

Development of a paraCEST and Fluorine MRI Contrast Agent

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Introduction

In Magnetic Resonance Imaging, different classes of contrast agents are studied to obtain a better detection of pathologies. Among them, paraCEST contrast agents, based on a saturation exchange between water molecules in the vicinity of a lanthanide complex, are very promising. Indeed, the generated contrast can be turned on at will by the application of a saturation pulse with the advantage that it does not require any pre-injection image. ¹⁹F MRI is also promising because there is no background noise, facilitating the detection of the generated contrast. In this study, the combination of an europium based paraCEST contrast agent with a ¹⁹F MRI contrast agent has been studied (figure 1). The interaction between the europium complex and the fluorine atoms can indeed reduce the ¹⁹F relaxation times, which are usually too long for clinical use.

Materials and methods

The paraCEST effect has been characterized by recording different Z-spectra at 600MHz, using a continuous wave irradiation of 10s at different saturation frequencies. The samples were prepared in PBS at pH 7.2. The exchange rate constants were measured at 25 and 37°C by varying the saturation power as described in the literature^[1]. The ¹⁹F relaxation times have been determined at 500MHz and 25°C in water.

Results and discussion

The europium complex (figure 1a) exhibits great CEST properties before the coupling of the fluorine agent. Exchange rate constants of 6415 s⁻¹ and 8407 s⁻¹ have been determined at 25°C and 37°C respectively, and the CEST effect remains detectable at concentrations in the millimolar range. After the grafting of the fluorinated agent (figure 1b), we observed an important decrease of the complex solubility as well as an increase of the exchange rate constant, making the detection of the CEST effect more difficult. However, a significant decrease of the ¹⁹F relaxation times after complexation of the agent with europium was obtained, with measured T₁ and T₂ of 887 ms and 468 ms respectively.

Conclusion

To conclude, the agent shows great paraCEST properties but the exchange rate constant increases after the grafting of the fluorinated molecule. We nevertheless observe a noticeable decrease of the ¹⁹F relaxation times thanks to the interaction of the fluorine atoms with the europium ion. Several perspectives can be envisaged, as the replacement of the europium ion by other paramagnetic ions in order to find the best candidate to have ideal CEST properties and fluorine relaxation times. An increase of the detection sensibility could also be obtained through the grafting of the agent at the surface of silica nanoparticles.

^[1]: W. T. Dixon *et al.*, "A Concentration-Independent Method to Measure Exchange Rates in PARACEST Agents";

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