Doping Gd-DTPA Solution with Water-Soluble Fullerene $C_{82}(OH)_n$ Increases the T_1 Relaxation Rate of Water Proton: In vitro and In vivo Studies

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Introduction

With the advent of gadolinium (Gd)-based MRI contrast agents, many efforts have been given for the development of new complex compounds of Gd, such as water-soluble metallofullerenes $Gd@C_{82}(OH)_{40}$ and $Gd@C_{60}[C(COOH)_2]_{10}$ [1,2]. It has been shown that metallofullerenes often possess much higher relaxivity than the commonly used Gd-chelate complexes [1,2], an attribute that may be associated with the unique physical/chemical properties of fullerene. In this study, we investigated the effect of water-soluble empty fullerene cage $C_{82}(OH)_n$ on the T_1 relaxation rate of water proton in Gd-DTPA solution by both in vitro and in vivo measurements.

Materials and Methods

All MR measurements were carried out a 4.7T/30cm Bruker Biospec scanner equipped with actively shielded gradients. A 75mm-diameter Bruker volume coil was used for both excitation and reception.

In vitro study: Commercially available Gd-DTPA solution (i.e, Magnevist) was mixed with custom-synthesized $C_{82}(OH)_n$ ($n\approx36$) stock solution and diluted by saline. The concentration of Gd-DTPA in all samples was kept constant at 0.1mM, while that of $C_{82}(OH)_n$ varied at 0, 0.05, 0.1, and 0.15mM. T_1 measurement was performed on bundled sample-filled 5mm NMR tubes using an inversion-recovery spin echo imaging sequence with FOV 3×3 cm^2, matrix size 64×64, TR/TE 10s/12ms, slice thickness 2mm and 9 TI values ranging from 15ms to 9s.

In vivo study: Six male Wistar rats (150-180g) were used. Each rat was anesthetized by i.p. injection of chloral hydrate (20%, 0.3ml/100g body weight), and catheterized in the right femoral vein for contrast agent injection. Abdominal T_1-weighted spin echo images were acquired continuously before and after intravenous injection of either 0.75ml of 1mmol/L Gd-DTPA solution (N=3) or mixed solution 0.75ml of 1mmol/L Gd-DTPA and 0.25ml of 0.4mmol/L $C_{82}(OH)_n$ (N=3). The imaging parameters were: FOV 5×5cm^2, matrix size 128×128, TR/TE 300ms/14ms, slice thickness 1.5mm and 5 averages.

Results

The T_1 relaxation rate of water proton (R_1) in the mixed solution of Gd-DTPA and $C_{82}(OH)_n$ as a function of $C_{82}(OH)_n$ concentration is shown in Fig. 1. Figure 2 shows the T_1-weighted abdominal images of two rats before and 7 minutes after injection of contrast agents. In the rat injected with Gd-DTPA only (Fig. 2, rat1), the signal enhancements observed for renal cortex, renal calyces and liver were 9.6%, 46.4% and 2.4%, respectively. In the rat injected with Gd-DTPA/$C_{82}(OH)_n$ mixture (Fig. 2, rat2), the signal intensities of renal cortex, renal calyces and liver increased 37.9%, 163.3% and 4.8%, respectively. Half hour after injections, the signal enhancements in renal cortex, renal calyces and liver were 1.7%, 27.8 % and -1.6% for the Gd-DTPA injected rat, respectively, and 35.3%, 216.5% and 3.2% for the Gd-DTPA/$C_{82}(OH)_n$ mixture injected rat.

Discussion

The results of the phantom experiments show that T_1 relaxation rate of water proton in $C_{82}(OH)_n$-doped Gd-DTPA solution increases linearly with the concentration of $C_{82}(OH)_n$. A putative non-covalent interaction between Gd-DTPA and $C_{82}(OH)_n$, which slows down the rotational correlation time of either Gd-DTPA or water, or both, and leads to increased exchange rate, might underlie the observation. Compared to the rats injected with the same dose of Gd-DTPA alone, the rats injected with Gd-DTPA/$C_{82}(OH)_n$ mixture showed stronger signal intensity enhancement in both kidney and liver (Fig. 2), especially in the renal calyces where the signal enhancement was almost 4 times of that with Gd-DTPA injection. Signal enhancement caused by Gd-DTPA/$C_{82}(OH)_n$ mixture injection also lasted much longer than that caused by Gd-DTPA injection, indicating a longer blood retention time and altered biodistribution of Gd-DTPA when interacted with $C_{82}(OH)_n$. The nature of the interaction between Gd-DTPA and polyhydroxyl fullerene needs further investigation.

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References: 1) Mikawa M. et al, *Bioconjugate Chem*., 12:510-514 (2001). 2) Bolskar RD. et al, *J. Am. Chem. Soc.*, 125:5471-5478 (2003).

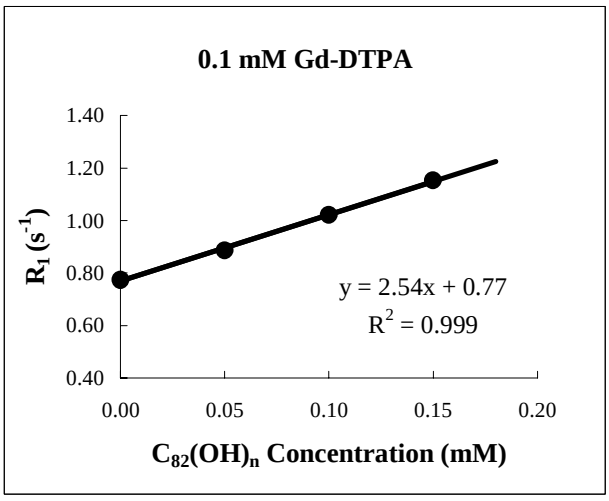

Figure 1. T_1 relaxation rate of water proton (R_1) in the mixed solution of Gd-DTPA and $C_{82}(OH)_n$ has a linear relationship with the $C_{82}(OH)_n$ concentration.

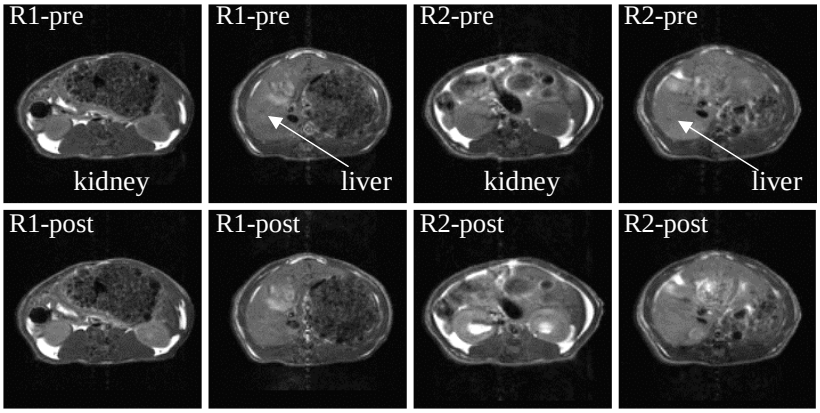

Figure 2. T_1-weighted abdominal images of two rats (R1 and R2) showing the kidneys and the liver before (-pre) and 7 minutes after (-post) intravenous injection of contrast agents. R1: 0.75ml of 1mmol/L Gd-DTPA; R2: 0.75ml of 1mmol/L Gd-DTPA mixed with 0.25ml of 0.4mmol/L $C_{82}(OH)_n$.