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Nuclear Overhauser enhancement (NOE) imaging in the human brain at 7 T☆

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ABSTRACT

Chemical exchange saturation transfer (CEST) is a magnetization transfer (MT) technique to indirectly detect pools of exchangeable protons through the water signal. CEST MRI has focused predominantly on signals from exchangeable protons downfield (higher frequency) from water in the CEST spectrum. Low power radiofrequency (RF) pulses can slowly saturate protons with minimal interference of conventional semi-solid based MT contrast (MTC). When doing so, saturation-transfer signals are revealed upfield from water, which is the frequency range of non-exchangeable aliphatic and olefinic protons. The visibility of such signals indicates the presence of a relayed transfer mechanism to the water signal, while their finite width reflects that these signals are likely due to mobile solutes. It is shown here in protein phantoms and the human brain that these signals build up slower than conventional CEST, at a rate typical for intramolecular nuclear Overhauser enhancement (NOE) effects in mobile macromolecules such as proteins/peptides and lipids. These NOE-based saturation transfer signals show a pH dependence, suggesting that this process is the inverse of the well-known exchange-relayed NOEs in high resolution NMR protein studies, thus a relayed-NOE CEST process. When studying 6 normal volunteers with a low-power pulsed CEST approach, the relayed-NOE CEST effect was about twice as large as the CEST effects downfield and larger in white matter than gray matter. This NOE contrast upfield from water provides a way to study mobile macromolecules in tissue. First data on a tumor patient show reduction in both relayed NOE and CEST amide proton signals leading to an increase in magnetization transfer ratio asymmetry, providing insight into previously reported amide proton transfer (APT) effects in tumors.

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Introduction

Chemical exchange saturation transfer (CEST) (Aime et al., 2009; Ali et al., 2009; Guivel-Scharen et al., 1998; Hancu et al., 2010; Sherry and Woods, 2008; van Zijl and Yadav, 2011; Ward et al., 2000; Zhou and van Zijl, 2006) is a type of magnetization transfer (MT) that employs the transfer of saturation from low concentration exogenous or endogenous pools of exchangeable protons to the bulk water proton pool. These include amide or imino (NH) protons, amine (NH_2) protons, and hydroxyl (OH) protons. Endogenous CEST studies of tissue have allowed the assessment of tumors (Jones et al., 2006; Zhou et al., 2003a, 2008) and ischemia (Sun et al., 2007, 2008; Zhou et al., 2003a) using the amide proton transfer signals of peptides and proteins, called amide proton transfer (APT) MRI. In addition, cartilage CEST studies using amide and hydroxyl protons (Ling et al., 2008) and tissue metabolite studies using OH and NH_2 protons (Cai et al., 2012; Haris et al., 2011; Van Zijl et al., 2007) have been reported. CEST MRI generally involves the acquisition of a so-called saturation spectrum or Z-spectrum (Bryant, 1996) in which the ratio of the saturated (S_{sat}) and unsaturated (S_0) water signals is plotted as a function of saturation frequency difference ($\Delta\omega$) with water. Because the exchangeable protons tend to resonate downfield (at higher frequency) from water and in an effort to remove the symmetric effects from direct water saturation (DS), CEST data are commonly analyzed

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using asymmetry analysis with respect to the water frequency set at $\Delta\omega = 0$ and normalized to unsaturated signal (S_0). Defining the MT ratio (MTR) as 1 – S_{sat}/S_0, this gives:

$$MTR_{asym}(\Delta\omega) = MTR(\Delta\omega) - MTR(-\Delta\omega) = [S_{sat}(-\Delta\omega) - S_{sat}(\Delta\omega)]/S_0. \quad (1)$$

Obviously such an analysis will not be completely correct if any MT effects occur upfield from water. This unfortunately is the case *in vivo* where MT effects of semi-solid tissue components (conventional MT contrast or MTC) cause a strong, broad (tens of ppm) and asymmetric component to the Z-spectrum (Hua et al., 2007a; Pekar et al., 1996; Swanson and Pang, 2003). To complicate matters, a recent study of glycosaminoglycans (Ling et al., 2008) indicated the presence of an additional upfield MT effect. This was attributed to nuclear Overhauser enhancements (NOE) in the NMR spectral range for aliphatic and olefinic protons, ranging from 0 to 5 ppm in the proton spectrum or −5 to 0 ppm in the Z-spectrum (Mori et al., 1998; van Zijl and Yadav, 2011; van Zijl et al., 2003). This was later confirmed by others (Jin et al., 2012; Jones et al., 2011a,b, 2012). Assuming removal of the DS, the asymmetry thus needs to be described by:

$$MTR_{asym}(\Delta\omega) = MTR^{CEST}_{asym}(\Delta\omega) + MTR^{MTC}_{asym}(\Delta\omega) + MTR^{NOE}_{asym}(\Delta\omega). \quad (2)$$

Notice that the MTC effects in (semi)-solid tissue components originate from fast dipolar transfer of NOEs through spin diffusion followed by transfer to water and are hidden in a broad solid-state spectrum. The sharper NOE-based signals measured in the aliphatic and olefinic spectral range, on the other hand, are from mobile macromolecular components with finite linewidth (Mori et al., 1998; van Zijl et al., 2003). The fact that signals originating from non-exchangeable protons appear in the Z-spectrum indicates the presence of a transfer mechanism to water, which has been attributed to either direct through-space dipolar transfer (Jin et al., 2012; Ling et al., 2008) or a relay mechanism via exchangeable protons (Van Zijl and Yadav, 2011). Irrespective of this, the opportunity to detect NOE-relayed signals based in mobile macromolecules offers an opportunity to study such compounds non-invasively with high sensitivity in vivo.

One problem to address is how these NOEs can be detected without too much MTC interference. Fortunately, the relative contributions of MTC and CEST effects can be tuned (Desmond and Stanisz, 2012; Song et al., 2012) by varying saturation pulse length (t_{sat}) and field strength (B_1). We recently showed that this approach can be optimized to detect slower transfer processes, such as due to exchanging amide protons and NOE-relayed effects, with minimal MTC interference (Jones et al., 2011a,b, 2012). This can be accomplished by performing a low-power steady state pulsed CEST experiment and removing the DS contribution using a Lorentzian difference analysis (LD). Here we show that, using this approach, NOE-relayed CEST images can be generated in vivo in the human brain. In order to obtain some insight into the origin of these upfield signals, we studied a buffered solution of the large mobile protein bovine serum albumin (BSA) where the occurrence of CEST effects and NOEs can be observed without interference of semisolid MTC effects and lipid presence. We compared the build-up processes of the CEST and NOE-relayed effects *in vitro* and *in vivo* as a function of separation time between saturation pulses. In addition, to find out whether direct through-space dipolar effects or NOE relay through exchangeable protons cause the transfer of the NOEs to water, we measured the pH dependence of these effects in the BSA solution.

Materials and methods

Phantom preparation

A 10% BSA phantom was created by dissolving 42 g of BSA (66.5 kD; Sigma-Aldrich, St Louis, MO) in 420 mL of phosphate-buffered solution, giving a 1.5 mM solution. The resulting mixture was poured into eight 50-mL Falcon tubes and the pH was titrated (Seven Compact, Mettler Toledo) to 5.70, 6.01, 6.33, 6.61, 7.01, 7.29, 7.60, and 8.00. A ninth tube was filled with PBS as a control. A solution of 0.2% sodium azide (Sigma-Aldrich, St. Louis, MO) was added to each of the nine tubes to preserve the phantoms. All tubes were capped and sealed with Parafilm (Lab Depot, Dawsonville, GA, USA). The phantoms were placed in the 32 channel head coil on the 7 T Philips system.

Human studies

The studies were approved by the Johns Hopkins Medicine IRB and performed on 6 normal controls and one brain tumor patient (30 year old male with a left occipital lobe infiltrating astrocytoma with early anaplastic transformation (histopathology confirmed WHO Grade III)) all of whom provided informed consent. All MRI data were acquired on a 7 T Philips Achieva system (Philips Healthcare, Best, The Netherlands) using a quadrature transmit head coil and a 32 channel Novamedical phased array receive coil (Nova Medical Inc., Wilmington MA). High dielectric pads (Haines et al., 2010; Yang et al., 2006) were placed on either side of the head by the temporal lobes for padding to minimize movement and to flatten the B_1 distribution across the head.

Pulse sequences and data acquisition

Fig. 1a shows the 3D steady-state pulsed (SSP-) CEST sequence used for whole-brain acquisition and described in detail previously (Desmond and Stanisz, 2012; Jones et al., 2012). Every TR contains a single-lobe sinc–gauss saturation pulse followed by gradient echo detection (TE/flip angle = 1.72 ms/12°). We used a low-B_1 approach (1 μT peak amplitude, 25 ms pulse resulting in a flip angle of 208°), which leads to slow build up (~3–4 s) of a saturation steady state that is maintained for the frequency being studied. Whole brain volumes were acquired across at $3 \times 3 \times 3$ mm^3 isotropic resolution using a FOV of 220×220 mm^2 (40 slices). The parallel imaging SENSE factor was 2 × 2 (RL × AP). The time for whole brain acquisition was 10.9 s per irradiation frequency. When switching frequencies to acquire a Z-spectrum, a negligible delay is needed between frequency points (Jones et al., 2012). The saturation frequency offsets (in ppm, relative to the water frequency) were acquired pseudo-randomly: unsaturated (unsat), unsat, unsat, −0.9, −30.0, −3.0, −0.6, 15.0, unsat, −0.8, −0.4, −2.9, −2.8, −1.2, unsat, −2.7, 1.6, −2.5, −1.0, 4.1, unsat, −0.7, −3.4, 4.3, −4.5, 4.7, unsat, 0.2, 40.0, −2.6, 20.0, 0.7, unsat, −4.7, 1.8, −2.2, 4.2, 9.0, unsat, −1.9, 3.2, 3.7, −4.0, 2.1, unsat, −15.0, 30.0, −0.2, −0.5, −4.4, unsat, 3.5, −0.1, −4.2, 3.9, 4.9, unsat, 13.0, −2.1, 1.4, −3.3, 1.1, unsat, 3.3, 1.0, 7.0, 1.7, −4.1, unsat, −3.9, 2.9, 4.5, −3.8, −0.3, unsat, 2.4, −4.9, 4.0, −20.0, 3.1, unsat, −4.3, 3.0, −3.1, −9.0, −3.6, unsat, 0.4, 11.0, −1.6, 0.1, 1.5, unsat, −1.4, −7.0, 3.6, 0.3, −2.4, unsat, 1.2, 2.8, −1.8, −40.0, 5.0, unsat, −1.3, 1.3, −2.0, 2.2, 3.8, unsat, −3.7, −13.0, 4.6, −5.0, 4.4, unsat, 0.9, 2.7, 0.6, 0.5, 0.8, unsat, −4.8, 3.4, −2.3, −1.1, -3.5, unsat, 2.3, 2.5, −1.7, 0.0, −4.6, unsat, −11.0, −3.2, 2.0, 4.8, −1.5, unsat, 2.6, 1.9, unsat, unsat. Total acquisition time was 26 min 24 s. The unsaturated references were acquired using the same sequence as the saturated volume (including the TR), except with the RF saturation pulse turned off.

Fig. 1b shows a variable-delay multi-pulse (VDMP-) CEST sequence in which a train of 32 sinc–gauss saturation pulses (t_{pulse} = 25 ms; 180° each for a B_1 peak amplitude of 0.89 μT) is applied at a certain frequency offset followed by a 2D single-shot gradient echo scan (TR/TE/flip angle = 14 ms/1.72 ms/12°). This sequence was used *in vitro* and

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