**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 T1, T2 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 (R1) 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 contrast (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 δ = 2500 rad·s⁻¹ (1 ppm at 9.4 T), a labile proton concentration of 10 mM, and water T1 and T2 of 2 s and 50 ms, respectively. Spin-lock contrast was calculated as the difference between T1ρ-weighted signals with and without CE, normalized by signal without irradiation (S0). CEST contrast was calculated as the difference between MTRassym(θ) 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 a 0.4 × 0.4 or 0.5 × 0.5 mm² 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 MnCl2 were dissolved in phosphate buffered saline titrated to pH = 7.0. Spin-lock R1ρ dispersion curves (i.e. R1ρ vs. B1) were measured at 37°C with spin-lock power γB1 = 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. T1ρ-weighted images were measured with and without a spin-lock preparation of γB1 = 500 Hz for 50 ms duration. Paradigm 2: Following 1 g/kg 2DG injection (n=4 rats), three T1ρ-weighted images, one without spin-lock preparation and two with spin-lock power of γB1 = 500 and 2000 Hz for 50 ms, were obtained in an interleaved manner to determine R1ρ dispersion. Time series of R1ρ maps were calculated from these T1ρ-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<<1, but drops quickly when k>>1. In contrast, the sensitivity of spin-lock reaches a peak for intermediate chemical exchange rates (kδ = 1), and is higher than CEST for kδ > ~0.9 (dashed blue line). Figure 1B shows that R1ρ changes due to glucose concentration changes (blue arrows) are independent of water T1 and T2 (modulations due to MnCl2). Fitting this R1ρ dispersion data to a recent theoretical R1ρ model [8], we found that the exchange rate between water and glucose hydroxyl protons is about 5000 s⁻¹, and the averaged chemical shift δ is 1.6 ppm, which is 4000 rad·s⁻¹ at 9.4 T (kδ = 1.25), suggesting spin-lock may be a good choice for glucose detection. In the t-map calculated from spin-lock R1ρ measurement during injection of 0.5 g/kg D-glucose, a widespread increase of R1ρ is robustly observed in the brain (Fig. 2A). Compared to phantom results (Fig. 1B), the cortical R1ρ change corresponds to a 1-2 mM increase in brain glucose concentration, indicating high sensitivity of R1ρ for glucose detection. Figure 2B shows the R1ρ time course during subsequent injections of three different D-glucose doses, and the dose-dependence of the R1ρ increases. With 1 g/kg D-glucose, the peak ΔR1ρ 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 ΔR1ρ 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 γB1 = 2000 Hz, ΔR1ρ 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 kδ 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 B0 shift much smaller in magnitude than the spin-lock pulse power, while CEST is highly susceptible to B0 shifts of only a few Hz. In addition, the sub-minute temporal resolution of spin-lock MRI (Fig. 2) provides a much higher statistical power for glucose detection compared to the low temporal resolution of gluco-CEST (~10 minutes in previous studies [1-3]). Unlike MTRassym which is coupled to other relaxations including T1, T2 and magnetization transfer effects [4-6] and usually used in CEST, our phantom results indicate that R1ρ changes are independent of T1 and T2, 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.

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**Fig. 1.** (A) Bloch-McConnell simulations comparing optimal spin-lock and CEST contrast from 10 mM of labile protons as a function of kδ. (B) Spin-lock R1ρ dispersion of 5 and 20 mM glucose without and with MnCl2.

**Fig. 2.** Rat brain spin-lock R1ρ changes. (A) Calculated t-maps (2-slices) are due to 0.5 g/kg D-glucose injection with γB1 = 500 Hz. Averaged R1ρ time courses represent cortical responses during (B) subsequent injection of three different D-glucose doses with γB1 = 500 Hz and (C) during injection of 1 g/kg 2DG with γB1 = 500 and 2000 Hz.

**References**