

Dual MR-PET probe for quantitative, noninvasive high resolution pH mapping

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Introduction

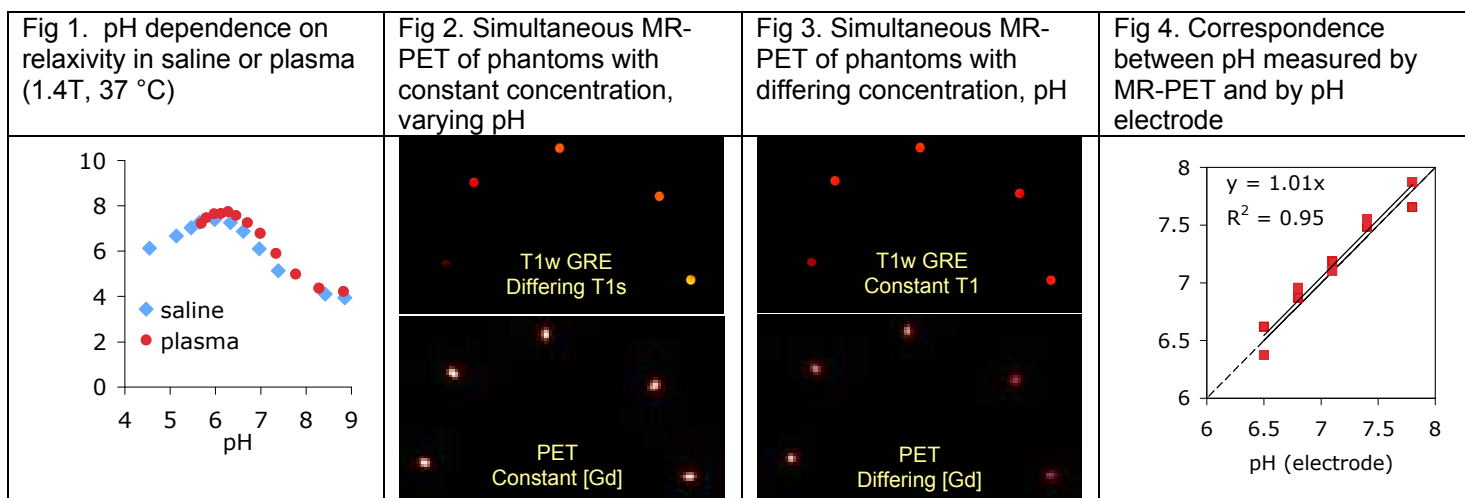
MR contrast agents act indirectly to relax water protons. The efficiency of contrast agents with respect to relaxation is termed relaxivity ($r_1 = \Delta(1/T_1)/[Gd]$) and depends on a number of molecular parameters including the hydration state of the molecule and its molecular reorientation rate. These molecular parameters can sometimes be altered by environmental factors such as pH changes, ion binding, or enzymatic activity. As a result, it is possible to design MR contrast agents that act as sensors or are activatable, and numerous in vitro examples have been described.¹ In vivo translation of most of these agents has lagged, likely because the concentration of the agent is not known in vivo. The MR signal can be proportional to T_1 , but the effect of the contrast agent on T_1 depends on both its relaxivity and its concentration (two unknowns). Thus regional differences in signal may arise from differences in contrast agent relaxivity, concentration, or both. In order to utilize such agents as “smart” probes, one requires an independent knowledge of probe concentration. One approach is to prepare an activatable contrast agent with a PET reporter. Using simultaneous MR-PET acquisition, the PET signal can report on concentration and this can be combined with the MR signal to extract relaxivity. Here we describe the synthesis of a new pH-responsive MR probe that uses “click” chemistry to incorporate a fluorine-18 containing group. The pH dependent relaxivity is described and images are obtained using a simultaneous MR-PET device. From the MR-PET images and the established pH dependence on relaxivity, pH is calculated for each sample.

Methods

The pH-responsive, dual MR-PET probe was based on an established pH responsive MR probe,² and was synthesized over 5 steps. The F-18 label was incorporated in 2 steps from $Na^{18}F$ by 1,3-dipolar cycloaddition of 2-fluoroethylazide with a pendant alkyne group of the gadolinium complex. Relaxivity was determined by measuring T_1 as a function of concentration at different pH in both saline solution and in serum at 37 °C, 1.4T and at room temperature at 3T. Phantoms containing different concentrations of probe at different pH values were simultaneously (MR + PET) imaged on a MR-compatible brain PET scanner prototype (called BrainPET) that operates inside the bore of a Siemens 3T TIM Trio MR scanner.³ pH values calculated from the MR-PET measurements were compared to those obtained from a pH electrode.

Results

The novel MR-PET pH probe showed similar pH-dependent relaxivity to the parent MR-only probe. Incorporation of the F-18 moiety did not impact relaxivity in saline. Relaxivity in serum was virtually unchanged compared to that measured in saline (Fig. 1), suggesting little/no serum protein binding. Fig. 2 shows MR and PET images of phantoms containing the same Gd concentration but differing pH, while Fig. 3 shows phantoms containing different Gd concentrations but with similar T_1 values. Fig. 4 shows the good correspondence (dashed line is 1:1, solid line is linear regression) between pH estimated from the MR and PET measurements compared to the gold standard of pH measured by pH electrode.



Conclusions

Simultaneous MR-PET with a dual MR-PET, pH-responsive probe can noninvasively report pH. The strategy of using simultaneous PET to determine concentration is generally applicable to activatable MR probes.

References: ¹Bonnet and Toth, AJNR 2010, EPub. ² Kalman et al. Inorg. Chem. 2007, 46:5260. ³ Schlemmer et al, Radiology, 2008; 248:1028