In vivo CEST-based molecular imaging using RGD-LipoCEST in U87 mice brain tumor

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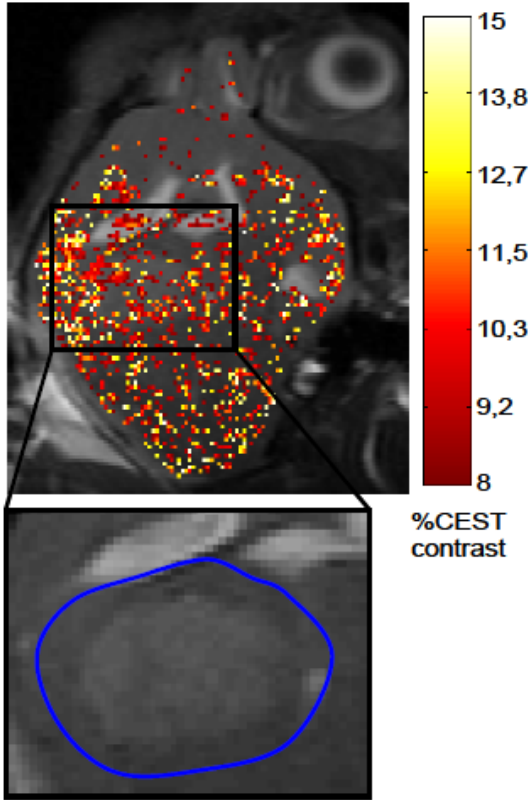
Fig.1. CEST image (in % of CEST effect) of tumoral mouse brain after 1h of RGD-LipoCEST injection; "tumor"+ surroundings" ROI is magnified.
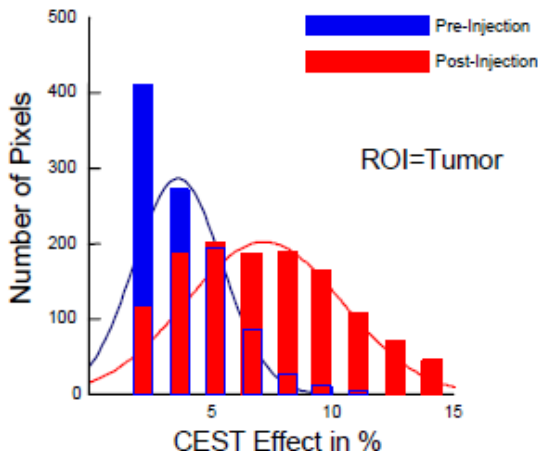

Fig.2. Histograms of CEST effects in "tumor + surroundings" ROI before (blue bars) and 1-hr after (red bars) RGD-LipoCEST i.v. injection in the tail vein.

Introduction

Recently, Guerbet Research [1] and Aime S. et al. [2] have introduced LipoCEST, a new class of contrast agents for CEST-MRI, which are lipid bilayer filled with a huge amount of lanthanide-chelate complexes. As compared to ParaCEST, LipoCEST contrast agents provide a tremendous amplification factor and a high biocompatibility due to composition of their membrane. Moreover, LipoCEST membrane can be functionalized by grafting specific peptides for molecular imaging purpose. In this study, we aim to target with a RGD-functionalized LipoCEST the $\alpha_v\beta_3$ integrin [3], which is known to be over-expressed during angiogenesis in many tumors vessels. In this abstract, we present our preliminary result on $\alpha_v\beta_3$ imaging with a RGD-LipoCEST contrast agent.

Subjects and Methods

Animal preparation. Tumor was induced by i.c. injection of 1.2×10^5 Glioma U87 human cells in a single immuno-depressed "nude" mouse brain [4]. Experiments were performed 10 days after.

MRI acquisition. Brain CEST images were acquired using a MSME sequence (TE/TR=54/5000ms, resolution $150 \times 150 \times 660 \mu m^3$, Tacq=14min) preceded by a CW saturation pulse (T_{sat} =400ms, B_{1sat} ~7µT, δ_{sat}=±9ppm) on a 7 T small animal MRI scanner (Bruker, Germany) using an home-made 2.8cm-diameter quadrature volumic ^{1}H coil. Images were acquired before (pre-injection) and 1-hr (post-injection) after i.v injection of 200µL of RGD-LipoCEST (Guerbet Research, France) in the tail vein.

Image analysis. %CEST images were obtained by the subtraction of images acquired with saturation applied at 9 and -9ppm normalized by the reference image without saturation. %CEST contrast was analyzed in different regions-of-interest corresponding to: the entire "brain", the "tumor and its surroundings" and the area "controlateral" to the tumor.

Results

Figure 1 shows a post-injection %CEST axial image at the tumor level. As illustrated by figure 2, the average %CEST contrast before injection in the "tumor" was 3.9% (corresponding to the endogenous MT background effect) and rose to 7.2% after injection which corresponds to an 84% elevation of the %CEST contrast following the RGD-LipoCEST injection. In the "controlateral" and "brain" ROIs, elevation of the %CEST contrast were detected as well (+47% and +61%, see Table 1).

Discussion and Conclusion

The first observation is that %CEST effect increases overall in the brain following i.v. injection. This proves that our imaging and LipoCEST CA administration protocol is compatible with *in vivo* CEST-based MR molecular imaging. Secondly, the preliminary comparison of %CEST contrast elevations in the tumor and in others part of the brain leads us to think that a majority of the %CEST contrast elevation is probably due to non-specific binding and/or distribution of the RGD-LipoCEST CA. Yet, the higher %CEST contrast elevation observed within the tumor and its surroundings represents a promising preliminary result that have to be completed by further experiments. This study constitutes to our knowledge the first attempt towards *in vivo* brain tumor detection using targeted-LipoCEST contrast agents.

References

1. Guerbet Research, WO 2006/032705
2. Aime S et al., Angew Chem 2005 44:55133
3. Dijkgraaf I et al., Front Biosci 2009, 14:887
4. Moats RA et al., Mol Imaging 2003, 2:150

ROI	Pre-injection	Post-injection	Relative variation
Tumor	3.9 ± 1.9	7.2 ± 3.2	+84%
Controlateral	4.5 ± 2.3	6.6 ± 3.4	+47%
Brain	4.1 ± 2.2	6.6 ± 3.4	+61%

Tab.1. Mean, standard deviation and relative variation of CEST signal in the whole "brain", "tumor"+ surroundings and "controlateral" ROIs