Development of Novel Intravascular MRI Contrast Agents Using Gadolinium Chelates

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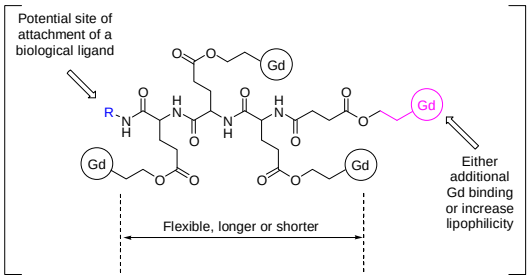
Introduction

Intravascular contrast agents have been widely used in magnetic resonance imaging (MRI) for angiography, measuring perfusion, and diagnosis of tumor (1-3). The most commonly used contrast agents (CAs) nowadays are thermodynamically and kinetically stable low molecular weight gadolinium (Gd) complexes. However, current clinically available Gd-based contrast agents are characterized by rapid excretion and transient tissue retention. Macromolecular Gd complexes have been developed as intravascular CAs for blood pool and tumor angiogenesis because they provide increased and prolong contrast enhancement within the blood pool at low doses (4-5). But large polymeric Gd complexes are associated with a few limitations, such as poorly define architectures, unpredictable pharmacokinetics, increasing possibility of Gd leakage from the Gd complex due to prolonged tissue retention (6).

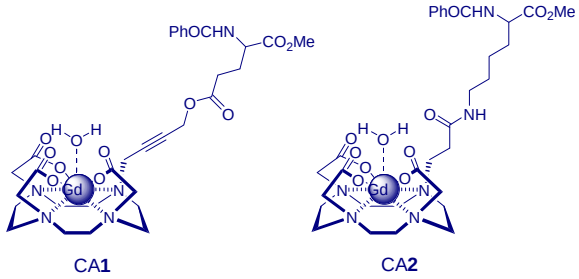
Materials and methods

We are undertaking the development of a new class of oligomer-based CAs by incorporating multiple-gadolinium complexes into peptides of controlled length and structure (Scheme 1). This therefore allows synthesis of a library of Gd-peptides with different sequences, peptide length and number of Gd-chelates. Screening this library of Gd-peptides will allow selection of oligomers with desired properties, such as high relaxivity and long blood half-life.

Relaxivity measurement and MRI were conducted on a Varian 9.4T MRI system (Palo Alto, CA, USA). T_1 was measured by inversion recovery spin echo in aqueous phantoms with concentrations 0.4, 0.2 0.1, 0.05, 0.025, 0.0125 and 0.00625 mM Gd. In vivo study was conducted on Wistar rats (male, weight 320-340 g) under 2% isoflurane anesthesia. CAs were injected (dosage: 0.04 mmol Gd/kg body weight) through tail vein. T_1-weighted images were acquired every 6.4 s for 48 min with T_1-weighted gradient echo sequence (TR/TE=50/3 ms, flip-angle = 20 degree, resolution=230 µm, thickness=2 mm).



Scheme 1. Proposed structures of oligomers



Scheme 2. Two structures of monomeric Gd complexes

Results and discussion

Initially, we have synthesized two GdDO3A conjugated amino acid building blocks derived from glutamic acid, CA1, and lysine, CA2 (Scheme 2). The study of their relaxitivities showed the r_1 of the two CAs (6.8 and 4.8 $mM^{-1}s^{-1}$ in H_2O at 25 °C for CA1 and CA2, respectively) are both higher than that of the clinically used ones (3.9 and 4.1 $mM^{-1}s^{-1}$ in H_2O at 25 °C for Gd-DOTA and Gd-DTPA, respectively). In vivo imaging studies of the two CAs in rats demonstrated that contrast enhancement in the brain artery immediately after tail vein injection (Fig.1). Time course of MRI signal intensity (up to 48 min post injection) in the brain artery showed considerable signal enhancement (about 50%) for CA2 while much lower for CA1. Compared with Dotarem (Guerbet, France), which showed similar peak enhancement as CA2, the enhancement by CA2 remained high (about 30%) even at 48 mins post-injection. This indicates CA2 has much longer blood half-life and could potentially advantageous for angiography and tissue targeting. Synthesis of oligomers with different number of Gd-peptides is in progress.

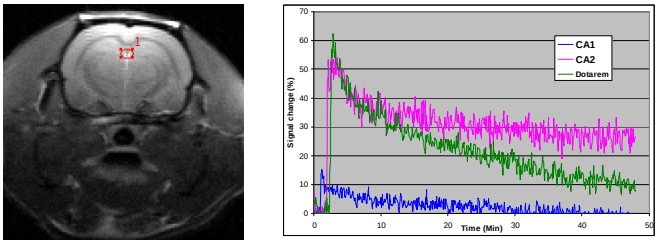


Fig. 1. Representative gradient echo image (left) shows the location of measured time course. Time course of MRI signal intensity (right) in the brain artery during with CA1**,** CA2 and Dotarem (dose 0.04 mmol Gd /kg of body weight).

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