

MRI of Glutamate Modulation *in-vivo*

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Introduction:

Glutamate (Glu) is the major neurotransmitter for fast excitatory synaptic transmission, and is likely involved in all signal processing functions of the central nervous system (CNS), and are altered in many CNS diseases. Because of its critical role in neurological and psychiatric disorders, Glu may also serve as potential surrogate marker for diagnosis, treatment, and evaluation of therapeutic efficacy. Traditional magnetic resonance spectroscopy (MRS) for detection of Glu requires long acquisition times (8-10 min) and generally provide poor spatial and temporal resolution. Given these shortcomings, there is a clear need for developing improved methods for imaging of these neurotransmitters, preferably with high spatial and temporal resolution using noninvasive and nonradioactive means. This study demonstrates that Glu exhibits a pH-dependent chemical exchange saturation transfer (CEST) effect (GluCEST) between its -NH₂ group and bulk water in a concentration dependent manner. Glu modulation via intravenous injection in a rat brain tumor model resulted in clear elevation of GluCEST as well as a comparable increase in the signal of -CH₂ resonance of Glu measured by single voxel spectroscopy (SVS).

Methods:

In-vitro experiments were performed at 37°C and on 7 T Siemens whole body MRI scanner using a single channel circular polarized (CP) transmit-receive head coil. Glu Phantoms (at different pH and concentrations) in PBS were imaged using a custom-built CEST sequence with frequency-selective and Hanning-windowed saturation pulses (peak B₁=250Hz for 2s) followed by a segmented RF spoiled gradient echo (GRE) readout. Tumor-bearing rats with compromised blood-brain barrier were imaged at a Varian 9.4T MR scanner with a continuous-wave rectangular saturation pulse (B₁=250Hz for 1s). After collecting the baseline CEST map and SVS spectra, the animals were slowly injected with 2.5ml, 100mM Glu solution intravenously. CEST and SVS data were gathered periodically for about 2 hours post injection. GluCEST maps were calculated by normalizing the difference of -3ppm and +3ppm images over -3ppm image. GluCEST contrast maps were corrected for B₀ and B₁ inhomogeneities.

Results:

CEST Z-spectra of 10mM Glu at varying pH are shown in Figure 1A. At lower pH (pH 4.0), the CEST peak of Glu is sharper and centered at 3ppm. At physiological intracellular pH 7.0, Glu showed a broad CEST effect. CEST contrast from Glu at different concentrations and pH 7.0 is shown in Figure 1B. The GluCEST effect is linearly proportional to the Glu concentration in the measured

range. This demonstrates that the GluCEST effect can serve as an index of Glu concentration. Glu modulation of a tumor-bearing rat brain was performed by injecting Glu solution intravenously. Figure 2B and C show GluCEST maps obtained before and 2 hour post Glu injection. GluCEST contrast increases, especially in the tumor region, due to the compromised blood-brain barrier. A comparable elevation in the amplitude of Glu -CH₂ resonance was seen from corresponding SVS (Figure 2D.). Numerical simulations of Bloch-McConnell equations of Glu-NH₂ Chemical Exchange also show that the exchange rate of Glu -NH₂ protons are in the slow to intermediate regime at field strength of 7Tesla.

Conclusion:

CEST effect of Glu has been characterized and its modulation *in-vivo* has been demonstrated by injection of Glu intravenously. The feasibility of quantifying Glu map in human brain and the potential overlap from other brain metabolites are under study. This method provides noninvasive, nonradioactive and high spatial and temporal resolution imaging of Glu modulations *in-vivo*. Future studies using this approach may provide new insights into Glu function and demonstrate its potential as a biomarker for the diagnosis and treatment of CNS disorders.

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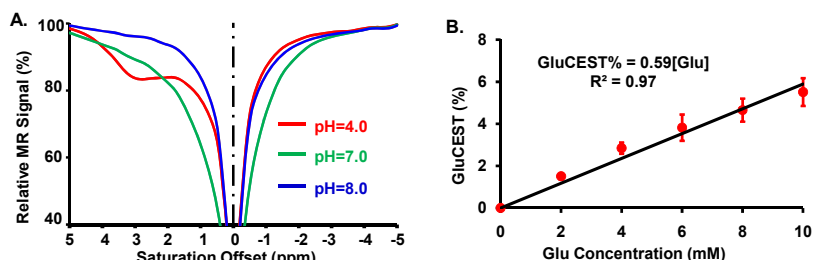


Figure 1. A. 7T Z-spectra of 10mM Glu in PBS at different pH and 37 °C acquired with saturation peak B₁ 250Hz for 2s. B. Percentage GluCEST effect as a function of Glu concentration at pH 7.0 under the same imaging parameters.

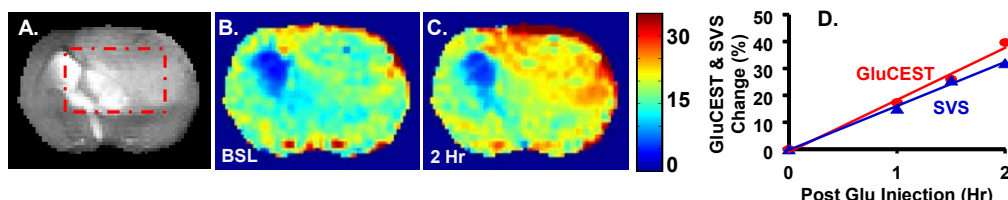


Figure 2. MRI of Glu modulation *in-vivo*. A. Proton image of a tumor-bearing rat brain. B. and C. shows GluCEST maps at baseline and 2 hours post i.v. injection of Glu. D. Correlation of the increment of SVS (taken from the highlighted voxel in A.) with GluCEST before and post Glu injection.