Improved Detection of Glycosaminoglycan Content in Cartilage Using PARACEST MRI Contrast Agents

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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, Yb-DO3A-Asp, and a neutral agent, Tm-DO3AM-AM, that can be selectively detected via the mechanism of Paramagnetic Chemical Exchange Saturation Transfer (PARACEST). Selective detection provides the opportunity to detect BOTH agents during the same scan session, which can improve quantification and patient comfort.

Methods

1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid–aspartate (DO3A-Asp) and 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid–acetamide (DO3A-AM) were synthesized and characterized with MS and NMR spectroscopy (Figure 1). Chelates of Yb-DO3A-Asp and Tm-DO3A-AM were obtained using standard protocols, and PARACEST spectra of these chelates were measured using a modified presaturation pulse sequence on 600 MHz Varian NMR scanner (Figure 2). Ex vivo rabbit ear cartilage was treated with trypsin (Sigma Aldrich) for 10 minutes at 32°C, and then soaked overnight with 20 mM of both contrast agents. PARACEST MR images of the soaked cartilage sample were acquired with a 7T Bruker Biospec animal MRI scanner equipped with a surface coil (Figure 3B and C).

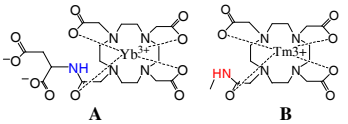

Figure 1. Structures of the PARACEST MRI contrast agents. A) negatively charged Yb-DO3A-Asp; b) charge neutral Tm-DO3A-AM.

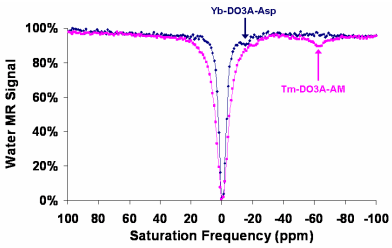

Figure 2 CEST spectra of Yb-DO3A-Asp and Tm-DO3A -AM

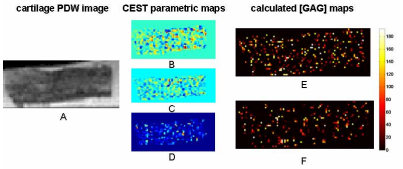

Figure 3 Detection of GAG content in ex vivo cartilage. **A**) proton density weighted image of the cartilage tissue; **B**) PARACEST parametric map of Yb-DO3A-Asp; **C**) PARACEST parametric map of Tm-DO3A-AM; **D**) ratiometric map of **B** and **C**; **E**) parametric map of relative GAG concentration calculated from **B**; **F**) parametric map of relative GAG concentration calculated from **D**.

Results and Discussion:

The PARACEST effects of Yb-DO3A-Asp and Tb-DO3A-AM were observed at -15ppm and -62ppm, respectively, so that each PARACEST agent can be selectively detected in the presence of the other agent. This selectivity is further confirmed by acquiring PARACEST MR images of each agent in the presence fo the other agent within the same cartilage tissue sample. Because the ratio of PARACEST effects within the same sample is linear with the ratio of contrast agent concentrations, and because the Donnan Field Charge Theory employs a ratiometric approach, the PARACEST MR images can be directly used to calculate parametric maps of relative GAG concentrations (Figure 3E). This methodology can also be used to calculate the parametric map fo GAG concentratiosn based on the ratio of the negatively charged contrast agent and neutral contrast agent (Figure 3F). Although detection sensitivity needs to be improved, these preliminary results clearly indicate that GAG content may be overestimated in cartilage tissues without incorporating a neutral contrast agent.

Conclusions:

We have developed two new PARACEST MRI contrast agents to improve detection of the GAG content cartilage tissues. The negatively charged Yb-DO3A-Asp can be used for GAG detection following the standard dGEMRIC methodology. Both agents can be simultaneously applied to the same cartilage sample, which may improve the determination of GAG content.

Reference:

1. Zhang S, Merritt M, Woessner DE, Lenkinski RE, Sherry AD. Acc. Chem. Res. 2003, 36:783-790.
2. Gillis A, Gray M, Burstein D. Magn. Reson. Med., 2002,48:1068–1071 .