Chemical exchange sensitive Spin-lock MRI of deoxyglucose transport and metabolism in brain

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Target Audience Researchers and clinicians interested in MR imaging of glucose and deoxyglucose transport and metabolism.

Purpose Glucose metabolism is a sensitive biomarker for cellular function and many diseases, and is often studied by a glucose analogue, 2-deoxy-D-glucose (2DG). Recent studies showed an increase of chemical exchange-sensitive spin-lock (CESL) MRI signal during administration of 2DG [1,2], with higher sensitivity than the chemical exchange saturation transfer (CEST) technique [2,3]. However, since dynamic change of the rotating frame spin-lattice relaxation rate **($R_1\rho$)** is similar to blood 2DG concentration when 1 g/kg 2DG dose is used [1], it is questionable whether the 2DG-CESL signal change is caused by both the transport and metabolism of 2DG. To answer this question, we acquired CESL data at different injection doses and anesthesia levels. Magnitudes and dynamic properties were compared across different conditions.

Materials and methods All MRI studies were performed at 9.4 T. CESL data were acquired at each rat brain with a single dose of i.v. injection of 2DG. Three sets of experiments were performed: *Paradigm 1*: A dose of 0.25 (n=4 rats) and 0.5 g/kg (n=6) of 2DG were given to determine the dose-dependence of 2DG-CESL MRI. Rats were anesthetized by 1.5% isoflurane. *Paradigm 2*: 2DG-CESL signals were measured on rat brain with 0.25 g/kg 2DG injection (n=6), under low isoflurane anesthesia of 0.5%, and infusion of muscle relaxant pancuronium bromide to suppress animal motion. Both Paradigms 1 and 2 used a volume coil-transmit and surface coil-receive setup, with single-shot spin-echo EPI acquisition and a lower in-plane resolution of 0.5cm×0.5cm. *Paradigm 3*: 2DG-CESL data were acquired on rat brain with 0.25 g/kg 2DG injection (n=3), also under low isoflurane anesthesia of 0.5% with infusion of pancuronium bromide. A volume coil was used for both transmit and receive, with two-shot spin-echo EPI acquisition and a higher in-plane resolution of 0.33cm×0.33cm. Time series of $R_1\rho$ maps were calculated from $T_1\rho$-weighted images measured with and without a spin-lock preparation of γB_1 = 400 Hz for 50 ms duration [1]. For data analysis, region of interest (ROI) was determined in each animal from the cortex area in Paradigms 1 and 2, and in the cortex and corpus callosum for Paradigm 3.

Results Figure 1A compares the dose-dependence of the 2DG-CESL signals under isoflurane anesthesia of 1.5%. The change of $R_1\rho$ from 1g/kg 2DG injection (n=4) was obtained from a recent study [1] and compared with that of 0.25 and 0.5 g/kg injections. Unlike the $R_1\rho$ change of 1g/kg injection which reached a peak at ~20-30 minutes post injection, the $R_1\rho$ increases monotonically for the two lower doses. The averaged $\Delta R_1\rho$ for the initial 20 minutes post injection is almost linearly dependent on the dose, whereas the change of $R_1\rho$ at later time points (>70 mins) are similar for the 0.5g/kg and the 1g/kg doses. The 2DG-CESL signal is strongly dependent on the anesthesia (Fig. 1B) and the change of $R_1\rho$ averaged from 60 to 80 minutes post injection is 43% higher with a 0.5% isoflurane than 1.5%. Region difference can be seen from the $R_1\rho$ change map where a lower threshold of 1.5% change was applied (Fig. 2A), showing large signal change in the cortical region, and less activated pixels in the corpus callosum (green arrows) region and subcortical regions (purple arrow). The time courses obtained from ROIs in the cortical and corpus callosum also showed significant difference (Fig. 2B).

Discussions Recent studies showed that the administration-induced brain CESL signal has minimal contribution from the intravascular blood and osmolality effect, and is mainly due to an increase of the total hydroxyl group [1]. Thus, the measured elevation of $R_1\rho$ with 2DG injection has contributions from the transport of 2DG from blood to the brain, and the phosphorylation product (i.e, 2DG-6-phosphate, or 2DG6P) which accumulates in the cells. In contrast to a previous CESL study in which the $R_1\rho$ increases linearly with the dose of D-glucose injection [1], the dose-dependence of 2DG-CESL signal is more complex, suggesting two mechanisms with different temporal characteristics. The increase of $R_1\rho$ in the initial 20 minutes is dominated by the 2DG transport, whereas at later time periods the signal may be mainly due to the accumulation of 2DG6P. This different time course of 2DG and 2DG6P agrees with a previously MR spectroscopy study [4]. It is plausible that the 2DG transport is not limited by our injecting doses; therefore, the initial $R_1\rho$ increases almost linearly with dose. Because the production of 2DG6P is limited by the availability of intracellular 2DG as well as the cerebral glucose metabolic rate, the accumulation of 2DG6P is slower and does not increase with the injection dose linearly. The observed larger $R_1\rho$ elevation with a lower isoflurane level can be explained by the expected higher metabolism at a lower anesthesia. Also, a higher metabolic rate in gray matter than white matter can explain the difference of $\Delta R_1\rho$ in those regions.

Conclusion Our results show that the 2DG-CESL signal is strongly dependent on the injection dose, anethesia level, and brain regions. It likely contains both transport and metabolisim components and can be used as a biomarker for studies of both processes.

References [1] Jin T et al., J Cereb Blood Flow Metab 34:1402 (2014). [2] Zu Z et al., Magn Reson Imaging 32:1078 (2014). [3]. Nasrallah FA et al., J Cereb Blood Flow Metab 33:1270 (2013). [4]. Kotyk JJ et al., J NeuroChem 53:1620 (1989).

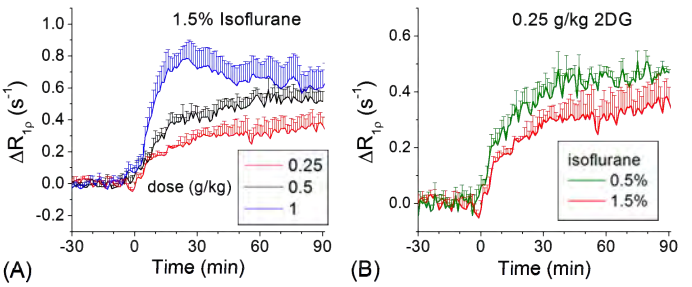

Fig. 1. Comparison of the time courses of the glucoCESL $R_1\rho$ change obtained from the rat brain cortex during injection of 2DG under 1.5% isoflurane for three doses of 0.25, 0.5 and 1g/kg (A), and for the same dose of 0.25 g/kg under 0.5% vs 1.5% isoflurane (B). The arrows indicate the time of injection.

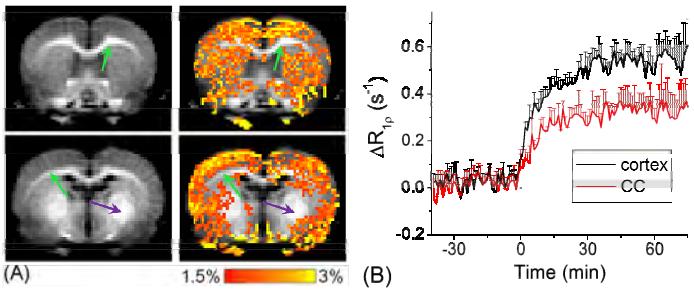

Fig. 2. Comparison of rat brain $R_1\rho$ changes measured at different brain regions with 0.25g/kg 2DG injection under 0.5% isoflurane. $R_1\rho$ percent change maps (two slices) were overlaid on T1-weighted images (A); and the time courses (B) were obtained from ROI at the cortex and the corpus callosum (CC, green arrows).