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

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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 ¹³C-labeled 2DG and NMR spectroscopy, ¹⁸F-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*.

Keywords

2DG; chemical exchange saturation transfer (CEST); spin-lock; $R_{1\rho}$

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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 analogues 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) 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.

MATERIALS AND METHODS

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_{1p} contrast simply as

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

Here, $S(\text{high})$ and $S(\text{low})$ 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.

CEST sequence and contrast

A typical CEST sequence contains a selective off-resonance irradiation pulse which lasts for several seconds, following 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, $S(\text{label})$ and $S(\text{reference})$ 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.

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_{1p} 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, 5 kHz), 2DG fractional population (f_s) (0.005, **0.01**, 0.015, 0.02, 0.025), water longitudinal relaxation time (T_1) (0.5, 1.0, **1.5**, 2.0, 2.5 s), water transverse relaxation time (T_2) (20, 40, **60**, 80, 100 ms), and solid component fraction (f_m) (0.03, 0.06, **0.09**, 0.12, 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 μ s); solid component-water exchange rate (25 s^{-1}); 2DG chemical shift offset

of 1.0 ppm; 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, 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 10000 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 Hz to 1500 Hz (-5 ppm to +5 ppm at 7 T) with an interval of 50 Hz (0.167 ppm at 7 T), RF irradiation power of 1 μ T, 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 7T), respectively, with irradiation power of 1 μ T, and irradiation time of 2 s.

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 mM, 25 mM, 50 mM, and 100 mM).

Animal preparation

2DG infusion experiments were performed on 4 healthy Sprague Dawley rats and 1 rat bearing 9L tumor. The rats were immobilized and anesthetized with a 2%/98% isoflurane/oxygen mixture. Respiration was monitored and adjusted 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). A polyethylene catheter (PE50) was inserted into the tail vein for 2DG infusion. 3 ml 0.5 M 2DG solution was injected to each rat through the catheter. This corresponds for a 250 gm rat to a dose of approximately 1 gm/kgm body weight. The solution was infused via the tail vein at a rate of 2 ml/h (90 minute infusion). All procedures were approved by the Institutional Animal Care and Use Committee at Vanderbilt University.

MRI Measurements

$R_{1\rho}$ dispersion curves on phantoms and homogenates were acquired with spin-locking amplitudes from 100 Hz to 10,000 Hz. $R_{1\rho}$ dispersion curves on rats were acquired with spin-locking amplitude from 100 Hz to 5623 Hz. Spin-locking times for the phantom and animal experiments were (1, 25, 50, 75, 100 ms) or (20, 44, 96, 210, 457, 1000 ms) for the homogenates. $R_{1\rho}$ contrasts for phantoms, homogenates, and rats were calculated from images acquired with low spin-locking power at 100 Hz, high spin-locking power at 3160 Hz, and spin-locking time of 50 ms. $R_{1\rho}$ dispersion curves and contrasts were acquired from 20 m before infusion to 1.5 h after start of infusion. CEST Z-spectra and CEST contrasts on

phantoms were acquired with irradiation power and irradiation time the same as those in the simulations.

All phantom, homogenate, and animal experiments were performed on a 7T Varian/Agilent small animal system with a 38-mm RF coil (Doty Scientific Inc. Columbia, SC). Both spin-lock and CEST data were acquired using single-shot spin-echo echo planar imaging (EPI) readouts and a recovery time of 2 s. Images had a field of view (FOV) of 30 mm $\times$ 30 mm, matrix size of 64 $\times$ 64, bandwidth (*BW*) of 250 kHz, echo time (*TE*) of 50 ms, number of acquisitions averaged (*NA*) of 1, and slice thickness of 2 mm.

RESULTS

Fig. 2a and 2g show the simulated $R_{1\rho}$ dispersion curves and CEST Z-spectra, respectively. Simulated $R_{1\rho}$ and CEST contrasts as a function of T_1 (b, h), T_2 (c, i), f_m (d, j), f_s (e, k), and k_{sw} (f, l), respectively, are also shown. $R_{1\rho}$ contrast depends linearly on f_s and varies with k_{sw} (peaking at a value that depends on the choice of locking field) but not on T_1 and less on f_m , while CEST contrast depends on all tissue parameters. The change of $R_{1\rho}$ contrast (11%) is only around one third of the change of CEST contrast (36%) when f_m was varied from 0.03 to 0.15. The dependence of $R_{1\rho}$ contrast on T_2 is discussed below. Fig. 2 indicates that CEST contrast may be contaminated by the variation of other tissue parameters even if the relevant resonance can be selectively saturated, while $R_{1\rho}$ contrast is less affected by several factors except for T_2 . In addition, it was found that the $R_{1\rho}$ contrast as defined above is higher (roughly 1.4 and 2.1 fold with k_{sw} of 2 and 3 kHz, respectively) than the CEST contrast for the same concentration of 2DG, indicating that spin-locking sequence may be a more sensitive imaging method for detecting fast exchanging molecules such as 2DG and glucose.

Fig. 3a and 3b show the experimental $R_{1\rho}$ dispersion curves and $R_{1\rho}$ contrast for 2DG phantoms containing different concentrations (50, 100, 150 mM). Fig. 3c and 3d show the experimental $R_{1\rho}$ dispersion curves and $R_{1\rho}$ contrast for homogenates containing different concentrations (0, 25, 50, 100 mM) of 2DG. It was found that the $R_{1\rho}$ contrast is linearly dependent on 2DG concentration.

Fig. 4a-4c show the experimental CEST Z-spectra and MTR_{asym} spectra for 2DG phantoms with different concentrations at irradiation powers of 1 μ T (a), 2 μ T (b), and 3 μ T (c), respectively. Note that the peaks of MTR_{asym} spectra in (b and c) are not at 1 ppm. The shifts of the peaks are caused by the larger direct saturation effects at higher irradiation powers. Fig. 4d shows the CEST contrast acquired at 1 ppm vs. 2DG concentration at different irradiation powers. Note that only the curve at irradiation power of 1 μ T in (d) is monotonic. Fig. 4 shows that to quantify 2DG, the irradiation power of the CEST sequence cannot be very high so that the contrast is not seriously influenced by direct saturation effects. However, relatively high irradiation powers are required to saturate the rapidly exchanging 2DG protons.

Fig. 5a and 5c show the $R_{1\rho}$ dispersion curves and CEST Z-spectra for healthy rat brain after infusion of 2DG. Fig. 5b and 5d shows the time courses of the $R_{1\rho}$ contrast and CEST

contrast before and after the infusion on the 4 healthy rats. It was found that R_{1p} contrast increases steadily after infusion of 2DG for all the rats, while the trends of the time course of the CEST contrast was not reliably repeatable. For rat #1, the change of R_{1p} contrast at 70 mins after infusion of 2DG (0.8%) is about 1.6 times that of the CEST contrast (0.5%), which is in agreement with our simulations in Fig. 2f and 2l (also around 1.6 times with k_{sw} a little more than 2000 s^{-1}). Fig. 6a shows the time course of R_{1p} contrast on one rat brain bearing 9L tumor before and after the infusion. The results show more increase in contrast with 2DG infusion in the tumor than in normal tissues, indicating higher uptake of 2DG in the tumor. Fig. 6b, 6c, and 6d show an anatomic image, the difference of R_{1p} contrast images, and the difference of CEST contrast images before and 70 mins after infusion. Arrows in Fig. 6b and 6c indicate the tumor. Hyperintense signal from tumor was found on the rat brain in Fig. 6c, but not in Fig. 6d.

DISCUSSION

Although several imaging techniques have been developed to detect glucose metabolism by measuring labeled agents directly, MRI methods sensitive to chemical exchange provide an alternative approach to indirectly detect glucose uptake in tissues with enhanced sensitivity. After a long saturation pulse is applied on the frequency offset of solute protons, there is a cumulative effect from chemical exchange between water and saturated solute protons. This amplification process enables CEST to indirectly detect solute molecules in the millimolar range. However, as an indirect method, CEST depends on multiple tissue parameters including water relaxation and background solid effects (Fig. 2). The variation of those parameters in different tissues or pathological states may cause confounding variations of CEST contrast. This can be seen in Fig. 5c where the Z-spectra decrease after infusion which might be caused by an increased water T_1 . Fig. 2b and 2d show that R_{1p} contrast is not influenced by T_1 and is less influenced by f_m . Both CEST and R_{1p} contrast are dependent on T_2 but in practice the effect is small for realistic values of transverse relaxation. The contrast in R_{1p} decreases if intrinsic transverse rates are high because then the chemical shift dependent exchange effect is relatively less important, but our results in phantoms and homogenates demonstrate that exchange effects are of major importance at high field. Both R_2 and R_{1p} have contributions from both chemical exchange and dipole-dipole interactions. Zhong *et al.* [15] has shown that T_2 of protein solutions at high field decreases with increasing field, consistent with contributions from chemical exchange rather than from dipole-dipole interactions. Our previous studies of R_{1p} have also shown exchange dominates at high fields [8-11].

We performed CEST experiments on 4 healthy rats. However, we found that the trends of the time course of the CEST contrast was reliably not repeatable, which is different from a previous report [4]. Our rats were not fasted which may influence the uptake of 2DG.

Fig. 2f shows that the R_{1p} contrast depends on k_{sw} , peaking at around 2 kHz, indicating that the spin-locking technique is sensitive to fast exchanging molecules (e.g. glucose and 2DG). CEST contrast also depends on k_{sw} , with its peak depending on the irradiation power. At higher irradiation power, the CEST contrast is also more sensitive to fast exchanging molecules. However, higher irradiation power causes large direct saturation and MT effects

which significantly decrease the CEST contrast. Because the resonance frequencies of glucose and 2DG (1 ppm) are close to water, the irradiation power applied on them cannot be high. In previous studies, the average irradiation power applied on glucose or 2DG is around 1 μ T. With this power, CEST is not a method that is very sensitive to fast exchanging molecules.

The R_{1p} contrast defined in Eq. (1) uses signal acquired with no spin-lock preparation cluster as the denominator instead of the signal acquired with high locking provided by Kogen [16]. The use of this definition of R_{1p} contrast is to more directly compare the ability of spin-lock and CEST techniques in detecting exchanging molecules at the same format. For CEST experiments and simulations, an irradiation time of 2 s was used which is enough to get the maximum contrast for fast exchange. For spin-lock experiments and simulations, a locking time of 50 ms was used to ensure enough dephasing effect on water signal. The maximum R_{1p} contrast depends on the locking time and some other parameters, and needs to be optimized in future work.

The numerical simulation for spin-lock and CEST signals in this work (see Appendix) is different from that previously used for CEST signals [14, 17]. The exchange terms from water transverse components to the solid pool, although they do not influence CEST signals, can affect the spin-lock signals. Here, we added those exchange terms to the coupled Bloch equations.

A further limitation of the current study is the potential toxicity of 2DG. Although the infusions were apparently well tolerated by the animals, high levels of 2DG are known to potentially affect blood pressure and respiration as well as normal glucose uptake. 2DG was chosen partly because its time course in the brain is expected to show a steady accumulation, as found here. However, these experiments suggest that glucose itself in similar concentrations should also be readily detectable in vivo, though its time course would be different. Experiments to optimize the delivery of glucose as a spin-lock agent are clearly warranted and are under investigation.

CONCLUSION

In this report, we describe a new approach for measuring the effects of 2DG or glucose uptake in tissues using spin-lock magnetic resonance imaging. Simulations and experiments show that the spin-lock technique may be a more specific and sensitive method than CEST for detecting 2DG. Spin lock methods can be used to emphasize protons with specific exchange rates rather than specific chemical shifts, which makes them less sensitive to main field inhomogeneities.

Since the preparation of this report we have become aware that very similar work has been completed by Jin et al. (Seong-Ji Kim, private communication) who also compared the effects of 2DG and glucose and demonstrated how spin lock methods perform well in detecting both. Together these reports confirm that spin lock exchange sensitive imaging may be used to detect the uptake of glucose and glucose analogues and have a useful role in studies of tissue metabolism.

APPENDIX: Numerical Simulation

The spin-lock and CEST signals were numerically simulated using a three-pool (2DG /solid component /water) exchange model in Matlab. The model contains seven coupled Bloch equations,

$$\frac{dM_{xs}}{dt} = -(\omega_{rf} - \omega_s) M_{ys} - R_{2s} M_{xs} - k_{sw} M_{xs} + k_{ws} M_{xw} \quad (A1)$$

$$\frac{dM_{ys}}{dt} = (\omega_{rf} - \omega_s) M_{xs} - \omega_1 M_{zs} - R_{2s} M_{ys} - k_{sw} M_{ys} + k_{ws} M_{yw} \quad (A2)$$

$$\frac{dM_{zs}}{dt} = -\omega_1 M_{ys} - R_{1s} (M_{zs} - M_{0s}) - k_{sw} M_{zs} + k_{ws} M_{zw} \quad (A3)$$

$$\frac{dM_{xw}}{dt} = -(\omega_{rf} - \omega_w) M_{yw} - R_{2w} M_{xw} + k_{sw} M_{xs} - k_{ws} M_{xw} - k_{wm} M_{xw} \quad (A4)$$

$$\frac{dM_{yw}}{dt} = (\omega_{rf} - \omega_w) M_{xw} + \omega_1 M_{zw} - R_{2w} M_{yw} + k_{sw} M_{ys} - k_{ws} M_{yw} - k_{wm} M_{yw} \quad (A5)$$

$$\frac{dM_{zw}}{dt} = -\omega_1 M_{yw} - R_{1w} (M_{zw} - M_{0w}) + k_{sw} M_{zs} - k_{ws} M_{zw} + k_{mw} M_{zm} - k_{wm} M_{zw} \quad (A6)$$

$$\frac{dM_{zm}}{dt} = -R_{1m} (M_{zm} - M_{0m}) - k_{mw} M_{zm} + k_{wm} M_{zw} - W M_{zm} \quad (A7)$$

where the subscripts w, s and m denote the water, 2DG, solid component pools. The water and 2DG pools each has three coupled equations representing their x, y, and z components. The solid component pool has a single coupled equation representing the z component, with an additional term for saturation effects [18]. ω_1 is the angular precession frequency induced by the pulse, ω_{rf} is the frequency offset of the applied saturation pulse compared to that of the water, ω_s is the frequency offset of the 2DG pool compared to that of the water pool, and ω_w is 0. W is the saturation rate of the solid component pool (which best fits biological tissue [19-21]),

$$W = \pi \omega_1^2 \int_0^{\frac{\pi}{2}} d\theta \sin \theta \sqrt{\frac{2}{\pi}} \frac{T_{2m}}{|3c - \omega^2 \theta_s - 1|} e^{-x} \left\{ p - 2 \left[\frac{2\pi \omega_{rf} T_{2m}}{3c - \omega^2 \theta_s - 1} \right]^2 \right\} \quad (A8)$$

All numerical calculations of the pulsed-CEST signal integrated the differential equations through the pulse sequence using the ordinary differential equation (ODE) solver in Matlab.

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FIG. 1.
Diagram of spin-locking sequence.

FIG. 2.

Simulated R_{1p} dispersion curves (a) and R_{1p} contrast as a function of T_1 (b), T_2 (c), f_m (d), f_s (e), and k_{sw} (f), respectively. Simulated CEST Z-spectrum (g) and CEST contrast as a function of T_1 (h), T_2 (i), f_m (j), f_s (k), and k_{sw} (l), respectively. The R_{1p} dispersion curves were simulated with f_m of 0 and 0.09, respectively, and other parameters kept the same.

FIG. 3.

Experimental R_{1p} dispersion curves (a, c) and R_{1p} contrast (b, d) on phantoms and homogenate with different concentration of 2DG. It was found that the R_{1p} contrast is roughly linearly depends on 2DG concentration.

FIG. 4.

Experimental CEST Z-spectra and MTR_{asym} spectra on 2DG phantoms with different concentration at irradiation power of 1 μT (a), 2 μT (b), and 3 μT (c), respectively. Solid line, dashed line, and dotted line in (a-c) represent the concentration of the 2DG phantom of 50 mM, 100, mM, and 150 mM, respectively. Note that the peaks of MTR_{asym} spectra in (b and c) are not at 1 ppm. (d) shows the CEST contrast acquired at 1 ppm vs. 2DG concentration at different irradiation powers. Note that only the curve at irradiation power of 1 μT in (d) is monotonic.

FIG. 5.

Experimental R_{1p} dispersion curve and CEST Z-spectra (a, c), and time course of R_{1p} contrast and CEST contrast before and after infusion of 2DG (b, d) on 4 healthy rat brains. Note in (a) that the R_{1p} increases (arrow) after infusion of 2DG at lower spin-locking power, but keeps constant (arrow) at higher spin-locking power. Also note in (b) that the R_{1p} contrast increases after infusion of 2DG, peaking at around 40-70 minutes from the start. The infusion time was approximately 90 minutes for this case. However, the trends of time course of CEST contrast in (d) are not repeatable.

FIG. 6.

(a) Variation of R_{1p} contrast; (b) Baseline EPI image; (c) Difference of R_{1p} contrast between start and 70 minutes after 2DG infusion on rat brain bearing 9L tumor; (d) Corresponding difference of CEST contrast. Arrows in (b) and (c) indicate the tumor. Note the clear observation of tumor in (c), but not in (d).