Synthesis and characterization of a redox- and light-responsive MRI probe

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Introduction

Redox reactions are one of the two energy resources available to living organisms. Biochemical redox couples are responsive to changes in oxidizing-reducing conditions which can result from changes in blood flow, oxygenation, and other variables. Thus, the ability to non-invasively monitor redox activity in a living system would provide a foundation for detailed studies of metabolism in relation to disease processes and therapies. Optical techniques to measure electrical activity were first suggested in 1968 based on the discovery that changes in electrical activity may be accompanied by innate optical changes. Today, exogenous dyes for measurement of electrical activity are a large and well-studied group of indicators. Among them spiropyran and spirooxazine attracted us because they experiences a significant structural rearrangement in response to changes in light and electrical activity. Recently, we reported a MRI contrast agent that is a combination of a spiropyran group and a Gd-DO3A complex. The access of water to the first coordination sphere of the chelated gadolinium ion is controlled by light activated, ring-opening/closing conformation changes. When in dark, the contrast agent is in its "open" form and has higher $T1$ relaxivity. After irradiation with visible light, the contrast agent experienced a color change due to the partial isomerization to "closed" form and $T1$ relaxivity decreases. The agent shows potential as an indicator in applications for gene expression in conjunction with light emitting gene markers such as lucerase-luciferin in deep tissues that are not accessible by optical methods. In this paper we report the redox response of this molecule to chemical redox agents.

Methods

A novel redox- and light-sensitive, T_1-weighted magnetic resonance imaging (MRI) probe which tethers a spiropyran(SP)/merocyanine(MC) motif to a Gd-DO3A moiety was synthesized and characterized. The MC and SP forms of the molecule are illustrated in the figure below. Cyclic voltammetry was performed to assess the reduction potential for the agent. The response of the probe to reduction and oxidation was tested using NADH and hydrogen peroxide as chemical redox agents. The effect of redox condition on relaxivity of the probe was monitored by MRI and relaxometry. Changes to the optical properties of the probe were monitored by spectroscopy and confocal microscopy.

Results

When in dark, the probe is in its MC form that has higher relaxivity (2.53 $mM^{-1}s^{-1}$) and signal intensity in MRI. After irradiation with visible light or exposure to NADH or hydrogen peroxide, the probe experiences a color change due to an isomerization to the SP form and relaxivity decreased 14%, 19% and 22%, respectively. Exposure of the probe with light, NADH, or hydrogen peroxide all significantly reduced signal intensity in MR images.

Conclusions

The redox properties of the probe described here are somewhat counter to the light response we have previously observed indicating that the isomerization in response to redox differs from that in response to light. These interesting properties are being further explored and we are investigating the effect of structural variations on the redox sensitivity of the probe. The ability to sense reduction and oxidation and the potential for REVERSIBLE response by an MR probe are promising for future in vivo applications.