Fast relaxing contrast agent for fluorine MRI

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Target audience: Researchers in animal preclinical research including cell tracking and cell transplantation with interest in ^{19}F MRI

Purpose

^{19}F MRI may represent an interesting tool for experimental and diagnostic imaging. Both resonance frequency and sensitivity of fluorine ions is close to hydrogen, therefore measurement of ^{19}F MR spectra or images requires minor hardware and software changes only on MRI scanners. A crucial task represents a fluorine probe bearing enough fluorine ions with suitable physical parameters. We present a novel ^{19}F probe with six equivalent fluorine nuclei and substantially shortened relaxation times by bound metal ion which might be potentially utilisable for both systemic administration and cell labelling.

Methods

Both empty ligands and nickel-coordinated ligands (complexes) based on tetraazacyclotetradecane with 6 equivalent fluorine nuclei (see Fig. 1) were synthesized. The contrast agent was compared to a reference trifluorethylalcohol (TFEOH). Empty ligands, complexes and TFEOH at different concentrations were subjected to MR spectroscopy, imaging and relaxometry at both ^{19}F and ^{1}H frequencies at 4.7 T scanner equipped with a ^{1}H/^{19}F homemade single-loop surface coil. T_1 was measured by a series of saturation recovery gradient echo sequences, T_2 by a series of spin echo or CPMG sequence, T_2* was determined from the spectral linewidth.

^{19}F MR images were obtained using gradient echo (GE) and turbospin echo (TSE) sequences; timing was optimized according to relaxation times of the samples. We used a TSE sequence (32 echoes, TE =3.24 ms, TR=2000 ms) for the empty ligand and TFEOH; a GE sequence (TE=1.32 ms, TR=4 ms) was used for the Ni-complex. Acquisition number was set to provide the same measurement time (approx. 30 minutes).

Results

Spectrum in Fig. 2 shows frequency differences between the empty ligand, TFEOH and Ni-complex. Relaxation times of the empty ligand were: T_1=1100 ms, T_2=11 ms, T_2*=3.1 ms, whereas the Ni-complex had following values: T_1=4.2 ms, T_2=1.8 ms, T_2*=1.1 ms. Proton relaxivities of the Ni-complex reached: r_1=0.12 s^{-1}/mM, r_2=0.15 s^{-1}/mM.

Fig. 3A shows a proton image of the phantom for the imaging experiment. We optimized a TSE sequence for the empty ligand (Fig. 3B) and a GE sequence for the complex (Fig. 3C) to fit their relaxation times. Both the empty ligand and complex have similar signal to noise ratio (S/N) in ^{19}F MR images (Fig. 3B-C) obtained within the same time period. TFEOH provided less than a half signal. The spatial signal shift of TFEOH in Fig. 3B and of the empty ligand in the image 3C corresponded to different resonance frequencies in the three samples. The ligand signal in Fig. 3C is very weak due to short TR.

Discussion

The Ni-complex in combination with a fast gradient echo seems to be a suitable alternative to so far used fluorine contrast agents as soon as toxicity tests are finalized. Due to its short relaxation times, one may also benefit from ultrashort or zero echo sequences. Quick timing of the used sequence not only enables more acquisitions to improve S/N, but may also reduce unwanted fluorine signal from other sources in future in vivo experiments. Although proton relaxivities are substantially lower than those of standard Gd-based contrast agents, the complex manifests itself even in proton MR images as an unspecific hyperintense signal, which may enable localize the fluorine signal (obtained with low spatial resolution) more precisely on anatomical proton images.

Conclusion

We synthesized and tested fluorinated Ni-complexes which revealed suitable relaxation properties. The complexes are identifiable on both ^{19}F and ^{1}H MR images which may make their localization easier.

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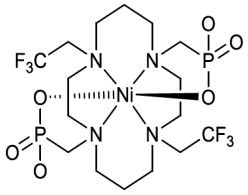

Fig. 1: Scheme of the Ni-complex

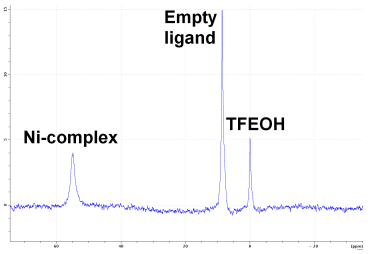

Fig. 2: 19F MR spectrum

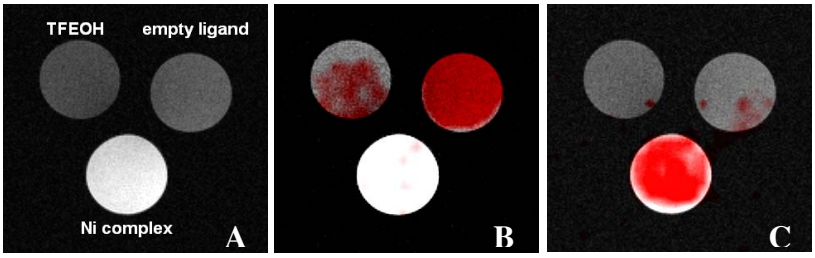

Fig. 3: 1H MR image of the phantom (A), 19F MRI turbospinecho sequence tuned to the ligand (B) and gradient echo sequence tuned to Ni-complex (C)