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The degradation and clearance of Poly(N-hydroxypropyl-L-glutamine)-DTPA-Gd as a blood pool MRI contrast agent

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ABSTRACT

Although polymeric magnetic resonance imaging (MRI) agents have significantly improved relaxivity and prolonged circulation time *in vivo* compared with current imaging agents, the potential for long-term toxicity prevents their translation into the clinic. The aim of this study was to develop a new biodegradable, nonionic polymeric blood pool MRI contrast agent with efficient clearance from the body. We synthesized PHPG-DTPA, which possesses two potentially degradable sites *in vivo*: protein amide bonds of the polymer backbone susceptible to enzymatic degradation and hydrolytically labile ester bonds in the side chains. After chelation with Gd^{3+}, PHPG-DTPA-Gd displayed an R_1 relaxivity of 15.72 $mM^{-1}\cdot sec^{-1}$ (3.7 times higher than that of Magnevist®). In vitro, DTPA was completely released from PHPG polymer within 48 h when incubated in mouse plasma. In vivo, PHPG-DTPA-Gd was cleared via renal route as shown by micro-single photon emission computed tomography of mice after intravenous injection of ^{111}In-labeled PHPG-DTPA-Gd. MRI of nude rats bearing C6 glioblastoma showed significant enhancement of the tumor periphery after intravenous injection of PHPG-DTPA-Gd. Furthermore, mouse brain angiography was clearly delineated up to 2 h after injection of PHPG-DTPA-Gd. PHPG-DTPA-Gd's biodegradability, efficient clearance, and significantly increased relaxivity make it a promising polymeric blood pool MRI contrast agent.

1. Introduction

Magnetic resonance imaging (MRI) is a powerful diagnostic technique because of its excellent soft tissue contrast and sub-millimeter resolution. To reduce ambiguity in disease diagnosis, about 25% of MRI examinations employ MRI contrast agents. All eight clinically approved gadolinium-based contrast agents, such as Magnevist (Gd-DTPA), Dotarem (Gd-DOTA), Prohance (Gd-HP-DO_3A), and Omniscan (Gd-DTPA-BMA), are small-molecular-weight hydrophilic contrast agents. These agents extravasate quickly and are rapidly cleared from intravascular and interstitial space, with a typical elimination half-life of about 1.5 h. This rapid clearance is generally beneficial to patient health; however, it also makes it difficult to conduct many time-dependent imaging studies. In contrast, polymeric agents with a molecular weight greater than the renal clearance threshold normally possess significantly prolonged blood circulation and preferential accumulation in solid tumors owing to an enhanced permeability and retention (EPR) effect. Moreover, polymeric contrast agents display enhanced relaxivity owing to the restricted rotation of large molecules. To date, a few polymeric contrast agents have been proposed and studied for MR angiography and cancer imaging in the preclinical setting [1–6]. However, the extended circulation time of polymeric MRI contrast agents is usually concomitant with slow excretion from the body, and prolonged retention of Gd-containing polymers in the body may increase the chances of trans-metalation between Gd^{3+} and endogenous metal ions such as Zn^{2+}, Cu^{2+}, and Ca^{2+}, resulting in the release of free Gd^{3+}, which may cause nephrogenic systemic fibrosis (NSF) [7,8]. Thus, biodegradability that ensures the clearance of DTPA-Gd within a relatively short time after MRI scanning has become crucial for the development of polymeric MRI contrast agents.

To address this long-term toxicity issue, imparting biodegradability to the polymers that act as carriers for MRI contrast agents

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