of localized DMR for imaging cerebral glucose metabolism by using dynamic 3D-chemical shift imaging (CSI) technique in rat brains at 16.4 T. Regional metabolic rates under two conditions, i.e., deep anesthesia with 2% isoflurane and constant morphine infusion, were compared to examine the sensitivity of DMR for detecting metabolic changes in response to altered brain states.

Method

Four male Sprague Dawley rats (BW=347±43 g) were anesthetized by 2% isoflurane, and their femoral arteries and veins were catheterized for blood sampling, physiological monitoring and deuterated glucose and/or morphine infusion. All MR experiments were conducted at 16.4 T/26 cm scanner (Varian/VNMRJ) using a passively decoupled ^{1}H/^{2}H surface coil. Dynamic ^{2}H CSI data of rat brains were acquired with 52 µL nominal resolution and 69 s temporal resolution for about 103 min to monitor the DMR signal changes before, during and after the D-glucose infusion. For each rat, 11.5 min baseline spectra were acquired followed by 2 min infusion of 400 mg D-Glucose-6,6-d_2 (Sigma-Aldrich) dissolved in 2.5 mL saline. One of the four rats was switched from isoflurane inhalation to constant morphine infusion (25mg/kg/hr) before the onset of dynamic 3D DMR acquisitions. A 20 Hz linebroadening was used before Fourier transformation to enhance spectral SNR. All resonance signals (deuterated water, glucose and glutamate/glutamine (Glx)) were fitted using a MATLAB-based program (1). The concentrations of metabolites were quantified as previously described (1). A short repetition time (TR=45 ms) was used in this study, thus, saturation effects on metabolites were corrected for quantification.

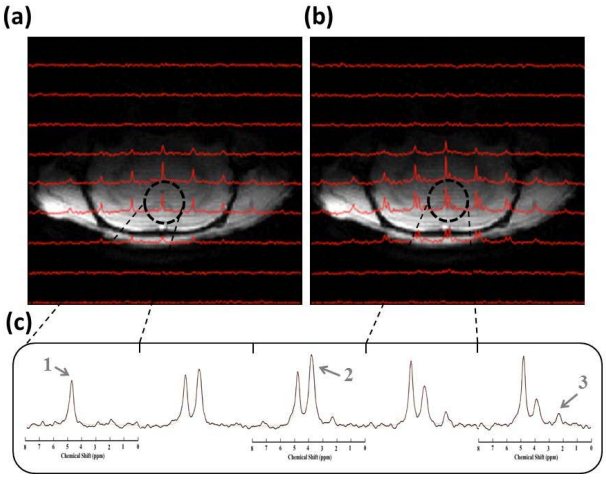

Figure 1. *In vivo* DMR spectra of a rat brain under isoflurane condition. Representative CSI slice extracted from the 3D data was overlaid on corresponding anatomical image for 5 min before **(a)** and 70 min after **(b)** glucose infusion. Spectra from circled voxels were enlarged and displayed in **(c)**. From left to right: 5 min before, 6-, 29-, 70- and 90-min after glucose infusion. Grey and red traces in **(c)** were original and fitted DMR spectra, respectively. Peak assignment in ppm: (1) Water (4.8), (2) Glucose (3.8) and (3) Glx (2.4).

Result

Figure 1 shows excellent *in vivo* spectral quality and fully resolved resonances of interest in the acquired DMR CSI data. Following the brief infusion of deuterated glucose, at least three well-resolved resonances (deuterated water, glucose and Glx) were detected from the individual voxel (Fig. 1a&b). Thus, their dynamic changes in certain location of the rat brain could be monitored. As shown in Fig. 2, when compared with the isoflurane condition, accelerated glucose consumption and labeled Glx accumulation were simultaneously observed in the central voxel of the morphine-infused brain. Delayed Glx appearance and onset of glucose decay were found in the isoflurane-anesthetized brain, which was consistent with the previous observations (1). All of these findings indicated a stimulated glucose metabolism with increased CMR_{glc} and V_{TCA} under morphine treatment, which also reflected in the increasing heart rate (423 vs. 335 bpm with isoflurane) and mean blood pressure (128 vs. 103 mmHg) of the animal.

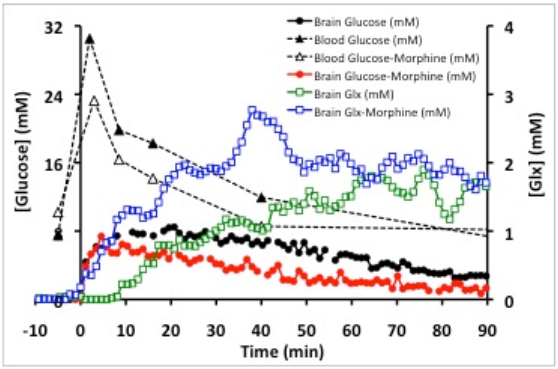

Figure 2. Time courses of blood glucose level and dynamics of labeled glucose and Glx concentrations from the central voxel (as indicated by circles in Fig.1) of two rat brains under isoflurane versus morphine conditions. Glucose was infused at 0 min.

Discussion & Conclusion

The results of this work demonstrated excellent spectral quality, sensitivity and temporal resolution of the *in vivo* dynamic 3D DMR imaging technique at ultrahigh field. When combined with metabolic modeling, regional glucose consumption rate and TCA cycle flux can be assessed simultaneously, which would provide an opportunity to map the spatial distribution of glucose metabolism in animal and human brains under normal and diseased states.

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References

(1) Lu, M. *et al.* (2014) *ISMRM*, 0537. (2) Gruetter, R. *et al.* (1994) *J. Neurochem.* 63, 1377-1385.