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Measurement of regional cerebral glucose uptake by magnetic resonance spin-lock imaging☆

Zhongliang Zu [a,b,*], John Spear [a,c], Hua Li [a,c], Junzhong Xu [a,b], John C. Gore [a,b,c,d,e]

[a] Vanderbilt University Institute of Imaging Science, Nashville, TN
[b] Department of Radiology and Radiological Sciences, Vanderbilt University, Nashville, TN
[c] Deparment of Physics and Astronomy, Vanderbilt University, Nashville, TN
[d] Department of Biomedical Engineering, Vanderbilt University, Nashville, TN
[e] Department of Molecular Physiology and Biophysics, Vanderbilt University, Nashville, TN

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ABSTRACT

Purpose: The regional uptake of glucose in rat brain *in vivo* was measured at high resolution using spin-lock magnetic resonance imaging after infusion of the glucose analogue 2-deoxy-D-glucose (2DG). Previous studies of glucose metabolism have used ^{13}C-labeled 2DG and NMR spectroscopy, ^{18}F-labeled fluorodeoxyglucose (FDG) and PET, or chemical exchange saturation transfer (CEST) MRI, all of which have practical limitations. Our goal was to explore the ability of spin-lock sequences to detect specific chemically-exchanging species *in vivo* and to compare the effects of 2DG in brain tissue on CEST images.
Methods: Numerical simulations of $R_{1\rho}$ and CEST contrasts for a variety of sample parameters were performed to evaluate the potential specificity of each method for detecting the exchange contributions of 2DG. Experimental measurements were made in tissue phantoms and in rat brain *in vivo* which demonstrated the ability of spin-lock sequences for detecting 2DG.
Results: $R_{1\rho}$ contrast acquired with appropriate spin-lock sequences can isolate the contribution of exchanging protons in 2DG *in vivo* and appears to have better sensitivity and more specificity to 2DG–water exchange effects than CEST.
Conclusion: Spin-lock imaging provides a novel approach to the detection and measurement of glucose uptake in brain *in vivo*.

1. Introduction

2-Deoxy-D-glucose (2DG) is a glucose analogue which, when administered *in vivo*, can be taken up by cells through glucose transporters. Once intracellular, it undergoes phosphorylation catalyzed by hexokinase but, unlike glucose itself, does not undergo further metabolism but is trapped and accumulates within cells [1]. 2DG has previously been used *ex vivo* to evaluate cellular function and metabolic activity, and non-invasive methods of measurement of 2DG or similar molecules would be valuable for studies of glucose uptake in a variety of applications including assessments of tumors and other pathologies.

^{13}C-labeled 2DG can be detected by nuclear magnetic resonance (NMR) spectroscopy [2], but the relatively low sensitivity for detection limits its applications. ^{18}F-labeled fluorodeoxyglucose (FDG) has been used extensively to image glucose uptake by positron emission tomography (PET) [3]. However, the radioactivity involved limits its repeated use, and PET imaging requires coordination with the production and delivery of short-lived isotopes. More recently, chemical exchange saturation transfer (CEST) has been used to image deoxyglucose and glucose [4,5]. Based on chemical exchange between the hydroxyl groups of glucose and water protons, CEST detects glucose or its analogs indirectly by measuring changes in the more abundant water signal after selective radiofrequency irradiation [6,7]. However, CEST contrast relies on being able to isolate the small chemical shifts of the exchanging hydroxyls, and in practice CEST signals depend on several other tissue and experimental parameters including water relaxation rates and magnetization transfer with “solid” components in tissues, which also vary.

At high field, the spin–lattice relaxation rate in the rotating frame, $R_{1\rho}$, may be dominated by the contribution of chemical exchange between labile and water protons [8–12] and is readily quantified using spin-lock imaging sequences. Moreover, the variation of $R_{1\rho}$ with the locking field in spin-lock sequences (the $R_{1\rho}$ dispersion)

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* Corresponding author at: Vanderbilt University Institute of Imaging Science, 1161 21st Ave. S, Medical Center North, AAA-3112, Nashville, TN 37232-2310. Tel.: + 615 875 9815; fax: +1 615 322 0734.
E-mail address: zhongliang.zu@vanderbilt.edu (Z. Zu).

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reflects the exchange rate of the exchanging species, and can be exploited to emphasize protons with a specific exchange rate and chemical shift [8,11]. Potentially therefore appropriate spin-lock imaging acquisitions may provide an alternative approach to detect and measure the chemical exchange between specific solutes and water protons. Here we evaluate the ability of spin-lock sequences to detect and measure 2DG *in vivo*, and compare the results with CEST imaging.

2. Materials and methods

2.1. Spin-lock sequence and $R_{1\rho}$ contrast

Fig. 1 shows a typical spin-lock preparation cluster designed to compensate for field inhomogeneities [13] consisting of an initial 90° flip, a pair of on-resonance locking pulses applied along the direction of the transverse magnetization with selectable amplitude and durations and separated by a 180° refocusing pulse, followed by a −90° flip back to the z direction. This preparation may be applied in front of imaging acquisitions such as echo-planar or fast spin echo sequences. $R_{1\rho}$ values are calculated based on fitting data acquired after spin-lock preparation clusters with different spin-locking times to a single exponential decay. The $R_{1\rho}$ values are dependent on the spin-locking amplitude. When the spin-locking power is low, chemical exchange may play a dominant role in $R_{1\rho}$ relaxation. However, when the spin-locking power is high, chemical exchange effects are decreased to a degree that depends on the exchange rate relative to the rate of nutation of the magnetization about the locking field. Previously we have shown how judicious selection of locking fields and combinations of data acquired with different powers can produce imaging contrast that emphasizes specific exchanging species [10]. Here we define the $R_{1\rho}$ contrast simply as

$$R_{1\rho}\text{contrast} = \frac{S(\text{high}) - S(\text{low})}{S_0} \quad (1)$$

Here, S(high) and S(low) are the signals acquired with high power and low power locking pulses in a spin-lock sequence, respectively. S_0 is the control signal acquired with no spin-lock preparation cluster. The signal acquired at low power has contributions from both chemical exchange and intrinsic spin–spin relaxation, whereas the signal acquired at high power has contributions mostly from intrinsic spin–spin relaxation. The subtraction of these two signals defined in Eq. (1) isolates mainly the chemical exchange effect.

2.2. CEST sequence and contrast

A typical CEST sequence contains a selective off-resonance irradiation pulse that lasts for several seconds, followed by data acquisition. A CEST Z-spectrum is acquired by sweeping the frequency offset of the RF irradiation pulses. The CEST effect is simply quantified by convention using an asymmetry analysis (MTR_{asym}) which subtracts the CEST water signal acquired with the irradiation pulse on the solute from that obtained when applied on the other side of water peak [14]. The CEST contrast is then defined to be [14],

$$\text{CESTcontrast} = \frac{S(\text{reference}) - S(\text{label})}{S_0} \quad (2)$$

Here, S(label) and S(reference) are the signals acquired with an irradiation pulse on the 2DG or glucose and the symmetrically opposite side of the water peak, respectively. S_0 is the control signal acquired with no irradiation.

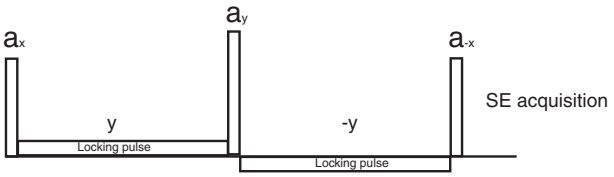

Fig. 1. Diagram of spin-locking sequence.

2.3. Numerical simulation

To evaluate the potential effects of 2DG on both CEST and spin-lock imaging, simulations were performed with a three-pool model which contains 2DG (the solute pool), a background solid component, and water. There is chemical exchange between the exchangeable species (2DG) and water, and magnetization transfer between the solid component and water, but negligible exchange between the 2DG and solid component. $R_{1\rho}$ and CEST contrasts as defined above were numerically calculated for a range of sample parameters. We varied the exchange rate between 2DG and water (k_{sw}) (1, **2**, 3, 4, and 5 kHz), 2DG fractional population (f_s) (0.005, **0.01**, 0.015, 0.02, and 0.025), water longitudinal relaxation time (T_1) (0.5, 1.0, **1.5**, 2.0, and 2.5 s), water transverse relaxation time (T_2) (20, 40, **60**, 80, and 100 ms), and solid component fraction (f_m) (0.03, 0.06, **0.09**, 0.12, and 0.15). Each parameter was varied individually, with all other parameters remaining at the values shown in **bold**. Other simulation parameters include: 2DG proton longitudinal and transverse relaxation (1.5 s and 15 ms); solid component longitudinal and transverse relaxation times (1.5 s and 15 μs); solid component–water exchange rate (25 s^{-1}); 2DG chemical shift offset of 1.0 ppm; and solid component offset of 0 ppm. For the simulations of the $R_{1\rho}$ dispersion curve, locking powers were varied from 10 to 10,000 Hz, and spin-locking times were 1, 20, 40, 60, 80, and 100 ms. For the simulations of $R_{1\rho}$ contrast defined in Eq. (1), S(high) and S(low) were simulated with low locking amplitude at 100 Hz and high locking amplitude at 10,000 Hz, respectively, with spin-locking time = 40 ms. For the simulations of the CEST Z-spectra, frequency offsets of the RF irradiation pulse were varied from −1500 to 1500 Hz (−5 to +5 ppm at 7 T) with an interval of 50 Hz (0.167 ppm at 7 T), RF irradiation power of 1 μT, and irradiation time of 2 s. For the simulations of CEST contrast defined in Eq. (2), S(reference) and S(label) were simulated with frequency offset of RF irradiation pulse at −300 Hz (−1 ppm at 7 T) and 300 Hz (1 ppm at 7 T), respectively, with irradiation power of 1 μT, and irradiation time of 2 s.

2.4. Phantom preparation

Two series of 2DG samples served as phantoms to test the ability of spin-lock and CEST to quantify 2DG–water exchange effects. Three samples were made by adding 2DG to phosphate buffered saline (PBS) to reach concentrations of 50, 100, or 150 mM. 0.05 mM $MnCl_2$ was added to the solution to shorten T_1 and T_2. pH was titrated to 7.0 for these three samples at room temperature. All chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA). A second series of samples were prepared by removing the brains from freshly sacrificed Sprague–Dawley rats. The intact tissue was washed in ice-cold PBS, homogenized, and mixed with various concentrations of buffered solutions of 2DG (0, 25, 50, and 100 mM).

2.5. Animal preparation

2DG infusion experiments were performed on 4 healthy Sprague Dawley rats and 1 rat bearing 9 L tumor. The rats were immobilized and anesthetized with a 2%/98% isoflurane/oxygen mixture.