A NEW TYPE OF RESPONSIVE MRI CONTRAST AGENTS THAT MODULATE T2EX RELAXATION: DETECTION OF NITRIC OXIDE

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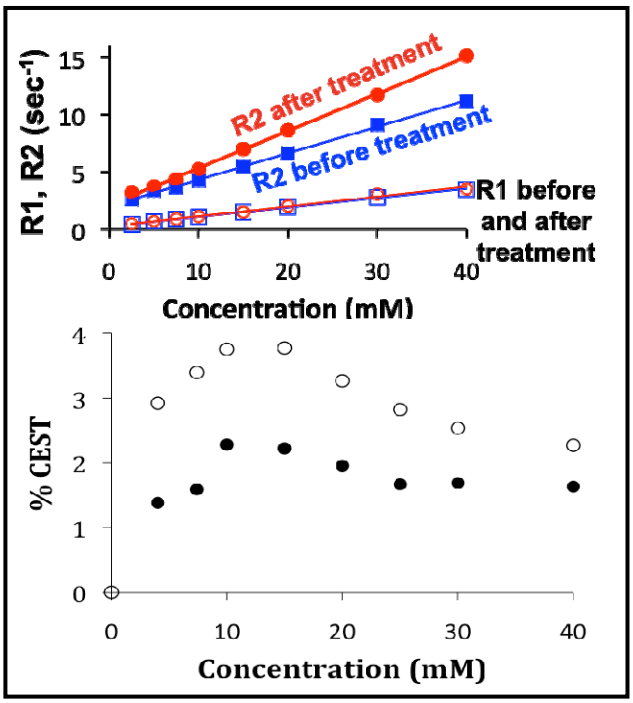
INTRODUCTION: PARACEST MRI contrast agents with a proton that has a large chemical shift and a fast chemical exchange rate can generate T2 exchange relaxation, which negatively impacts the sensitivity of CEST detection [1]. We sought to use this disadvantage as an advantage to create a new class of molecular imaging agents, known as responsive T2ex MRI contrast agents. Specifically, Yb(III)-(1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid)-orthoaminoanilide (Yb-DO3A-oAA) has been shown to be responsive to nitric oxide, but in vivo CEST detection of this agent is difficult due in part to T2ex relaxation caused by the agent [2]. We designed a similar agent, Tm-DO3A-oAA, which has a larger chemical shift and therefore should have a stronger T2ex relaxation effect. A chemical reaction with nitric oxide should modify the chemical exchange rate of the agent and therefore cause T2ex to be responsive to nitric oxide.

METHODS: We synthesized and characterized Tm-DO3A-oAA using previously published methods [3]. This agent was treated for 2 hours with DEA-NONOate that releases nitric oxide [2], and the identity of the agent after treatment was confirmed with mass spectrometry. Treated and untreated samples, and mixtures of treated and untreated samples, were characterized using a 7T Bruker MRI scanner at temperatures ranging from 27°C to 47°C. We acquired CEST MR images and CEST spectra with a saturation time of 6 seconds and a saturation power of 20 μT that ranged in saturation frequency from +100 to -100 ppm. We measured T1 and T2 relaxation rates as a function of concentration from 0 to 40 mM to determine T1 and T2 relaxivities.

RESULTS: The T2 relaxivity increased by 34%, from 0.23 $mM^{-1}sec^{-1}$ before treatment with nitric oxide, to 0.32 mM^{-1} sec^{-1} after treatment with nitric oxide, at 37°C. This change in T2 relaxivity was statistically significant relative to the experimental error of 1.2% for T2 relaxation time measurements. The T1 relaxivity was invariant, changing from 0.082 $mM^{-1}sec^{-1}$ before treatment with nitric oxide, to 0.086 mM^{-1} sec^{-1} after treatment, for a 3.6% change that was statistically insignificant relative to the experimental error of 5.3% for T1 relaxation time measurements. The ratio of T2- and T1-relaxivities changed 34% from 2.81 before treatment to 3.78 after treatment, and this change in the ratio was inherently independent of concentration. The ratio of T2-weighted MR signal to T1-weighted MR signal changed 27.5% as the ratio of untreated and nitric oxide-treated agents was changed form 0% to 100%, which demonstrated that only a single T2-weighted MR image and a single T1-weighted MR image are needed to detect the treatment with nitric oxide. This ratio of T2- and T1-relaxivities decreased by 2.2% per °C of temperature change from 27 to 47°C, indicating that this ratio was only mildly dependent on temperature.



For comparison, the CEST effect of Tm-DO3A-oAA increased as the concentration was increased from 0 to 10 mM, and then decreased as the concentration was further increased from 10 mM to 40 mM. This non-monotonic behavior was attributed to T2ex relaxation that increased with increasing concentration, and this non-monotonic behavior prevents the agent from being used to measure response to nitric acid in a concentration-independent manner. Furthermore, the maximum CEST generated with a concentration of 10 mM was 3.8% and 2.3% for the amine and amide, respectively, which is impractical for CEST detection at typical in vivo CEST MRI noise levels.

DISCUSSION: These results demonstrate that Tm-DO3A-oAA can detect nitric oxide via T2-weighted MRI. Importantly, the T1 relaxivity does not change after treatment with nitric oxide, and the ratio of T2 and T1 relaxivities is independent of concentration, so that this ratio can detect nitric oxide in a concentration-independent manner. This ratio of T2 and T1 relaxivities is only mildly dependent on temperature, which improves the specificity of the nitric oxide detection. These results demonstrate that a new class of responsive MRI contrast agents can be developed based on changing the chemical exchange rate of an agent and obtaining T2-weighted and T1-weighted MR images.

REFERENCES:

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