Chemical exchange sensitive Spin-lock MRI of 3-O-methyl-D-glucose transport in brain

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

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, the toxicity of 2DG is a concern for its clinical and preclinical application. 3-O-methyl-D-glucose (3OMG) is a non-metabolizable glucose analogue with minimal toxicity; therefore, it may have better potential as a contrast agent for the study of glucose transport. In this work, we measured the chemical exchange properties of 3OMG by phantom and the sensitivity of 3OMG-CESL by in vivo experiments.

Materials and Methods: All MR images were acquired at 9.4 T by a single shot spin-echo EPI. *Phantom:* To study the concentration dependence and the relaxation properties, 0, 10, 15, 20, 30 mM of 3OMG with the addition of 0.15 mM of $MnCl_2$ were dissolved in phosphate buffered saline (PBS) and titrated to pH = 7.07. To study the pH-dependence, 20 mM of 3OMG was dissolved in PBS and titrated to pH = 6.3, 6.6, 7.05, and 7.5. Spin-lock $R_1\rho$ dispersion curves ($R_1\rho$ vs. spin locking frequency ω_1) were measured at 37°C with ω_1 = 125 – 4000 Hz. *In vivo:* CESL MRI studies of Sprague Dawley rats were performed with i.v. injection of 3OMG under 1.5% isoflurane anesthesia. Dose of 1 g/kg of 3OMG (n = 6) were given to determine the temporal characteristics of 3OMG-CESL. To determine the dose dependence, four 1 g/kg injections every 30 minutes of 3OMG (n = 5) were given. Time series of $R_1\rho$ maps were calculated from $T_1\rho$-weighted images measured with and without a spin-lock preparation of ω_1 = 400 Hz for 50 ms duration [1]. Images were acquired with 0.5 x 0.5 mm^2 in-plane resolution, 2-mm slice thickness and repetition time of 3 s. For data analysis, region of interest (ROI) was determined in each animal from the cortex area.

Results: Figure 1A compared the dispersion curve of PBS with those of 3OMG at four difference concentrations. The increase of $R_1\rho$ due to 3OMG (vs. PBS only) is linearly proportional to the concentration, and a linear fit of the $R_1\rho$ vs. concentration gave $R_1\rho$ of 0.063 s^{-1}/mM at ω_1 = 500 Hz. Figure 1B compared the $R_1\rho$ dispersion for 3OMG with 4 different pH. The $R_1\rho$ at low ω_1 value reaches maximum for the pH = 7.05 phantom, indicating that 3OMG hydroxyl-water proton exchange is close to the intermediate exchange regime for this pH value [4]. Fitting the $R_1\rho$ dispersion data to a recent theoretical model [4,5], we determined the exchange rate between water and 3OMG hydroxyl protons is 4544 s^{-1} for pH of 7.05 with a chemical shift, δ = 1.4 ppm. In Fig. 2A, the time course of the $R_1\rho$ change during injection of 1g/kg 3OMG was compared with those of D-glucose (Glc) and 2DG obtained from a recent study [1]. The increase in $R_1\rho$ averaged between 10 to 30 minutes after injection is for Glc, 2DG and 3OMG is 0.28 s^{-1}, 0.71s^{-1} and 0.42 s^{-1}, respectively. Unlike Glc which returns to baseline after approximately 60 min, 2DG and 3OMG return to baseline much slower. Specifically, the $\Delta R_1\rho$ is relatively stable for 3OMG for about 1 hour post injection. The non-toxicity of 3OMG implies a high injection dose may be used to increase the sensitivity of CESL signal. Fig. 2B showed the effect of 4 consecutive 1g/kg 3OMG injection. $\Delta R_1\rho$ increases stepwise and the magnitude of increase is almost linearly proportional to the injecting dose.

Discussion: Our phantom results show that 3OMG has similar chemical exchange properties with Glc and 2DG. The $R_1\rho$ per mM concentration is similar to that of Glc (0.066 s^{-1}/mM) but is higher than 2DG (0.05 s^{-1}/mM) reported from a recent study [1], while the hydroxyl water exchange rate is very close to that of Glc and 2DG (4500 to 4700 s^{-1}). The *in vivo* sensitivity of 3OMG-CESL is higher than Glc due to the increase in $\Delta R_1\rho$ by approximately 50% (Fig. 2A). The increase in 3OMG sensitivity is presumably due to the non-metabolizable nature of 3OMG which serves to hold a higher concentration, relative to glucose, in the blood and, therefore, the brain. If long acquisition time is possible (e.g, >40 min), the detection sensitivity can be further enhanced due to it relatively slow return to baseline. Imaging of 3OMG transport in tumor was recently studied by a CEST technique, which reported a higher CEST signal in extracted tumors treated with 3OMG than Glc [6]. Note 2DG has higher sensitivity than 3OMG, likely because the 2DG-CESL signal is a combination of 2DG with it phosphorylated product, i.e, 2DG-6-phosphate, which accumulates in the cells. Despite the lower sensitivity of 3OMG-CESL than that of 2DG, an important advantage of 3OMG is its non-toxic nature and a higher injection dose may be used.

Conclusion: We have demonstrated that 3OMG has similar chemical exchange properties as 2DG and Glc and unique advantages relative to 2DG and Glc for in vivo studies. This glucose analog can be an enticing molecule to study in disease models that affect glucose transport.

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]. Jin T et al., Magn Reson Med 65:1148 (2011). [5] Trott and Palmer, J Magn Reson 154:157 (2002). [6]. Rivlin M et al., Magn Reson Med 72:1375 (2014).

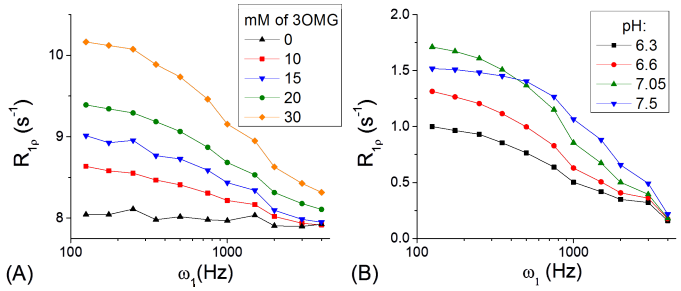

Fig. 1. (A) $R_1\rho$ dispersion is linearly proportional to the 3OMG concentrations (B) $R_1\rho$ dispersion curves of 20 mM 3OMG in PBS titrated to different pH values shows that the 3OMG hydroxyl-water exchange is close to the intermediate exchange regime for pH = 7.05.

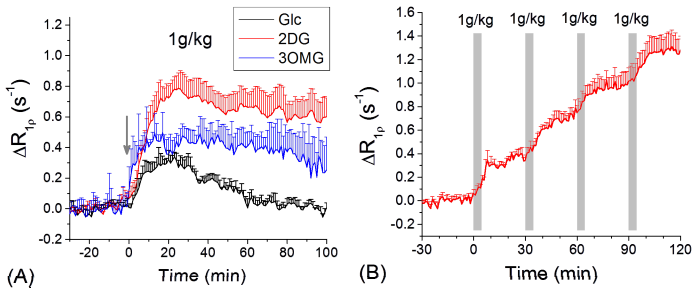

Fig. 2. (A) Comparison of rat brain $R_1\rho$ changes measured with 1g/kg injection of D-glucose (Glc), 2DG and 3OMG, where the injection time is indicated by the gray arrow. (B) Change of $R_1\rho$ measured with 4 consecutive doses of 1g/kg 3OMG injection (indicated by the gray bars) every 30 minutes.