Development of PARACEST MRI Contrast Agents to Assess Cartilage Glycosaminoglycan Concentrations

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Abstract

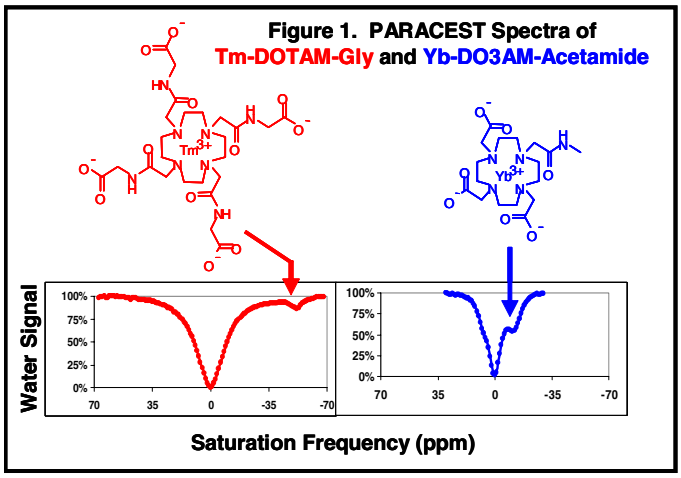
We have developed negatively-charged and charge-neutral PARACEST MRI agents to more accurately quantify the glycosaminoglycan content in cartilage. We can selectively detect a minimum CEST agent concentration of 2.8mM at a minimum 5% change in MR signal. The ratio of PARACEST agent concentrations that are simultaneously applied to healthy and GAG-depleted ex vivo rabbit cartilage samples correlated well with correlated with histopathological measurements. These results are being used to develop a single quantitative assessment of glycosaminoglycan content in cartilage during a single MRI scan session.

Introduction:

Glycosaminoglycans (GAG) are naturally present in healthy cartilage tissue, and the loss of GAG from cartilage is an early marker of osteoarthritis. Magnetic resonance imaging (MRI) methods can evaluate the spatial distribution of GAG concentrations in cartilage by detecting the relative distribution of a negatively charged MRI contrast agent that is repulsed by negatively charged GAG (1). Improved quantification can be obtained by comparing distributions of a charged MRI contrast agent and a neutral agent, which accounts for variable pharmacokinetics of contrast agents in cartilage that are unrelated to charge properties (2). However, standard MRI agents can't be selectively detected, requiring the serial administration of charged and neutral agents, which creates technical challenges and can compromise the accurate comparison of the MRI agents. To address this problem, we've synthesized a negatively charged MRI contrast agent, Tm-DOTAM-Gly, and a neutral agent, Yb-DO3AM-Acetamide, that can be selectively detected via the mechanism of paramagnetic chemical exchange saturation transfer (PARACESTCEST). Selective detection provides the opportunity to detect BOTH agents during the same scan session, which can improve quantification and patient comfort.

Methods:

Tm-DOTAM-Gly and Yb-DO3AM-Acetamide were synthesized and chelated using standard protocols (3). Healthy and GAG-depleted ex vivo rabbit cartilage were soaked with a solution of one or both PARACEST agents at physiologically-relevant concentrations (3.0 mM - 25 mM); chemical solutions were also prepared to evaluate the PARACEST effect. Selective-saturation MRI methods were used to quantify the concentrations of PARACEST agents (4). Similar studies were performed with Gd-chelated compounds and MR relaxivity experiments. The MR results were correlated with histopathological measurements of GAG concentrations in each cartilage sample.



Results and Discussion:

Relaxivity experiments with Gd-chelates verified that contrast agent concentrations in cartilage are not dependent only on charge-charge repulsion with GAG. Yet these relaxivity experiments demonstrated that a relative comparison of negatively charged and neutral agents may still accurately quantify GAG content. PARACEST experiments verified that Tm-DOTAM-Gly and Yb-DO3AM-Acetamide show PARACEST effects after selective irradiation at -51 and -16ppm, respectively. Our results indicate that we can measure a minimum CEST agent concentration of 2.8mM at a minimum 5% change in MR signal, which is less than the concentrations of contrast agents typically measured in cartilage. Preliminary results show that the ratio of PARACEST agent concentrations in healthy and GAG-depleted ex vivo rabbit cartilage samples correlated well with correlated with histopathological measurements. Additional studies are ongiong to establish statistical significances and evaluate the PARACEST measurements at different temperatures and pH conditions.

Conclusions:

This work demonstrates that PARACEST agents can be used to more accurately and more easily assess glycosaminoglycan concentrations within cartilage. This work also demonstrates that PARACEST agents can be selectively detected, so that multiple MR agents can be administered during the same scan session and one of the agents can serve as an internal control.

References

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