In vitro study of CEST effects from endogenous metabolites at 3 T and 7 T

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Target Audience: Researchers in the field of chemical exchange saturation transfer (CEST).

Purpose: In biological tissues and organs, many endogenous CEST agents coexist, and their CEST effects often overlap. Characterizing individual CEST effects from different metabolites would be useful for interpreting such overlapped CEST effects and for designing new CEST applications. Here we performed an *in vitro* study to evaluate individual CEST effects arising from common metabolites found in biological tissues and organs. The CEST effects of those common metabolites were compared between 3 T and 7 T, in consideration of the exchange regime and the acidity of the exchangeable protons.

Method: CEST phantom solutions of glutamic acid (Glu), creatine (Cr), *myo*-Inositol (MI), chondroitin sulfate (CS), glycogen, glucose, bovine serum albumin (BSA), glutamine (Gln), γ-aminobutyric acid (GABA), choline (Cho), taurine, and aspartic acid (Asp) were prepared at the concentration of 100 mM and pH 5.6, 6.2, 6.8, 7.4, and 8.0. CEST experiments were performed on whole-body scanners (Siemens, Erlangen, Germany) with a Tx/Rx 15-channel knee coil (Siemens, Erlangen, Germany) at 3 T and with a volume-transmit, 24-element receive head coil array (Nova Medical, Boston, MA) at 7 T. The off-resonance RF irradiation was performed by a train of ten 100 ms-long Gaussian pulses. Their nominal flip angles were 1440° ($B_{1,rms}$ = 1.4 μT), and the frequency offsets were varied from -2500 Hz to 2500 Hz with a step size of 100 Hz. For imaging, a GRE acquisition with centric phase encoding order was used with flip angle = 15°, TR = 24 ms, TE = 3.5 ms, dwell time = 15 μs, FOV = 170 × 170 mm^2, slice thickness = 5 mm, matrix size = 96 × 96. A B_0 map was obtained from the WASSR acquisition [1], in which the off-resonance RF irradiation was implemented by a train of two 100 ms-long 180° Gaussian pulses. The frequency offsets were varied from -500 Hz to 500 Hz with a step size of 20 Hz. For each phantom solution, a Z-spectrum was obtained by averaging the signal intensity, spline-interpolated, and B_0-corrected, from which the MTR_{asym} curves were evaluated. In addition, the ^{1}H NMR spectra were obtained at 11.7 T to identify the exchangeable protons for individual solutions.

Results: **Table 1** summarizes the functional groups carrying the exchangeable protons, the chemical shifts, and the exchange regime at 3 T and 7 T for the metabolites studied in this work, together with pK_a, the measure of the acidity [2]. **Figure 1** presents the MTR_{asym} curves, obtained at 3 T and 7 T, from MI, Cr, Glu, Cho, Asp, GABA, Taurine, and Asp solutions for pH 7.4. Between 3 T and 7 T, Glu, Asp, and GABA showed the most noticeable changes in their CEST effects, which appeared broadly along the frequency offset at 7 T (**Fig. 1b**) but were very small at 3 T (**Fig. 1a**). At both of 3 T and 7 T, the CEST effects from Cr, MI, and Cho were focused at the chemical shifts of their exchangeable protons, while Gln and taurine manifested very little CEST effects.

Discussion: The CEST effects from amine protons could be measured at 7 T if pK_a is high enough so the exchangeable protons fall into the intermediate exchange regime. Cr can be a good candidate for CEST applications at both of 3 T and 7 T due to its slow chemical exchange. Gln has amine protons as well as amide protons but shows very little CEST effects at pH 7.4, for its amine protons belong to the fast exchange regime and the chemical exchange of its amide protons is too slow.

Conclusion: The CEST methodology is believed to benefit from a higher magnetic field due to the increased frequency separation between different proton species, which also helps to detect protons with higher exchange rates. For example, amine protons might not be visible at 3 T, but some of them can be probed at 7 T. However, those amine protons belong to the intermediate exchange regime at 7 T, and their CEST effects may overlap with those from coexisting amide and hydroxyl protons, which may make it complicated to interpret the CEST contrast.

References: [1] Kim M, Gillen J, Landman BA, Zhou J, van Zijl PCM. Magn. Reson. Med. 2009;61:1441. [2] Dawson RMC, Data for Biochemical Research, Oxford, Clarendon Press, 1959. [3] Zhou J, van Zijl PCM. Prog. Nucl. Magn. Reson. Spectrosc. 2006;48:109.

Table 1 Functional groups carrying exchangeable protons, chemical shifts, exchange regime at 3 T and 7 T, and pK_a for the metabolites studies in this work.

Functional Group	Hydroxyl	Guanidine	Amine	Amide
Metabolites	MI, Cho, CS, Glucose, Glycogen	Cr	Glu, Gln, Asp, GABA, Taurine	Gln, CS
Chemical shift [a] (ppm)	0.8 – 1.1 2.2[b], 2.9[b]	~2	2.7 – 3	2.7 for Gln 3.2 for CS
Exchange regime at 3 T[c]	Intermediate	Slow	Fast	Slow
Exchange regime at 7 T[c]	Intermediate	Slow	Intermediate or fast	Slow
pK_a [2]	n/a	11.02	8.7 – 10.4	n/a

[a] From ^{1}H NMR spectra at 11.7 T. [b] For glucose and glycogen only [3]. [c] For pH = 7.4.

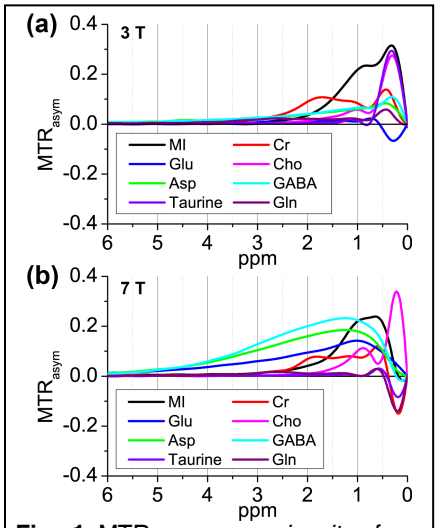

Fig. 1 MTR_{asym} curves *in vitro* from some endogenous metabolites, obtained at (**a**) 3 T and (**b**) 7 T.