Spin-lock MRI of glucose and deoxyglucose concentration changes in brain

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Target Audience Researchers and clinicians interested in imaging glucose and deoxyglucose transport and metabolism and/or the CEST technique.

Purpose With chemical exchange dependent saturation transfer (CEST) MRI, recent animal studies administering natural D-glucose demonstrated results comparable to PET [1-2], and showed wide potential applications in diseases such as cancer and Alzheimer's. However, this gluco-CEST approach has low sensitivity, and previous studies suggest tissue glucose concentration changes must be ~5-10 mM as a threshold for detection at 9.4 T [3]. Furthermore, the CEST signal is strongly affected by other relaxation effects such as T_1, T_2 and magnetization transfer [4-6], and lacks a reliable means to quantify glucose concentration. In this study we showed that the spin-lattice relaxation rate in the rotating frame ($R_1\rho$) measured by spin-lock MRI, is highly sensitive to administration of D-glucose and 2-deoxy-D-glucose (2DG) with a much lower detection threshold, and is able to quantify concentration changes.

Materials and methods *Simulations*: The maximal chemical exchange (CE) contrast was compared by on-resonance spin-lock and CEST approaches for varied exchange rates (k). The simulation of Bloch-McConnell equations assumed a chemical shift between water and labile proton of $\delta = 2500$ rad·s^{-1} (1 ppm at 9.4 T), a labile proton concentration of 10 mM, and water T_1 and T_2 of 2 s and 50 ms, respectively. Spin-lock contrast was calculated as the difference between $T_1\rho$-weighted signals with and without CE, normalized by signal without irradiation (S_0). CEST contrast was calculated as the difference between $MTR_{asym}(\delta)$ values with and without CE. At each k value, the maximum contrast of spin-lock and CEST was obtained by adjusting irradiation power and duration.

MRI experiments: All MR images were acquired at 9.4 T by single shot spin-echo or gradient-echo EPI with 0.4×0.4 or 0.5×0.5 mm^2 in-plane resolution, 2–mm slice thickness, and a repetition time of 3 s. *Phantom*: 5 and 20 mM of D-glucose with and without addition of 0.1 mM $MnCl_2$ were dissolved in phosphate buffered saline titrated to pH = 7.0. Spin-lock $R_1\rho$ dispersion curves (i.e, $R_1\rho$ vs. B_1) were measured at 37°C with spin-lock power $\gamma B_1 = 125$ to 4000 Hz. *In vivo*: Spin-lock brain studies of Sprague Dawley rats were performed with i.v. injection of glucose and 2DG. *Paradigm 1*: Three consecutive doses of 0.25, 0.5, and 1 g/kg D-glucose (n=4 rats) were given to determine the detection limit of spin lock MRI. $T_1\rho$-weighted images were measured with and without a spin-lock preparation of $\gamma B_1 = 500$ Hz for 50 ms duration. *Paradigm 2*: Following 1 g/kg 2DG injection (n=4 rats), three $T_1\rho$-weighted images, one without spin-lock preparation and two with spin-lock power of $\gamma B_1 = 500$ and 2000 Hz for 50 ms, were obtained in an interleaved manner to determine $R_1\rho$ dispersion. Time series of $R_1\rho$ maps were calculated from these $T_1\rho$-weighted images [7], and statistical maps corresponding to glucose injection were determined.

Results Figure 1A compares the maximum sensitivity of CEST and spin-lock approaches for different chemical exchange rates. The CEST sensitivity is optimal when $k/\delta \ll 1$, but drops quickly when $k/\delta > 1$. In contrast, the sensitivity of spin-lock reaches a peak for intermediate chemical exchange rates ($k/\delta = 1$), and is higher than CEST for $k/\delta >$ ~0.9 (dashed blue line). Figure 1B shows that $R_1\rho$ changes due to glucose concentration changes (blue arrows) are independent of water T_1 and T_2 (modulations due to $MnCl_2$). Fitting this $R_1\rho$ dispersion data to a recent theoretical $R_1\rho$ model [8], we found that the exchange rate between water and glucose hydroxyl protons is about 5000 s^{-1}, and the averaged chemical shift is $\delta = 1.6$ ppm, which is 4000 rad·s^{-1} at 9.4 T ($k/\delta = 1.25$), suggesting spin-lock may be a good choice for glucose detection. In the t-map calculated from spin-lock $R_1\rho$ measurement during injection of 0.5 g/kg D-glucose, a widespread increase of $R_1\rho$ is robustly observed in the brain (Fig. 2A). Compared to phantom results (Fig. 1B), the cortical $R_1\rho$ change corresponds to a 1-2 mM increase in brain glucose concentration, indicating high sensitivity of $R_1\rho$ for glucose detection. Figure 2B shows the $R_1\rho$ time course during subsequent injections of three different D-glucose doses, and the dose-dependence of the $R_1\rho$ increases. With 1 g/kg D-glucose, the peak $\Delta R_1\rho$ is 0.3 s^{-1} and a 50-60 min to return to baseline, while injection of 1 g/kg 2DG (Fig. 2C), gives a much larger peak $\Delta R_1\rho$ of 0.75 s^{-1} and a much slower return to baseline vs. D-glucose. This indicates that 2DG accumulates within the cells, while D-glucose metabolizes quickly [3]. With a higher spin-lock power $\gamma B_1 = 2000$ Hz, $\Delta R_1\rho$ is much smaller than with 500 Hz, as expected from phantom data (Fig. 1B).

Discussion Previous rat brain studies at 9.4 T indicated that gluco-CEST signal changes could not be detected with a 0.5 g/kg D-glucose injection and were very weak even with 1 g/kg injection [3]. Our results show this detection threshold may be significantly lower with the spin-lock approach. This sensitivity advantage may be partly because the hydroxyl-water proton exchange is in the intermediate to fast exchange regime, where spin-lock sensitivity is better vs. CEST. Since k/δ increases at lower magnetic fields, this advantage will be more prominent at clinical fields such as 3 T (Fig. 1A). Another important advantage of spin-lock is its insensitivity to any B_0 shift much smaller in magnitude than the spin-lock pulse power, while CEST is highly susceptible to B_0 shifts of only a few Hertz. In addition, the sub-minute temporal resolution of spin-lock MRI (Fig. 2) provides a much higher statistical power for glucose detection as compared to the low temporal resolution of gluco-CEST (~10 minutes in previous studies [1-3]). Unlike MTR_{asym}, which is coupled to other relaxations including T_1, T_2 and magnetization transfer effects [4-6] and usually used in CEST, our phantom results indicate that $R_1\rho$ changes are independent of T_1 and T_2, and provide a quantitative index to glucose concentration changes.

Conclusion Our results show that spin-lock MRI is highly sensitive to the administration of D-glucose and 2DG, provides a quantitative index to glucose concentration changes, and therefore may have significant advantages over gluco-CEST for imaging of glucose transport and metabolism.

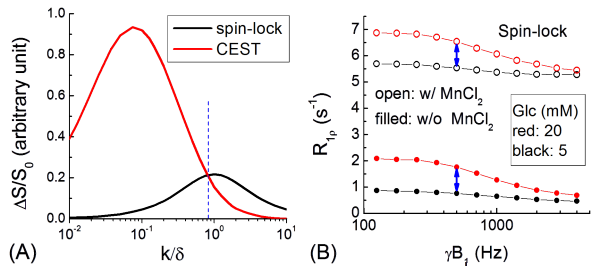

Fig. 1. (A) **Bloch-McConnell simulations** comparing optimal spin-lock and CEST contrast from 10 mM of labile protons as a function of k/δ. (B) **Spin-lock $R_1\rho$ dispersion** of 5 and 20 mM glucose without and with $MnCl_2$.

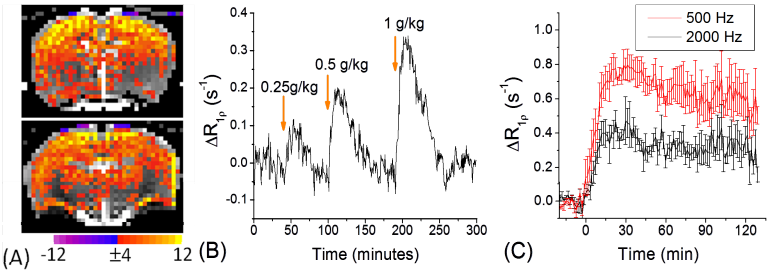

Fig. 2. Rat brain spin-lock $R_1\rho$ changes. (A) Calculated t-maps (2-slices) are due to 0.5 g/kg D-glucose injection with $\gamma B_1 = 500$ Hz. Averaged $R_1\rho$ time courses represent cortical responses during (B) subsequent injection of three different D-glucose doses with $\gamma B_1 = 500$ Hz and (C) during injection of 1 g/kg 2DG with $\gamma B_1 = 500$ and 2000 Hz.

References [1] Walker-Samuel S et al, Nat Med 19:1067 (2013). [2] Chan KWY et al., MRM 68:1764 (2012). [3]. Nasrallah FA et al., JCBFM 33:1270 (2013). [4]. Jin T et al., MRM 68:1056 (2012). [5] Sun PZ, MRM 67:936 (2012). [6] Vinogradov E et al., JMR 229:155 (2013). [7]. Jin T et al., NeuroImage 78:385 (2013). [8]. Trott O et al., JMR 154:157 (2002).