MRI Detection of Brain Glucose Uptake using Gluco-CEST

K-H. Chuang[1], C. Yong[2], Y. Wang[2], G. K. Radda[3], and X. Golay[4]
[1]MRI Group, Singapore Bioimaging Consortium, A*STAR, Singapore, Singapore, [2]MRI Group, Singapore Bioimaging Consortium, A*STAR, Singapore, [3]Singapore Bioimaging Consortium, A*STAR, Singapore, [4]Institute of Neurology, University College of London, United Kingdom

Introduction

Since the seminal work by Sokoloff et al (1), radio-isotope labeled 2-Deoxy-D-glucose (2DG) has been established as a way to measure glucose uptake and metabolism. It is based on the fact that 2DG can be taken up into cells through the same glucose transporters as glucose. It is then phosphorylated by the same hexokinase into 2DG-6-phosphate (2DG6P) but not further into the metabolic cycle. Since the enzyme hydrolyzing 2DG6P back to 2DG has very low amount in the mammalian brain, most of the 2DG will be metabolized to 2DG6P and trapped in the cell, allowing for an imaging method to be used. Various co-labeling of 2DG have been developed to enable its detection by different methods, including ^{18}F labeled fluorodeoxyglucose (FDG) for positron emission tomography(2) and ^{13}C labeled 2DG for NMR(3). However, even at a high dose of 0.5g/kg, the sensitivity of the ^{13}C NMR is still not enough to allow an image to be made. Chemical exchange saturation transfer (CEST) based MRI has recently been used to show amplification factors of detection by up to 500,000 (4), allowing very small quantities of exogenous or endogenous compounds to be measured in vivo (5, 6). In addition, a recent study on glycogen production has shown that glucose should be measured equally well by CEST(7). Since 2DG and glucose shares similar structures, 2DG can potentially be detected in a similar way.

Methods

Animal experiments were approved by the institutional animal care and use committees (BMSI, Singapore). Male Lister Hooded rats (240-350g; n = 4) were fasted for 24 h before imaging. The rats were anesthetized with isoflurane, orally intubated and mechanically ventilated. End-tidal CO_2 was monitored and rectal temperature was maintained at 37 ^{o}C by a feedback-controlled air-heater. 2DG and 2DG6P (Sigma, Singapore) were prepared by dissolution in Milli-Q water. For the phantom study, concentrations from 10 to 75 mM were studied. For the in vivo study, 1g/kg or 0.5g/kg of 2DG was injected via the tail vein in a bolus, followed by repeated scanning for a least 1 h to assess uptake curves.

MRI was conducted on a Varian 9.4 T magnet (Agilent, Inc, USA). Single-shot spin-echo echo-planar imaging was used to acquire a slice crossing the somatosensory area with thickness = 2 mm, 64x32 matrix and FOV= 32 x 32 mm2. A train of saturation pulses of 1.5uT amplitude and 58 ms duration was applied at 33 different frequency offsets spanning ±4ppm to produce the desired CEST effect. To calibrate for B_0 shifting, the WASSR method (8) was used with 0.1uT pulse amplitude and offset frequencies within ± 1ppm. The scan time was 10.2 min per CEST scan and 1.2 min for the WASSR scan, making a temporal resolution of about 11.5 min.

Data was processed using custom-written software in Matlab (Mathworks, USA). The data at each pixel was corrected for the B_0 offset using polynomial fitting in phantom or WASSR in vivo. The z-spectra were calculated by interpolation with cubic spline function and the magnetization transfer asymmetry was calculated by subtraction of the negative frequency offset from the positive part. The intensity of the CEST image was calculated as the integral of the spectral intensity within ±0.25 ppm at a 1ppm, incorporating most of the exchangeable protons from the hydroxyl groups (7), see Fig. 1.

Results and Discussion

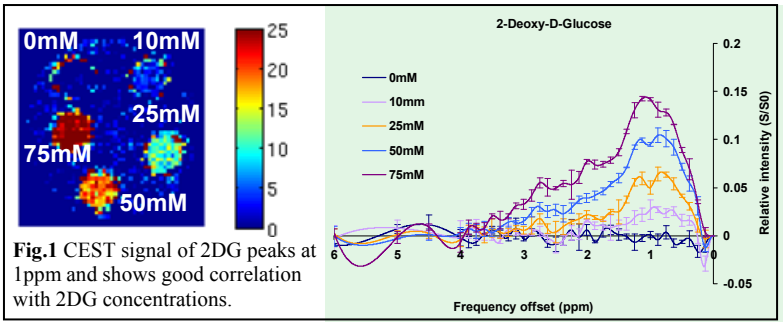

Fig.1 CEST signal of 2DG peaks at 1ppm and shows good correlation with 2DG concentrations.

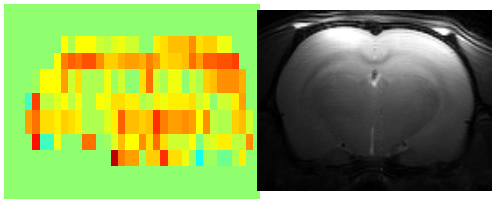

Fig.2 CEST signal change (left) of a rat brain after 2DG injection indicates high 2DG uptake in the cortex and thalamus.

We demonstrated that 2DG uptake can be detected by CEST MRI. The calculated map is very similar to published FDG PET in rat brains. The benefits of this method as compared to 13C NMR is that no additional labeling of the compound is needed, and that it provides an intrinsic molecular amplification factor, allowing for a much larger signal to be detected. This technique therefore opens up new possibilities to map the glucose uptake in vivo for diagnosis and prognosis of diseases like cancer and neurodegeneration.

Reference

1. Sokoloff, L., Reivich, M., Kennedy, C., Des Rosiers, M. H., Patlak, C. S., Pettigrew, K. D., Sakurada, O. & Shinohara, M. (1977) *J Neurochem* **28,** 897-916.
2. Alavi, A., Dann, R., Chawluk, J., Alavi, J., Kushner, M. & Reivich, M. (1986) *Semin Nucl Med* **16,** 2-34.
3. Kotyk, J. J., Rust, R. S., Ackerman, J. J. & Deuel, R. K. (1989) *J Neurochem* **53,** 1620-8.
4. Goffeney, N., Bulte, J. W. M., Duyn, J., Bryant, L. H. & van Zijl, P. C. M. (2001) *J Am Chem Soc* **123,** 8628-8629.
5. Zhou, J., Payen, J. F., Wilson, D. A., Traystman, R. J. & van Zijl, P. C. (2003) *Nat Med* **9,** 1085-90.
6. Hancu, I., Dixon, W. T., Woods, M., Vinogradov, E., Sherry, A. D. & Lenkinski, R. E. (2010) *Acta Radiologica* **51,** 910-923.
7. van Zijl, P. C., Jones, C. K., Ren, J., Malloy, C. R. & Sherry, A. D. (2007) *Proc Natl Acad Sci U S A* **104,** 4359-64.
8. Kim, M., Gillen, J., Landman, B. A., Zhou, J. & van Zijl, P. C. (2009) *Magn Reson Med* **61,** 1441-50.