Liver Directing Uridine-based Paramagnetic Amphiphilic T1 MRI Contrast Agent with High Relaxivity

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Introduction

Magnetic resonance imaging (MRI) is a powerful noninvasive technique that provides high quality three dimensional images of tissues, including information on anatomy, function, and metabolism of tissue *in vivo*. The chelated Gd^{3+} metal ion improves imaging contrast by increasing the longitudinal relaxation time (T_1) of proximal water protons, which appear brighter in the T_1-weighted image. Current advanced medical diagnosis techniques stipulate high-resolution images with a high magnetic field scanner; however, current Gd^{3+}-based contrast agents (CAs) ligated with polyamino carboxylate are incapable of meeting requirements as they do not have optimal relaxivity profiles at high magnetic fields. This requirement drives the research for smart contrast agents with high relaxivities (r_1) for better tissue contrast at high magnetic fields and non-covalent binding affinity for human serum albumin (HSA) to enhance *in vivo* retention time in MR angiography applications.

Materials and methods

We have chosen a nucleoside as a molecular platform with Gd-DTPA to generate a MRI contrast agent. The relaxation efficiency of these newly synthesized amphiphilic MR CAs was determined by measuring longitudinal relaxivity (r_1) and transverse relaxivity (r_2) at 20 (0.47 T) and 60 MHz (1.41 T) in phosphate buffered saline (PBS) at 36°C, considering clinically prescribed conditions as shown in Table 1. In vivo MRI was performed by using a 4.7 T MRI system (Biospec 47/40; Bruker, Ettlingen, Germany). A spin-echo (SE) pulse sequence was used with the following parameters: TE/TR = 10/400 ms, number of average = 4, matrix size = 256 × 256, and slice thickness = 1 mm, and field of view = 50 × 30 mm^2 .

Results and discussion

We have synthesized uridine nucleoside-based amphiphilic gadolinium complexes as MRI contrast agents. The highest relaxivities achieved were 30.3 and 23.4 $mM^{-1}s^{-1}$ in PBS (pH 7.4) at 0.47 and 1.41 T, respectively, for LGd3. The new complexes demonstrated binding affinity towards HSA with further enhanced relaxivity. Moreover, the relaxivity of amphiphilic CA LGd3 can change depending on the pH of solution. *In vivo* pharmacokinetics of the novel complex LGd3 showed that the complex is highly specific for hepatocytes causing excretion into bile ducts, gall bladder, and intestines, and therefore it may be a highly potential T_1 contrast agent to provide small lesions in liver. LGd3 is first example of a self-assembled paramagnetic amphiphilic with high relaxivity, significant binding ability with HSA, pH response and highly liver specific among other reported amphiphilic gadolinium-based contrast agents. These new uridine-based amphiphilic CAs represent an important and highly efficient nanosystem for MRI applications.

Compounds	Relaxivity						
	20MHz (0.47T)				60MHz (1.41T)		
	r_1	r_2	r_2/r_1	r_1[a]	r_1	r_2	r_2/r_1
LGd1	5.10	7.20	1.41	5.62	4.17	21.50	5.15
LGd2	14.70	15.90	1.08	31.90	12.40	32.40	2.61
LGd3	30.30	31.30	1.03	41.00	23.40	55.90	2.47
LGd4	27.10	26.20	0.96	38.50	16.50	47.20	2.86
LGd5	20.10	28.71	1.40	26.40	17.20	49.80	2.89
Magnevist®	4.70	5.60	1.19		3.81	18.80	4.93
Omniscan®	4.41	5.60	1.26		3.68	19.60	5.32

Table 1. Relaxivities (r_1 and r_2) (in units of $mM^{-1}s^{-1}$ per mM of MR contrast agents) in PBS solution without and with 0.65mM HAS (a) at 0.47 T, 1.41 T, and at 36°C. Chain lengths of LGd1 to LGd5 are 0, 6, 8, 10, and 12, respectively.

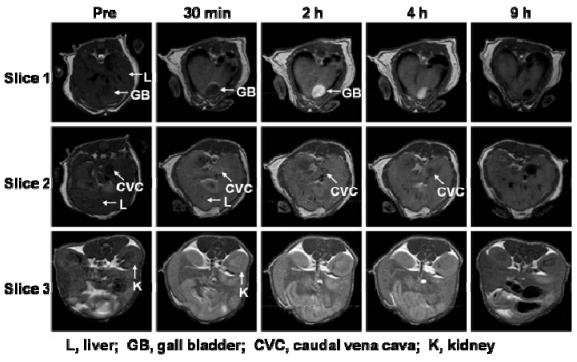

Figure 1. Dynamic 2D MR images in the three axial slices of mice injected with 0.1 mmol of Gd/kg of LGd3 at five representative time points.

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