Optimization of the inner-sphere water molecule exchange rate to increase the contrast of paraCEST contrast agents

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Introduction

ParaCEST MRI

ParaCEST agents show a great interest in MRI imaging. This imaging technique, which is based on a saturation transfer from exchangeable protons to bulk water molecules, has several advantages over the common MRI contrast agents. The contrast can easily be turned on or turned off by the application of the saturation pulse. Thus, the exam does not require a pre-injection image. Then, several contrast agents can be injected at the same time and turned on separately, their biodistribution can hence be differentiated. It is called multi-color imaging.

Europium based DOTA derivatives have interesting CEST properties. Indeed, after the modification of the carboxylate functions into amides, some paramagnetic complexes show an increased water residence time, which is one of the most significant parameter for the CEST effect. [1] The saturation transfer can either occur with the inner sphere water molecule or with the amide protons.

However, the sensitivity of paraCEST contrast agents is limited, mostly after injection in-vivo. To overcome this issue, the design of new complexes tends to decrease the inner sphere water molecule exchange rate. This research will focus on that subject.

Goal of the study

In this study, a DOTA derivative was substituted by 3 glycine, to ensure water solubility of the complex. The same ligand was also substituted by aspartic acid pendant arms and a strong decrease of the inner sphere water molecule exchange rate was observed. This property leads to an increase of sensitivity of the contrast agent.

To further study this phenomenon, tetra-substituted europium complexes were studied, to comprehend the influence of the carboxylic acids on the exchange rate.

Finally, an amphiphilic complex was synthesized to prepare active nanostructures in paraCEST MRI: micelles. The influence of the distance between the complexes on the exchange rate will hence be evaluated.

Results

All Z-Spectra were recorded at 600MHz, 37°C and pH 7.4, using a saturation pulse of 655Hz. The exchange rates were measured using the omega-plot method [2].

The introduction of carboxylate slows down the exchange rate, Eu-DOTA-Asp3 is a great improvement compared to the commonly used Eu-DOTA-Gly3. The Eu-DOTA-Gly3 data was obtained in the literature [2].

Conclusion

This study demonstrated the importance of the number of carboxylic acids on the inner sphere water molecule exchange rate kinetics. The carboxylate functions interact with it by hydrogen bonding, slowing down the exchange rate and increasing the generated contrast. The aspartate derivatives are hence an interesting alternative to the well-known Eu-DOTA-Gly3.

Finally, micelles were prepared. They generate a strong decrease of the water peak intensity, up to 50%. The maximum contrast is obtained at around 18mM.

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