Mapping Glutamate in Mice Using Chemical Exchange Saturation Transfer at 9.4T

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Target Audience: Investigators and clinicians working on the development of image contrast based on chemical exchange saturation transfer (CEST).

Introduction: Both the amide proton transfer (APT) and glutamate CEST (GluCEST) effect in brain is based on the exchange between bounded (amide and amine) protons and free water (1-2). pH maps can been created from the APT effect using the relationship between the exchange rate and pH (1,3). The GluCEST is pH and glutamate concentration dependent. The glutamate concentration could be measured using the pH and the GluCEST effect. A linear relationship between the GluCEST and the pH value (6 ~ 7.5) at a given concentration (at 10 mM, $GluCEST\% = -9.5\,pH + 71.2$), or between the GluCEST and the concentration at a given pH value (at pH 7.0, $GluCEST\% = 0.6\,Glu$), has been previously shown (2). The purpose of this work was to generate high-resolution glutamate images using the APT effect (pH) and the GluCEST effect, which could be generated within one CEST scan.

Methods: CEST Z-spectra images (Two images at offsets -1000 and 1000 ppm were also acquired as reference) of one healthy mouse and one mouse with a U87MG tumor with saturation offsets from -6 to 6 ppm and a step-size of 0.25 ppm were collected on a 9.4T Agilent small animal MR scanner using a 2D FLASH pulse sequence with parameters: TR: 10 ms, TE: 4 ms, FOV: 19.2x19.2 mm^2, matrix: 128x128, saturation time: 1 second, saturation power: 5-μT, and a 5-second delay was used between each image. The CEST spectra were B_0 created by using the minimal value as zero frequency offset. The APT and GluCEST were estimated using the signal difference at ± 3.5 ppm and ± 3.0 ppm, respectively. pH was generated from the APT effect, and glutamate was created from the GluCEST effect and pH value.

Results: The APT map, pH map, GluCEST map, and glutamate map from the healthy mouse and the mouse with tumor are shown in Fig. 1A, B, C, D, and Fig. 2A, B, C, D, respectively. In the healthy mouse, the averaged APT, pH, GluCEST, and Glutamate on the right side are APT = 1.85 ± 0.34, pH = 6.90 ± 0.08, GluCEST = 3.55 ± 0.40, Glu = 6.17 ± 0.97 mM, and left side APT = 1.95 ± 0.34, pH = 6.92 ± 0.08, GluCEST = 3.66 ± 0.40, Glu = 6.46 ± 0.85 mM. In the mouse with tumor, the averaged APT, pH, GluCEST, and Glutamate in the tumor (right) are APT = 2.86 ± 0.46, pH = 7.09 ± 0.07, GluCEST = 5.18 ± 0.58, Glu = 10.91 ± 1.30 mM, and control (left) APT = 1.77 ± 0.29, pH = 6.88 ± 0.07, GluCEST = 3.36 ± 0.46, Glu = 5.74 ± 0.92 mM.

Discussion: In the healthy mouse, the APT, pH, GluCEST, and glutamate are very similar throughout the brain. But the APT, pH, GluCEST, and glutamate level inside the tumor are much higher then on the contralateral side, which is consistent with the literature (1,2). For the first time, a high-resolution glutamate concentration map, not a glutamate-weighted image, was generated.
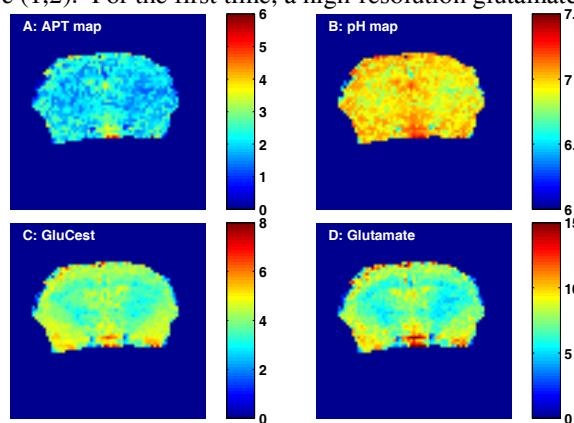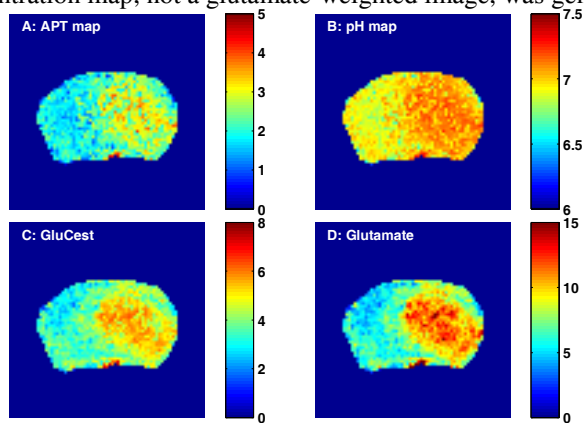

Figure 1. Healthy mouse

Figure 2. Tumor mouse

Conclusion: A high-resolution glutamate map was created by combining the chemical exchange saturation transfer effects from both the APT and GluCEST.

Reference: 1. Zhou J., et. al., Nature Medicine 2003;9:1085-1090. 2. Cai K., et. al., Nature Medicine 2012;18:302-306. 3. McVicar N., et. al., J Cereb Blood Flow Metab 2014;34:690-698.