Using T_2-exchange from Dy^{3+}DOTA-based chelates for contrast-enhanced molecular imaging with MRI

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INTRODUCTION

Magnetic resonance imaging (MRI) offers superior anatomic resolution and soft tissue contrast compared to x-ray computed tomography, making it an excellent tool for cancer imaging studies. The endogenous contrast created by the varying T_1 and T_2 relaxation times of different tissue types can be greatly enhanced by the use of exogenous contrast agents. Currently, the effectiveness of MRI for functional and molecular imaging is limited due to the lack of highly sensitive molecularly targeted contrast agents. Creating such agents would greatly improve the use of MRI for the early detection and diagnosis of cancer. We have recently shown that lanthanide-based Ln^{3+}DOTA chelates ($Ln^{3+} \neq La^{3+}$, Gd^{3+}, Lu^{3+}) create enhanced T_2 contrast (i.e., darkening) in MRI through the chemical exchange of water molecules (1). The magnitude of this "T_2-exchange" contrast, which adds to the inherent paramagnetic T_2 contrast of the Ln^{3+} ion, reaches a maximum at a specific water molecule exchange rate (see Fig. 2). We have also recently demonstrated that T_2-exchange contrast can be increased by several orders of magnitude through simple linear polymerization of the Ln^{3+}DOTA chelate (2). We hypothesize that by using these methods, a highly sensitive molecule-sized T_2 contrast agent can be created. The transverse relaxivity (r_2) would be an order of magnitude greater than any currently existing contrast agent (e.g., super paramagnetic iron oxide nanoparticles), while retaining the advantages of using small molecules rather than nanoparticles for improved biological targeting, uptake, and clearing.

METHODS

Four different monomer versions of Dy^{3+} chelates were synthesized (DyTETA, DyDOTA, DyDOTA-$(gly)_2$, DyDOTA-$(gly)_4$) each having a different water molecule exchange rate at 37 °C. The Dy^{3+} ion was chosen because it has the largest bound water chemical shift ($\Delta\omega$) and one of the largest paramagnetic relaxation enhancements (PRE) of the lanthanides (second only to Gd^{3+}). Both characteristics, combined with the ideal water molecule exchange rate, will maximize the amount of T_2 contrast that can be achieved on a per molecule basis (r_{2ex} approximately 16 s^{-1} mM^{-1}, see Fig. 2). The total r_2 (i.e., T_2 versus concentration) for each chelate was measured in vitro on an Agilent 400 MHz NMR system using the Carl-Purcell-Meiboom-Gill sequence. Initial in vivo images were acquired using an Agilent 9.4 T animal scanner during glomerular filtration of each agent in healthy mice to assess the sensitivity of each agent (TR/TE = 2500/8.5 ms, echo train = 8, averages = 4, FOV = 32x32x2 mm, matrix = 128x128x1 pixels, scan time = 2m52s).

RESULTS

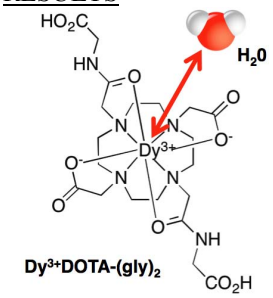

Fig. 1

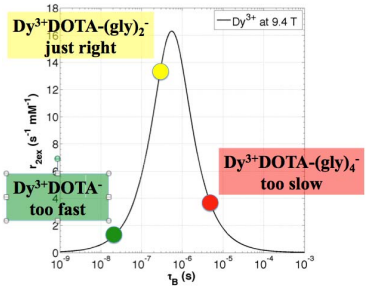

Fig. 2

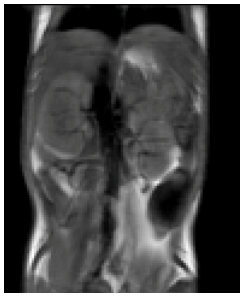

Fig. 3

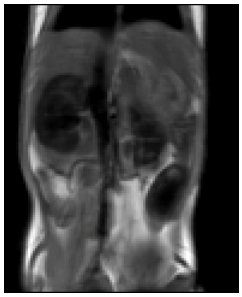

Fig. 4

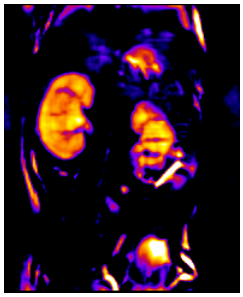

Fig. 5

Fig. 1: A schematic showing the structure of DyDOTA-$(gly)_2$ and water molecule exchange with the inner sphere of the Dy^{3+} ion. **Fig. 2:** A "Swift-Connick" plot showing the relation between the relaxivity due to water molecule exchange (r_{2ex}) and the bound water lifetime (τ_B). The measured intermediate exchange rate of DyDOTA-$(gly)_2$ gives the highest r_{2ex} value of the three chelates at 37 °C. **Fig. 3:** MRI Fast Spin-Echo images of healthy house kidneys before injection, and **Fig. 4:** 15 minutes after a 0.1 mmol/kg intravenous dose of DyDOTA-$(gly)_2$. **Fig. 5:** A difference image (Fig. 3 minus Fig. 4) revealing a 60% drop in kidney signal intensity due to the presence of the DyDOTA-$(gly)_2$ agent.

CONCLUSIONS

By using chemical principles to adjust the water molecule exchange characteristics of each chelate, highly sensitive T_2-exchange MRI contrast agents can be designed and evaluated. Previous examples of Dy^{3+}-based T_2* chelates relied primarily on the paramagnetic effects of the lanthanide ion to create contrast in vivo (3,4). The results here represent the first time the water molecule exchange has been adjusted to maximize the T_2-exchange contribution to the total transverse relaxivity (r_2), thereby greatly increasing the overall sensitivity of the T_2 contrast agent. Such T_2-exchange systems can be polymerized to even further enhance the molecular sensitivity of these agents by 100-fold or more (r_2 > 1600 s^{-1} mM^{-1}). One can also attach molecular targeting groups (e.g., NER2/neu and PSMA) to the linear backbone of such polymers for targeting specific receptors that are over-expressed on many types of cancer cells. These novel T_2-exchange chelates have the potential to be highly sensitive molecule-sized MRI contrast agents that could accurately image the location and size of cancerous lesions and differentiate between indolent and aggressive forms, thereby performing disease staging entirely non-invasively.

REFERENCES

(1) Soesbe TC, et al., MRM 2011;66:1697-1703.
(2) Wu YK, et al., JACS 2008;130:13854-13855.
(3) Saeed M, et al., Radiology 1989;173:763-767.
(4) Roberts TPL, et al., Investigative Radiology 1994, 29:S24-S26.