Ytterbium (Yb)-based PARACEST agent: feasibility of CEST imaging on a clinical 3.0 T scanner

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Introduction

Chemical Exchange-dependent Saturation Transfer (CEST) is a novel contrast mechanism for magnetic resonance (MR) imaging [1-3]. It is based on the chemical exchange between protons of bulk water and diluted exchangeable solutes. The CEST effect is dependent on pH, temperature, concentration or enzyme activity. Therefore, one of the promising clinical aspects of CEST imaging is pH-mapping for assessment of tumor and ischemic disease [1,2,4,5]. Besides, saturation ON/OFF imaging is attractive for molecular imaging using the specific resonance frequency of presaturation RF pulse [1,2]. Paramagnetic CEST (PARACEST) agents can increase sensitivity and specificity on CEST imaging and provide more detailed physiological and functional information [1,3]. A number of approaches have been described to increase the sensitivity of PARACEST agents [1,3]. We have newly synthesized PARACEST agents using three kinds of ytterbium (Yb) complexes, which allow the highest practical CEST effect among the lanthanide ions and their effects have been evaluated on a high field NMR system [3]. This study investigated the feasibility of CEST imaging using these PARACEST agents with a clinical MRI scanner.

Materials and Methods

<Paramagnetic CEST agents>

The following three kinds of ytterbium complex of PARACEST agent were synthesized [3]. (Fig.1)
$[Yb(ttham)]^{3+}$: ytterbium-triethylenetetramine-*N,N,N',N'',N''',N''''*-hexaacetamide
$[Yb(1bttpam)]^{3+}$: ytterbium-N-benzyl-triethylenetetramine-*N,N',N'',N''',N''''*-pentaacetamide
$[Yb(4bttpam)]^{3+}$: ytterbium-N-benzyl-triethylenetetramine-*N,N,N'',N'',N''''*-pentaacetamide

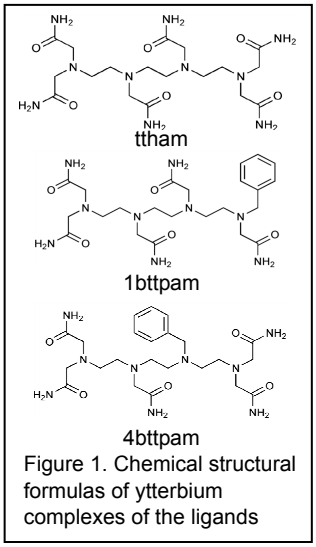

Figure 1. Chemical structural formulas of ytterbium complexes of the ligands

<Phantom>

The agents were diluted by 4-Morpholine-propanesulfonic acid (MOPS) buffer preparing with the concentration of 5, 10, 20 and 50 mM. Each concentration was adjusted by pH of 3.0, 5.0, 7.4 and 9.5. The phantom contained 2 mL of each solution and its temperature was set within range of 36.0 ± 2.0 ℃ during the scan. Human plasma was also used as a solvent for evaluating the effect of endogenous protein.

<Imaging Protocols>

The CEST imaging was performed on a 3T clinical MR System (Achieva 3.0T, Quasar Dual, Philips Healthcare) using a quadrature head coil. MR CEST images were obtained by turbo spin echo sequence with TR/TE=1500 ms/6 ms, TSE factor = 20, FOV = 230 mm, slice thickness = 4mm, matrix size = 256 x 256, number of acquisition = 4, Number of slice = 1, pulse duration = 496 ms, pulse amplitude = 3.8 μT. Presaturation offset frequencies were from -5,000 Hz (-39 ppm) to 5,000 Hz (+39 ppm) with intervals of 500 Hz (4 ppm).

<CEST effect calculation>

The CEST effect was calculated with following equation; $\%CEST = (M_{-s} - M_s) / M_\infty \times 100$. M_s is signal intensity with presaturation RF pulse at resonance frequency of the paraCEST's exchangeable protons. M_{-s} is signal intensity with saturation RF pulse at symmetrically on the opposite side of M_s. M_∞ is signal intensity of second reference that is not affected by magnetization transfer effect.

Results

The CEST effect by PARACEST agents could be observed at around ±31 ppm, and between -23 ppm and -8 ppm (Fig. 2). Among 3 agents, $[Yb(4bttpam)]^{3+}$ showed the strongest and $[Yb(ttham)]^{3+}$ did the weakest CEST effect, respectively. The CEST effect was increased depending on the increase in the concentration up to 50mM (Table 1). With regard to pH dependency, the maximum CEST effect was shown at pH 7.4 and was decreased at higher degrees of acidity or alkalinity (Table 2). In comparison with diluted solutions, CEST effects of the agents in human plasma remained almost the same as or weaker than those in MOPS buffer.

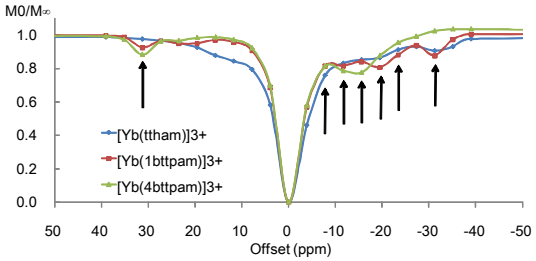

Figure 2. Z-spectra of three kinds of PARACEST agent (MOPS buffer, 50 mM, pH 7.4)

Table 1. Concentration-dependency of CEST effect (%)

PARACEST agent (offset)	5 mM	10 mM	20 mM	50 mM
$[Yb(ttham)]^{3+}$ (-23 ppm)	1.14	1.53	1.98	4.06
$[Yb(1bttpam)]^{3+}$ (-12 ppm)	1.64	3.48	6.06	14.04
$[Yb(4bttpam)]^{3+}$ (-16 ppm)	1.36	2.93	7.46	20.85

(MOPS buffer, pH 7.4, 37.0 ± 1.0℃)

Table 2. pH-dependency of CEST effect (%)

PARACEST agent (offset)	pH 3.0	pH 5.0	pH 7.4	pH 9.5
$[Yb(ttham)]^{3+}$ (-23 ppm)	0.34	0.66	1.10	0.02
$[Yb(1bttpam)]^{3+}$ (-12 ppm)	2.82	3.31	6.61	3.29
$[Yb(4bttpam)]^{3+}$ (-16 ppm)	5.44	6.66	7.64	4.18

(MOPS buffer, 20 mM, 36.0 ± 1.0℃)

Discussion and Conclusion

Our findings suggest that CEST imaging with PARACEST agents is feasible on a 3T MR scanner. However, the CEST effect was weaker than those reported in previous studies at 7T [3]. It is likely due to the limited power and durations of the presaturation pulses in our experimental setting imposed by a limitation of specific absorption ratio (SAR). The dependence of our results on the pH of the agents suggests the potential for pH mapping in hypoxic tumors or ischemic regions at a clinically available magnetic field strength. We showed the clinical potential of CEST imaging using PARACEST agents, but further modifications, such as an optimized presaturation RF pulse, imaging protocols or other techniques, may be necessary before its application in clinical practice.

References

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