Gd-Containing Dendrimer as a Novel T1-weighted lung MRI contrast agent

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Synopsis

Synthesis of a novel and hitherto unknown "starburst" Gd-containing dendritic contrast agent from pentamethylcyclopentasiloxane and polyethylene glycol (PEG) and its contrast enhancement on the lung tissue of mice during MR imaging were described. This study present great enhancement of lung imaging using MRI with novel T1 contrast agnet.

Introduction

Magnetic Resonance Imaging (MRI)[1] is one of the most important noninvasive diagnostic techniques used to visualize soft tissue anatomy and disease, such as tumors, which in part can be attributed to the rapid development of MRI contrast agents. The low molecular weight T1-weighted MRI contrast agents suffer from their non-specificity, rapid renal excretion and relatively low relaxivity. Hence, the need for the multifunctional macromolecular gadolinium ions carriers becomes increasingly important. Dendrimers[2,3] are unique synthetic macromolecules that have attracted much interest due to their unique structures and properties. While applications of dendrimers have been explored in a very broad range of fields, their use in MRI has become increasingly important. Currently, lung image can be acquired by hyperpolarized 3He MRI technique. However, this technique highly requires the equipment to prepare hyperpolarized gas and efficiently transfer the gas into MRI room without energy loss. Therefore, it is important to develop MRI technique with cheap and convenient novel contrast agent to specific enhance lung organ. Dendrimers are proven to be versatile carriers with high affordability contrast agents specific for various types of lung or brain cancers. This would greatly improve the diagnosis and treatment of patients with these conditions (Figure 1).

Material and Methods

A new type of cyclosiloxane core dendrimer with five arms has been synthesized starting from pentamethylcyclopentasiloxane, PEG and 2,2-bis(hydroxymethyl)propionic acid and conjugated with diethylenetriaminepentaacetic acid (DTPA) followed by doped with Gd^{3+} ions. Images were performed on a 4.7-T Biospec 47/40 MR scanner with an active shielding gradient. All experiments were carried out on male balb/c mice. The mice were initially anesthetized with 5% isoflurane at 1L/min air flow. When fully anesthetized, the animal was placed in a prone position and fitted with a custom-designed head holder inside the magnet. Isoflurane was then maintained with 1~1.2% at 1L/min air flow throughout the experiments. Images were acquired using a 35-mm quadrature coil as both transmitter and receiver. T1-weighted images (T1WI) were performed before and after an injection of Gd-dendrimer at a dose of 0.03 mmol/kg. T1WI were acquired using spin echo sequence with a TR of 600 ms, TE of 10 ms, 2 averages, FOV = 5 cm × 5 cm, slice thickness of 1.5 mm, and acquisition matrix = 256×128.

Results and Discussion

A five-armed derivative of pentamethylcyclopentasiloxane (D_5-Me-H) was prepared by the reaction of pentamethylcyclosiloxane with monomethyl ether of polyethylene glycol of m.wt. 5000. Terminal methoxy group cleavage followed by reaction with benzylidene-2,2'-bis(oxymethyl)propionic anhydride and the benzylidene de-protection afforded the hydroxyl-terminated G_1 generation dendrimer. Conversion of the hydroxyl-terminals into carboxyl group and subsequent conjugation with 2-(4-aminobenzyl)diethylenetriaminepentaacetic acid (Bz-DTPA) led to the star-burst cyclosiloxane core dendrimer (Figure 2). The preparation of gadolinium complex of dendrimer was performed by adding the required equivalent of gadolinium salt ($GdCl_3.6H_2O$) to the dendrimer dissolved in demineralized water and by adjusting the pH between 6.0-6.5 using 0.1 M meglumine solution. The absence of free gadolinium ions was tested by using xylenol orange indicator at pH 5.8 (acetate buffer). The numbers of gadolinium ions doped were determined experimentally by using ICP-AES (Inductively Coupled Plasma-Atomic Emission Spectroscopy). The Gadolinium loaded dendrimer was evaluated for its capacity to alter the relaxation rate of water using a NMR spectrometer (20 MHz, 0.47 T) with standard pulse program of inversion-recovery (IR). The water proton relaxation results indicate that these materials are having an inherent nature to act as contrast-enhancing agent in MRI.[4] The relaxivity values are measured and compared with Magnevist™. The ionic relaxivity values are (in $mM^{-1}S^{-1}$) $r_1 = 41.0$, $r_2 = 45.8$ (No. of Gd by ICP-AES = 4.1). MR imaging was performed on a 4.7-T Biospec 47/40 MR scanner with an active shielding gradient. T1-weighted images (T1WI) were performed before and after an injection of Gd-dendrimer at a dose of 0.03 mmol/kg on male balb/c mice. Figure 3 shows the lung tissue of mice with the bright signal after the injection of novel contrast agent, Gd-dendrimer and demonstrates the lung tissue has highest sensitivity to Gd-dendrimer compared to neighboring tissues.

Conclusion

A "starburst" dendritic contrast agent, consisting of both hydrophobic cyclosiloxane and hydrophilic PEG arms was synthesized and conjugated with Bz-DTPA follwed doped with Gd^{3+} ions. T1WI on male balb/c was performed by injecting the synthesized Gd-dendrimer and the results showed that lung tissue has highest sensitivity towards Gd-dendrimer illustrated by a bright signal.

References

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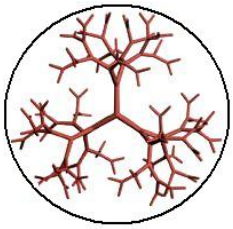

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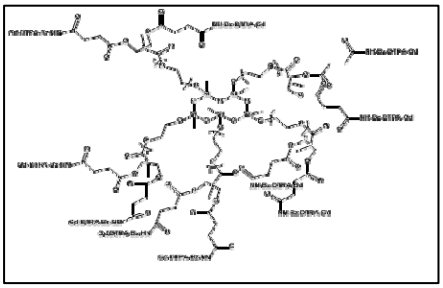

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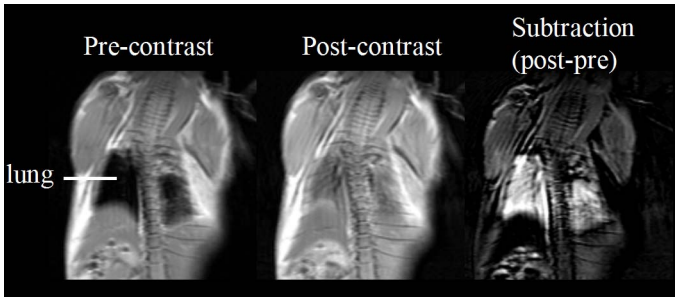

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Figure 1: Tree-like structure of a dendrimer; **Figure 2**: Structure of cyclosiloxane-dendrimer; **Figure 3**: Contrast enhancement of lung tissue in MR imaging with Gd-dendrimer.