In vivo magnetic resonance imaging beyond the MT window using SWIFT-CEST and a Tb-based PARACEST contrast agent

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Introduction

Exogenous paramagnetic chemical exchange saturation transfer (PARACEST) agents create negative contrast (i.e. darkening) in MR images using a combination of proton spin saturation and water molecule exchange with lanthanide ions ($Ln^{3+} \neq$ La, Gd, or Lu) (1,2). If the water molecule exchange rate between the bound and bulk water pools is much slower than their frequency difference (i.e. $k_{ex} << \Delta\omega$) then spin saturation at the shifted bound water frequency ($\Delta\omega$) will cause indirect partial saturation of the bulk water signal through chemical exchange (3). We have recently shown for Eu^{3+}-based PARACEST agents ($\Delta\omega$ = +50 ppm) that the same water molecule exchange that enables the CEST effect can also facilitate severe bulk water line broadening via the T_2-exchange (T_{2ex}) mechanism (4). T_{2ex} can significantly reduce the bulk water T_2 (i.e. negative contrast) even without spin saturation, causing the PARACEST agent to behave like a susceptibility or T_2 agent. This makes "Off" (saturation at $-\Delta\omega$) minus "On" (saturation at $+\Delta\omega$) imaging of PARACEST agents difficult since, when using conventional pulse sequences like Fast Spin-Echo (TE ≈ 10 ms) and Gradient Echo (TE ≈ 1 ms), the regions of uptake appear dark in both images. We have also recently shown that the ultra-short TE times (TE < 10 μs) used in the Sweep Imaging with Fourier Transform (SWIFT) pulse sequence can reclaim the loss in signal due to T_{2ex} to enable fast and sensitive in vivo PARACEST imaging using simple "Off" minus "On" image subtraction (5). Here, we use the same SWIFT-CEST method established in (5) to image a Tb^{3+}-based PARACEST agent in vivo (6). One benefit over Eu^{3+} is that the Tb^{3+} exchange peak ($\Delta\omega$ = -600 ppm) is far outside the magnetization transfer (MT) effect window (7). The MT effect arises from dipolar exchange of protons with endogenous tissue materials, typically spans from +100 to -100 ppm, and can severely reduce the level of contrast produced by PARACEST agents. Compared to Eu^{3+}, Tb^{3+} has an increase in both T_{2ex} (which is proportional to $|\Delta\omega|$) and paramagnetic relaxation enhancement (4,2). Although this will lead to an increase in bulk water line broadening, we show that the ultra-short TE times used in SWIFT are nonetheless able to recapture the loss in signal due to T_2 shortening. We prove this by performing simple "Off" minus "On" CEST imaging of a Tb^{3+}-based PARACEST agent in healthy mouse kidneys at 9.4 T.

Materials and Methods

An Agilent 9.4 T small animal MRI system using the SWIFT-compatible 33 mm diameter surface coil and software from Steady State Imaging were used for in vivo imaging. The internal temperature of the anesthetized 19 g mouse was held at 37 °C during all scans. The Fast Spin-Echo settings were TR/TE = 2500/8.5 ms, ETL = 8, averages = 4, FOV = 32x32x2 mm, matrix = 128x128x1 pixels, scan time = 2m52s. The SWIFT-CEST settings were TR/TE= 1.23 ms/9μs, averages = 1, dummy scans = 512, np = 128, views/spirals = 8192/4, sw = 125 kHz, FOV = 48 mm, scan time = 4m57s. The SWIFT "fatsat" pulse was used to create a 0.5 second long, 20 μT saturation pulse for each nturbo (64 views). A 0.18 mmol/kg dose of Tb^{3+}DOTA-4AmP-4Bu was administered in 175 μL to the healthy mouse via tail vein injection.

Results

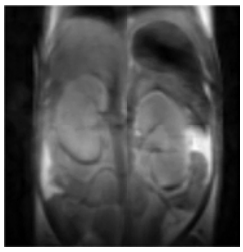

Fig. 1

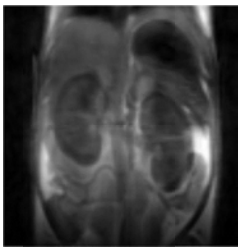

Fig. 2

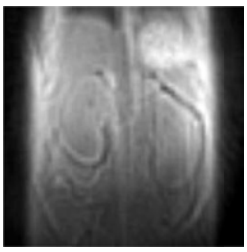

Fig. 3

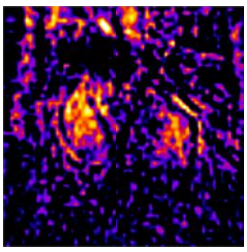

Fig. 4

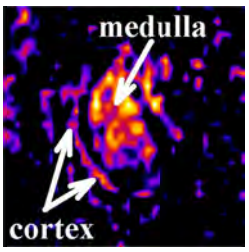

Fig. 5

Fig. 1: A 2 mm thick Fast Spin-Echo coronal slice of the mouse kidneys before injection. **Fig. 2:** The same Fast Spin-Echo slice as in Fig. 1, now at 9 minutes post-injection. A 55% drop in kidney signal due to T_{2ex} from PARACEST agent uptake can be seen, demonstrating the need for ultra-short TE times. **Fig. 3:** A 2 mm thick SWIFT-CEST coronal slice of the same mouse kidneys at 10 minutes post-injection, with saturation at the "Off" frequency (+568 ppm). Note that the T_{2ex} darkening is no longer seen. **Fig. 4:** A SWIFT-CEST "Off" minus "On" image showing a modest PARACEST signal in the kidneys, along with respiration motion noise from the non-gated images. **Fig. 5:** Anatomic details of the right kidney.

Conclusions

At this dose, the average decrease in kidney signal between the "Off" and "On" SWIFT-CEST images was approximately 4%. This relatively low CEST signal is somewhat obscured by the respiration motion noise seen in the CEST image (Fig. 4). Nonetheless, these promising initial results show the first in vivo images of a Tb^{3+}-based PARACEST agent. They also prove that SWIFT-CEST can be used to image PARACEST agents that have bound water frequencies outside of the MT window, where T_{2ex} can be large. We hope to improve the Tb^{3+} agent signal-to-noise ratio by implementing respiration gating, injecting a higher dose of the current Tb^{3+} agent, or by using a different ligand form of the Tb^{3+} agent (Tb^{3+}DOTA-4AmP-8Bu) which has five times the CEST signal at 37 °C (6).

References

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