A Smart PARACEST MRI Contrast Agent for Nitric Oxide Detection

G. Liu[1], M. D. Pagel[2]

[1]Biomedical Engineering, Case Western Reserve University, Cleveland, OH, United States, [2]Case Western Reserve University, Biomedical Engineering, Cleveland, OH, United States

Abstract

We have developed a "smart" PARACEST MR agent that changes its PARACEST effect only after chemical modification by Nitric Oxide. The amine and amide of Yb-DOTA-ortho-Aminoanilide show a PARACEST effect, but reaction with Nitric Oxide converts these functional groups to a hydrazine that doesn't demonstrate a PARACEST effect. This PARACEST MR agent can also be used to measure pH. This example constitutes a fundamentally new technology platform for "smart" MR agents.

Introduction:

Molecular imaging has been shown the great potential for disease diagnosis. However, relaxivity-based MRI contrast agents have many inherent limitations. To circumvent these limitations, we propose a novel technology platform based on Paramagnetic Chemical Exchange Saturation Transfer (PARACEST) to create "smart" MRI agents. Here, we present a new PARACEST agent based on a DOTA-oAA motif that detects Nitric Oxide (NO), which is a biomarker of Nitric Oxide Synthases that are involved in a variety of biological processes and disease states.[1]

Methods:

The "smart" NO deactivable MRI contrast agent was synthesized from 1,4,7,10-Tetraazacyclododecane -1,4,7,10-tetraacetic acid o-Aminoanilide (DOTA-oAA) and chelated with lanthanide (III) (e.g. Yb, Tm, and Er) to obtain highly shifted exchangeable protons from amine and amide functional groups. PARACEST spectra were assessed by a modified presaturation pulse sequence on 600 MHz Varian NMR scanner.[2] The deactivation of PARACEST properties by NO was assessed by same NMR conditions in the solution of NONOate (a NO donor). The PARACEST effect of Ln-DOTA-oAA before and after reaction has been evaluated at pH of 3-10, temperatures of 5-37ºC, and concentrations of 20 – 200 mM.

Results and Discussion:

We have obtained 2 PARACEST effects from the amine and amide of Yb-DOTA-oAA at +8 ppm and -11 ppm, respectively (Figure 1). The agent shows no PARACEST effect after reacting with NO. Yb-DOTA-oAA shows different degrees of PARACEST from the amine and amide at different pH values, which can be used to measure a wide range of pH with a high dynamic range (Figure 2). The sensitivity of Yb-DOTA-oAA is 11.2 mM and 18.8 mM for saturation of the amine and amide, respectively, at the 5% MR signal change threshold.[3] We are developing additional strategies to improve sensitivity for in vivo applications. To validate that disappearance of the PARACEST effect of Yb-DOTA-oAA is related to reaction with NO during in vivo studies, we are synthesizing a control agent that has the same pharmacokinetics but does not react with NO.

Conclusion:

We have characterized the novel MRI agent Yb-DOTA-oAA agent and proved the ability of this designed agent to detect NO through molecular imaging. These results demonstrate that "smart" PARACEST MRI agents represent a fundamentally new technology platform for molecular imaging.

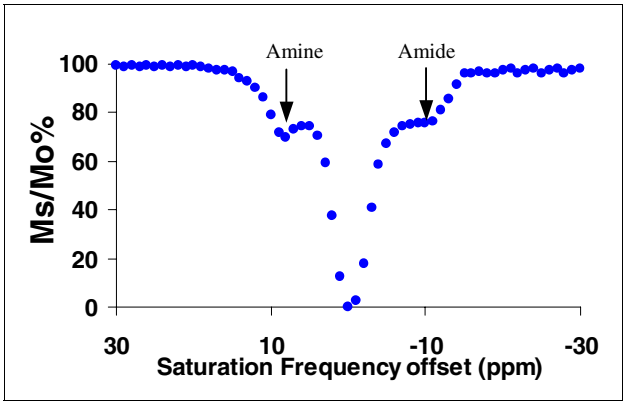

Figure 1: PARACEST Spectrum of Yb-DOTA-oAA

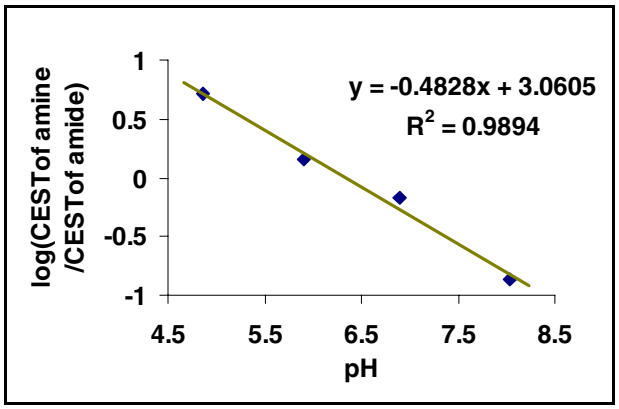

Figure 2: pH Dependence of the PARACEST Effect of Yb-DOTA-oAA

References

1. John W. Coleman. Int. Immunopharmacol, 1:1397-1406 (2001).
2. Aime S, Barge A, Castelli D, Fedeli F, Mortillaro A, Nielsen F, Torreno E. Magn Reson Med 47: 639-648 (2002).
3. Zhang S, Merritt M, Woessner E, Lenkinski R, Sherry AD. Acc Chem Res, 36:783-790 (2003).