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Spin-lock Imaging of 3-o-Methyl-D Glucose (3oMG) in Brain Tumors

Zhongliang Zu^{1,2}, Xiaoyu Jiang^{1,2}, Junzhong Xu^{1,2,3,4}, and John C. Gore^{1,2,3,4,5}

¹Vanderbilt University Institute of Imaging Science, Vanderbilt University, Nashville, Tennessee, USA

²Department of Radiology and Radiological Sciences, Vanderbilt University, Nashville, Tennessee, USA

³Department of Physics and Astronomy, Vanderbilt University, Nashville, Tennessee, USA

⁴Department of Biomedical Engineering, Vanderbilt University, Nashville, Tennessee, USA

⁵Molecular Physiology and Biophysics, Vanderbilt University, Nashville, Tennessee, USA

Abstract

Purpose—To evaluate the ability of spin-lock imaging to detect the uptake of 3-o-methyl-D-glucose (3oMG) in normal brain and brain tumors in animals.

Methods—Measurements of the longitudinal relaxation rate in the rotating frame ($R_{1\rho}$) were made over a range of spin-lock powers in rat brains bearing 9L tumors. The dispersion of $R_{1\rho}$ values was quantified by $R_{1\rho}$, the difference of $R_{1\rho}$ values acquired with low and high locking powers. The glucose analogue 3-o-methyl-D-glucose (3oMG) was administered intravenously and the differences of $R_{1\rho}$ values ($R_{1\rho}^{\text{diff}}$) before and as a function of time after administration were calculated to isolate the contribution of 3oMG to the dispersions, which at high fields mainly reflects chemical exchange effects. In addition, the ratio of image signals from low and high locking fields (the spin-lock ratio, SLR), which requires fewer acquisitions and varies directly with $R_{1\rho}$, was computed as an alternative measure of the variation with locking power, and changes in SLR (SLR^{diff}) after 3oMG were evaluated.

Results—Both $R_{1\rho}^{\text{diff}}$ and SLR^{diff} in tumors increased rapidly after injection, whereas intact brain showed a gradual increase up to 1h. $R_{1\rho}^{\text{diff}}$ and SLR^{diff} were significantly different between tumors and contralateral normal tissues.

Conclusion—Spin-lock methods can be used to detect 3oMG *in vivo* after injection, and appropriate analyses of MRI signals allow tumors to be distinguished from normal brain.

Keywords

$T_{1\rho}$; molecular imaging; 3oMG

INTRODUCTION

Most cancer cells have high glycolytic rates and enhanced uptake of glucose or its analogues (e.g. 2-deoxy-D-glucose (2DG) and 2-deoxy-fluoro-D-glucose (FDG)) which provides the basis for imaging detection and assessment of tumors by microscopy or PET (1). High-sensitivity imaging of the uptake and kinetics of administered glucose or its analogues may provide information on tumor metabolism and the levels of glucose transporters in tissues, and enhance the diagnosis of cancer. 3-o-methyl-D-glucose (3oMG) is a non-toxic glucose analogue that is taken up by cells through glucose transporters but which is not metabolized and which, unlike FDG, is not phosphorylated by hexokinase. 3oMG is therefore a candidate contrast agent for detection by MRI. Glucose and its analogues contain exchanging protons in hydroxyl groups. In MRI, by labeling the exchanging protons with selective RF irradiation for some time, an accumulated chemical exchange with the water causes a significant reduction in the water signal. By measuring this change in the water signal, the presence of the solute molecules can be indirectly detected with higher sensitivity than by direct measurement. Recently, chemical exchange saturation transfer (CEST) imaging, which applies a long, frequency-selective RF pulse to saturate specific solute protons prior to measurement of the water signal, has been used to detect glucose and its analogues after intravenous administration (2–10). However, hydroxyl protons exchange very rapidly, and are in the fast exchange regime, so their CEST effects extend over a broad range and overlap with the water proton resonance (11,12). The detection and quantification of glucose or its analogues by CEST is therefore challenging.

Spin-lock imaging is another technique which is also sensitive to chemical exchange effects especially at high fields (13). Recently, a few studies have applied spin-lock techniques to detect glucose and its analogues *in vivo* after intravenous injections, and their results suggest that spin-lock techniques can have better sensitivity than CEST for detecting chemical exchange effects in the fast exchange regime (14–19). $R_{1\rho}$, the longitudinal relaxation rate in the rotating frame, can be measured by comparing signals at a fixed locking power but at different locking times, and is well estimated by linearly adding individual exchange contributions (20).

Glucose transport and uptake have been studied with glucose analogues by imaging. 2DG has been detected by both CEST and spin-lock techniques in tumors. 2DG is phosphorylated by hexokinase into 2DG-6-phosphate (2DG6P) which is then trapped in brain cells for many hours (21). Thus signals from 2DG may accumulate over time and be detected later than those of D-glucose. However, 2DG is toxic at high concentrations, which limits its clinical applications. 3oMG is a glucose analogue, which also targets the glucose transporter but which is not metabolized and which also should provide higher MR signals than those of D-glucose. In addition, 3oMG is generally considered to be nontoxic (6,17,22), though detailed studies of its toxicity have not been reported. Although CEST has been applied to detect 3oMG in tumors *in vivo*, spin-locking techniques have not been evaluated for this purpose. In this paper, we demonstrate the ability of spin-lock imaging to detect the uptake of 3oMG in tumor bearing rat brains.

METHODS

Spin-lock signal-based and $R_{1\rho}$ -based contrasts

A spin-lock sequence usually contains a preparation cluster followed by data acquisition. The acquired spin-lock signal (S) after the spin-lock preparation can be described by,

$$S = S_0 \cdot \exp(-R_{1\rho} \cdot \text{SLT}) \quad (1)$$

where S_0 is the water signal measured without applying the spin-lock preparation, and SLT is the spin-lock time. $R_{1\rho}$ is sensitive to slow molecular motions and chemical exchange processes on a time-scale corresponding to the Larmor precession about the spin-locking pulse amplitude (23,24). Assuming a two-pool (solute and water) exchange process, $R_{1\rho}$ can be expressed as (25),

$$R_{1\rho} = \frac{f_s \cdot k_{sw} \cdot \Delta\omega_s^2}{\Delta\omega_s^2 + (2\pi f_1)^2 + k_{sw}^2} + R_{2,0} \quad (2)$$

where f_s , k_{sw} , and $\Delta\omega_s$ are the fractional solute concentration, solute-water exchange rate, and solute resonance frequency offset from water, respectively, $R_{2,0}$ is the intrinsic transverse relaxation rate of water protons without any chemical exchange contribution, and f_1 is the Larmor frequency associated with the locking field.

After the administration of contrast agents in tissues, not only may the chemical exchange contributions from the agents (e.g. f_s and k_{sw}) change, but non-exchange related effects (e.g. changes in S_0 , $R_{2,0}$) which influence the signal and $R_{1\rho}$ may also change. A change in $R_{2,0}$ after agent administration may, for example, be due to osmotic effects that cause shifts in water compartmentation (16,17). Previously, we have shown how judicious selection of locking powers and combinations of data acquired with different powers can isolate chemical exchange effects from non-chemical exchange related effects (20,26,27). This notion is based on the premise that the dominant exchange processes occur at rates whose effects may be reduced with locking fields in a range of moderate to relatively high values, giving rise to a dispersion of $R_{1\rho}$ values for different f_1 . Here we define a simple $R_{1\rho}$ -based contrast as,

$$\Delta R_{1\rho} = R_{1\rho}(f_1^{low}) - R_{1\rho}(f_1^{high}) \quad (3)$$

where low and high denote the relative values of f_1 used in the measurement. This metric quantifies the contributions mainly of exchange processes. To calculate the specific contributions to $R_{1\rho}$ of an agent after administration *in vivo*, the resultant difference in $R_{1\rho}$ is obtained by subtracting $R_{1\rho}$ values before injection from those after injection. This

separates the exchange effects of the agent from other endogenous exchanging pools in tissues. Eq. (4) defines $R_{1\rho}^{diff}$

$$\Delta R_{1\rho}^{diff} = \Delta R_{1\rho}|_{\text{after injection}} - \Delta R_{1\rho}|_{\text{base line}} \quad (4)$$

While explicit calculation of rates provides more complete information, more convenient measures of contrast effects can be obtained with shorter acquisition times and higher signal to noise ratio by fixing SLT and comparing two spin-lock weighted images. We define the spin-lock ratio (SLR) and SLR^{diff} in Eq. (5) and Eq. (6).

$$SLR = \log \left(\frac{S(f_1^{high})}{S(f_1^{low})} \right) = \Delta R_{1\rho} \cdot SLT \quad (5)$$

$$SLR^{diff} = SLR|_{\text{after injection}} - SLR|_{\text{base line}} = \Delta R_{1\rho}^{diff} \cdot SLT \quad (6)$$

Here, we used $R_{1\rho}$ and SLR to quantify the effects of 3oMG in samples and $R_{1\rho}^{diff}$ and SLR^{diff} to quantify the effects of 3oMG after administration *in vivo*.

Sample preparation

A series of 3oMG solutions were used to evaluate the dependence of $R_{1\rho}$ on solute concentration. Four samples were made with 10, 20, 30, and 40 mM 3oMG in $1 \times$ phosphate buffered saline (PBS) buffer and pH was titrated to 7.0 using NaOH/HCl. All chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA).

Animal preparation

Five rats bearing 9L tumors were used in this study. Each rat was injected with 1×10^5 9L glioblastoma cells in the right brain hemisphere to induce tumors, and was then imaged after 2 to 3 weeks when the tumor reached appropriate size. All rats were immobilized and anesthetized with a 2%/98% isoflurane/oxygen mixture during imaging. Respiration was monitored to be stable, and a constant rectal temperature of 37°C was maintained throughout the experiments using a warm-air feedback system (SA Instruments, Stony Brook, NY). The rat jugular vein was catheterized for intravenous injections. 1.5g/kg 3oMG was injected to each rat in 1–2 min. All animal experiments were approved by the Animal Care and Usage Committee of Vanderbilt University.

MRI

We used a spin-lock preparation cluster ($90_x - \tau_y/4 - 180_y - \tau_y/4 - \tau_y/4 - 90_x$) introduced in a recent patent (28) which shows better performance than several other approaches to compensate for B_0 and B_1 field inhomogeneities (29). Each RF pulse in the spin-lock

preparation cluster is a hard pulse. Spin-lock signals were acquired with f_1 varying from 100 to 3162 Hz. Spin-locking times were 1, 250, 500, 750, 1000 ms for samples or 1, 25, 50, 75, 100 ms for animal experiments. For the studies of 3oMG injections, spin-lock signals were continuously acquired over 10 minute intervals before, during and after injection. The total acquisition time was roughly 7 mins to acquire data to derive each $R_{1\rho}$ dispersion using 8 different locking fields, and roughly 100 s and 20 s to acquire spin-locking signals with two locking powers to calculate only $R_{1\rho}$ and SLR, respectively. Water longitudinal relaxation rate (R_{1w}) and semi-solid pool size ratio (PSR) were obtained using a selective inversion recovery (SIR) quantitative magnetization transfer (MT) method before injection (30). Specifically, a 1-ms inversion hard pulse was applied to invert the free water pool and the subsequent longitudinal recovery times were set to be 4, 5, 6, 8, 10, 12, 15, 20, 50, 200, 500, 800, 1000, 2000, 4000, and 6000 ms. Spin-echo Echo Planar Imaging (SE-EPI) was used for image readout followed by a saturation pulse train to shorten the total acquisition time as described previously (31). A constant delay time of 3.5 s was set between the saturation pulse train and the next inversion pulse.

All measurements on both samples and animals were performed on a Varian DirectDrive™ horizontal 9.4T magnet with a 38-mm Litz RF coil (Doty Scientific Inc. Columbia, SC) at 37°C. Spin-lock images on animals were acquired using single-shot SE-EPI sequences. All images were acquired with matrix size 64×64 , field of view $30 \text{ mm} \times 30 \text{ mm}$, slice thickness 2 mm, and 1 acquisition. Spin-lock data on phantoms were acquired with free induction decay (FID) acquisitions.

Data analysis

$R_{1\rho}$ values were calculated by fitting the signal variation with SLT to a three-parameter mono-exponential decay function in MATLAB (The MathWorks, Inc. Natick, MA). The average of three measurements before injection was used as baseline. $R_{1\rho}$ and $R_{1\rho}^{\text{diff}}$ were calculated by comparing values at low power (100 Hz) and high power (3162 Hz). SLR and SLR^{diff} were calculated by comparing values of signals acquired with SLT of 50 ms at low power (100 Hz) and high power (3162 Hz). These two powers were chosen to isolate and maximize chemical exchange contributions while avoiding off-resonance effects at low power and remaining well within the maximum rating of the RF coil and amplifiers. $R_{1\rho}$ and $R_{1\rho}^{\text{diff}}$ were obtained before and every 10 mins after injecting 3oMG. f_s , k_{sw} , and

$R_{2,0}$ were obtained by fitting the $R_{1\rho}$ dispersion difference 10 minutes after injection to Eq. (2). Here, f_s represents the fractional solute concentration of the injected agent and $R_{2,0}$ represents the variation of $R_{2,0}$ due to the injected agent. Table 1 lists the starting points and boundaries of the fit of these three parameters. To increase signal to noise ratio, the $R_{1\rho}$ dispersion difference was obtained by averaging the data from 5 rats. ω_s was set to 1.4 ppm (560 Hz at 9.4 T) in the fitting.

Regions of interest (ROIs) in tumors were outlined from the PSR map with values less than a threshold of 7%. ROIs of contralateral normal tissue were chosen to mirror the tumor ROIs. Student's t-tests were employed to evaluate differences between results, which were considered to be statistically significant when $p < 0.05$.

RESULTS

Fig. 1 shows results of the spin-lock experiments on 3oMG solutions. Note in Fig. 1b and 1c that both $R_{1\rho}$ and SLR are linearly proportional to the concentration, although the fitted lines do not cross 0 at concentration of 0 mM. Also note in Fig. 1a that $R_{1\rho}$ increases with locking power from 100 Hz to 316 Hz which may be due to the transverse relaxation in the rotating frame ($R_{2\rho}$) off-resonance effect introduced by inhomogeneities in the static main field (see simulations in Supporting Figure S1) (18).

Fig. 2a and 2b show the $R_{1\rho}$ dispersions from rat brains before (blue line) and at 10 mins after (red line) injecting 3oMG, from normal tissues and tumors, respectively. The $R_{1\rho}$ dispersion acquired before injection was used as a baseline. We found that the $R_{1\rho}$ values from both tumors and normal tissues acquired 10 mins after injecting 3oMG increased compared with baseline values. Also note that $R_{1\rho}$ increases with locking power from 100 Hz to 562 Hz similar to the sample data in Fig. 1a which is caused by $R_{2\rho}$ effects. Fig. 2c and 2d show the $R_{1\rho}$ dispersion differences $R_{1\rho}^{\text{diff}}$ from normal tissues and tumors, respectively. The $R_{1\rho}$ dispersion difference removes pre-injection, endogenous chemical exchange effects, and thus can isolate the contribution from only the injected agent. Note that the increase with locking power from 100 Hz to 562 Hz in the $R_{1\rho}$ dispersion difference curve is negligible, confirming that off-resonance effects have little influence on $R_{1\rho}^{\text{diff}}$. We also fitted the $R_{1\rho}$ dispersion difference to Eq. (2) (black dashed curve) to obtain the exchange parameters. Table 2 lists the fitting results.

Fig. 3a shows the mean time courses of $R_{1\rho}$ from rat brains. Fig. 3b and 3c show the mean time courses of $R_{1\rho}^{\text{diff}}$ with lock power of 100 Hz (named $R_{1\rho}(100\text{Hz})$ difference) and with lock power of 3162 Hz (named $R_{1\rho}(3162\text{Hz})$ difference), respectively. Note that the $R_{1\rho}(100\text{Hz})$ difference in tumor is higher than that in normal tissues, but the $R_{1\rho}(3162\text{Hz})$ difference in tumor is lower than in normal tissues, consistent with different degrees of dispersion. Fig. 3d shows the mean time course of $R_{1\rho}^{\text{diff}}$ from rat brains. It was found (Fig. 3d) that $R_{1\rho}^{\text{diff}}$ in tumors increases quickly after injection, whereas intact brain showed a more gradual increase up to 1 h. Fig. 3e shows the mean time course of SLR^{diff} from rat brains, which is in agreement with $R_{1\rho}^{\text{diff}}$ in Fig. 3d. It was also found that there are significant differences of both $R_{1\rho}^{\text{diff}}$ and SLR^{diff} between tumors and contralateral normal tissues.

Fig. 4 shows maps of $R_{1\rho}$ from base line, $R_{1\rho}$ after injection, $R_{1\rho}^{\text{diff}}$, SLR from base line, SLR after injection, SLR^{diff} , R_{1w} , and PSR from a representative rat brain, respectively (Maps from the other 4 rats are shown in Supporting Figures S2–S5). Note that all parametric maps show clear contrast between brain and tumors, but $R_{1\rho}^{\text{diff}}$ and SLR^{diff} reveal significant inhomogeneity inside the tumor. Weak artifacts in the contralateral hemisphere in the $R_{1\rho}^{\text{diff}}$ and the SLR^{diff} maps may reflect residual off-resonance effects and the small effects in normal brain. However, the values of $R_{1\rho}^{\text{diff}}$ and SLR^{diff} in the tumors are significantly greater than for normal tissue, especially within the tumor boundary in Fig. 4.

DISCUSSION

We applied spin-lock techniques to detect 3oMG in animal brains and tumors *in vivo*. 3oMG increases $R_{1\rho}$ values by chemical exchange between hydroxyl and water protons, but the effect decreases at higher locking fields. Subtractions of $R_{1\rho}$ values acquired before and after injection of 3oMG isolate the contribution of the compound from other endogenous chemical exchange effects. Fitting the dispersion of 3oMG can be used to estimate the exchange parameters of the administered 3oMG. Results in Table 1 indicate that our fitted k_{sw} (8145 s^{-1}) in normal tissues is roughly in agreement with a previous report (7480 s^{-1}) (17). Our fitted f_s and $R_{2,0}$ in normal tissues (0.00025 and 0.15 s^{-1}) are also roughly in agreement with this previous report (0.0009 and 0.75 s^{-1}) considering the 2.7 times higher dose of 3oMG used in the previous study (17). The fitted f_s in tumors is roughly two times that in normal tissues, which indicates an enhanced uptake of 3oMG in tumors; the fitted k_{sw} in tumors is roughly 70% of that in normal tissues, which may be due to differences in pH. The fitted $R_{2,0}$ in tumors and normal tissues is small, which suggests that changes in non-exchange effects in due to 3oMG administration is negligible.

Based on Eq. (2), $R_{1\rho}$ at low lock powers may be dominated by chemical exchange effects, but $R_{1\rho}$ at high lock powers may be dominated by non-exchange effects. This can be confirmed by the comparison between the $R_{1\rho}$ values and the fitted $R_{2,0}$ values. The $R_{1\rho}(100\text{Hz})$ differences from tumors and normal tissues at 10 mins after injection in Fig. 3b (0.67 s^{-1} and 0.44 s^{-1}) are much greater than the corresponding fitted $R_{2,0}$ values (0 s^{-1} and 0.15 s^{-1}). The $R_{1\rho}(3162\text{Hz})$ differences from tumors and normal tissues at 10 mins after injection in Fig. 3c (0.07 s^{-1} and 0.21 s^{-1}) are comparable to the corresponding fitted $R_{2,0}$ values (0 s^{-1} and 0.15 s^{-1}). Non-exchange related effects are relatively insensitive to lock power (17), so subtraction of two $R_{1\rho}$ values acquired with a low and a high lock power can remove non-exchange related contributions, while retaining most of the chemical exchange effect, depending on the rate of exchange compared to the locking frequency. The $R_{1\rho}(100\text{Hz})$ difference in tumors is higher than that in normal tissues in Fig. 3b, but the $R_{1\rho}(3162\text{Hz})$ difference in tumors is lower than that in normal tissues in Fig. 3c consistent with their being greater dispersion in tumors over this range. Therefore, the subtraction of two $R_{1\rho}$ acquired with a low and a high lock power can enhance the contrast between tumors and normal tissues.

As shown in Fig. 4 and parametric maps of other rats in Supporting Figures S2–S5, R_{1w} , PSR, $R_{1\rho}^{\text{diff}}$ and SLR^{diff} all demonstrate significant contrast between tumor and contralateral normal brain tissues. However, R_{1w} and PSR appear relatively uniformly distributed, but $R_{1\rho}^{\text{diff}}$ and SLR^{diff} are clearly inhomogeneous inside tumors. R_{1w} and PSR provide information on macromolecular content, and hence are capable of distinguishing tumor and brain tissues based on underlying differences in gross composition, but they are not highly sensitive to relatively smaller differences in cellular content within tumors. By contrast, $R_{1\rho}^{\text{diff}}$ and SLR^{diff} may reflect different levels of glucose uptake by tissues, which is different not just between tumors and normal brain tissues, but also variable between different tumor regions.

After intravenous injection, 3oMG may leave the circulation into the extracellular space, and then enter cells through glucose transporters. Therefore, $R_{1\rho}^{\text{diff}}$ and SLR^{diff} may depend on several physiological properties including vascular permeability and surface area, blood flow, the rate of glucose uptake by cells, and tissue pH. Further studies of their relative contributions are warranted, which may provide insight into the specificity of spin-lock techniques for assessing glucose uptake. Note that $R_{1\rho}$ values obtained at a single locking field, as well as simpler R_2 measurements, may also be sensitive to exchange (32,33), but can not remove non-exchange related effects. SLR and SLR^{diff} require measurements at only one SLT, and thus can significantly reduce the total acquisition time without loss of specificity.

CONCLUSIONS

We show that spin lock imaging can be applied to detect 3oMG in vivo as a potential contrast agent that is taken up in a fashion similar to glucose.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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FIG. 1.

R_{1p} dispersion (a), R_{1p} (b), and SLR (c) on 30MG samples with a series of concentrations. Dashed lines in (b) and (c) are the fitted lines from the measured data (dots).

FIG. 2.

$R_{1\rho}$ dispersion and $R_{1\rho}$ dispersion difference from normal tissues (a, c) and tumors (b, d) of rat brains. Fitted dispersions (black dashed lines) were also shown in (c and d). Error bars are the standard deviations across five subjects.

FIG. 3.

Mean time courses of $R_{1\rho}$ (a), $R_{1\rho}(100Hz)$ difference (b), $R_{1\rho}(3162Hz)$ difference (c), $R_{1\rho}^{diff}$ (d) and SLR^{diff} difference (e) from rat brains. Error bars are the standard deviations across five subjects.

FIG. 4.

Maps of $R_{1\rho}$ from base line (a), $R_{1\rho}$ after injection (b), $R_{1\rho}^{diff}$ (c), SLR from base line (d), SLR after injection (e), SLR^{diff} (f), R_{1w} (g), and PSR (h) from a representative rat brain.

$R_{1\rho}$ after injection and SLR after injection were obtained at 10 mins after injection of 30MG. Note that R_{1w} and PSR show a relatively uniform tumor structure while $R_{1\rho}^{diff}$ and SLR^{diff} show significant inhomogeneity inside tumors.

Table 1Starting points and boundaries of f_s , k_{sw} , and $R_{2,0}$.

	Start	Lower	Upper
f_s	0.1	0	1
k_{sw} (Hz)	5000	0	10000
$R_{2,0}$ (s^{-1})	0.5	0	2

Table 2

Fitted f_s , k_{sw} , and $R_{2,0}$ in tumors and contralateral normal tissues.

	Normal	Tumor
f_s	0.00025	0.00042
k_{sw} (Hz)	8145	5638
$R_{2,0}$ (s^{-1})	0.15	0