COMPARISON OF THREE MRI MOLECULAR IMAGING MODALITIES: APPLICATION TO ANGIOGENESIS IMAGING IN A BRAIN TUMOR MOUSE MODEL

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Introduction

The recent development of targeted contrast agents (CA) has opened the way for MRI molecular imaging. Here we evaluated three different CA based on different principles: Gd-based emulsion (paramagnetic agent), lipoCEST **[1]** (shifting agent) and fluorine emulsion (^{19}F MRI). A comparison of the three modalities sensitivity and specificity was performed on a mouse model of brain tumor using CA grafted with RGD peptides to specifically target $\alpha_v\beta_3$ integrins over-expressed in angiogenic vessels.

Materials and Methods

Animal model. Brain tumors (Ø~2 to 6mm) were induced in nude mice by IC injection of U87MG cells. Animals were sorted to remove experiments with low SNR and animals with untypical behavior.

CA. For each modality, 2 CA were used (RGD and Ctrl): 2 Gd-based emulsions (r_1=2,4.10^{5}mM^{-1}s^{-1}), 2 lipoCEST exhibiting maximum MTRasym (asymmetric Magnetization Transfer Ratio) contrasts for B_{1opt}=7µT and δ_{opt}=±8ppm, and 2 ^{19}F emulsions (PFOB, 40% w/w).

MRI. Acquisitions were carried out with a 7T Bruker rodent scanner, before and within the 2h following IV injection of each CA.

Gd: A T_1 mapping IR-FGE sequence **[2]** (R=150x150x660µm^3, T_{acq}=12,5min) was acquired on 10 mice (5 RGD and 5 Ctrl). Concentration maps were derived using the CA relaxivity r_1.

CEST: A Multi-Slice Multi-Echo (MSME) sequence (R=150x150x660µm^3, T_{acq}=14min) preceded by a saturation was acquired on 24 mice (12 RGD and 12 Ctrl).

^{19}F: A MSME sequence optimized for the CF_3 peak of PFOB **[3]** (R=500x500x6000µm^3, T_{acq}=18min) was acquired on 12 mice (6 RGD and 6 Ctrl).

Results and Discussion

As illustrated by Figure 1, CA are detected with a sub-nanomolar sensitivity by the three modalities. Moreover a higher contrast is systematically observed for RGD contrast agents inside the tumor. This difference can be ascribed to a specific association of RGD peptides to $\alpha_v\beta_3$ integrins expressed at the neo-vessels surface. As summarized in Table 1, time courses (RGD vs Ctrl) are significantly different ($p<0.05$) from the first time point for Gd-based and ^{19}F emulsions but only after 1h with the lipoCEST. For each RGD-CA a plateau is rapidly reached at concentrations specified in Table 1. A contrast decrease is only observed for the Ctrl lipoCEST, probably due to a shorter half life of flowing liposomes (~1h30) compared to emulsions (~4h). The lowest concentrations are obtained with ^{19}F emulsions due to partial volume effect. Advantages and limitations of each approach are summarized in Table 1. Gd-based approach seems to offer the best compromise to ensure a high spatial resolution and sensitivity of detection, highlighting significant differences with functionalized CA, even on a small number of animals. However, quantification method is based on *in vitro* measurement of the CA relaxivity r_1. CEST approach also leads to a high spatial resolution and is quite insensitive to flowing CA. Nevertheless, this method is sensitive to B_0 and B_1 inhomogeneities and quantification is hampered by endogenous MT contrast. Finally, ^{19}F approach allows direct quantification thanks to both lack of endogenous fluorine and linearity between MRI signal and CA concentration, but suffers from a lower spatial resolution compared to ^{1}H modalities.

	Gd	lipoCEST	^{19}F
Spatial resolution	150x150x660µm^3	150x150x660µm^3	500x500x6000µm^3
1st significant time point	12,5min	60min	18min
Concentration at the plateau	0.4nM	1.6nM	80pM
Advantages	Spatial resolution Specificity Quantification	Spatial resolution Quite insensitive to movements	Quantification
Limitations	Access to *in vivo* r_1 relaxivity	Endogenous MT B_0 et B_1 inhomogeneities	Spatial resolution

Table 1. Main characteristics of Gd, CEST and ^{19}F modalities

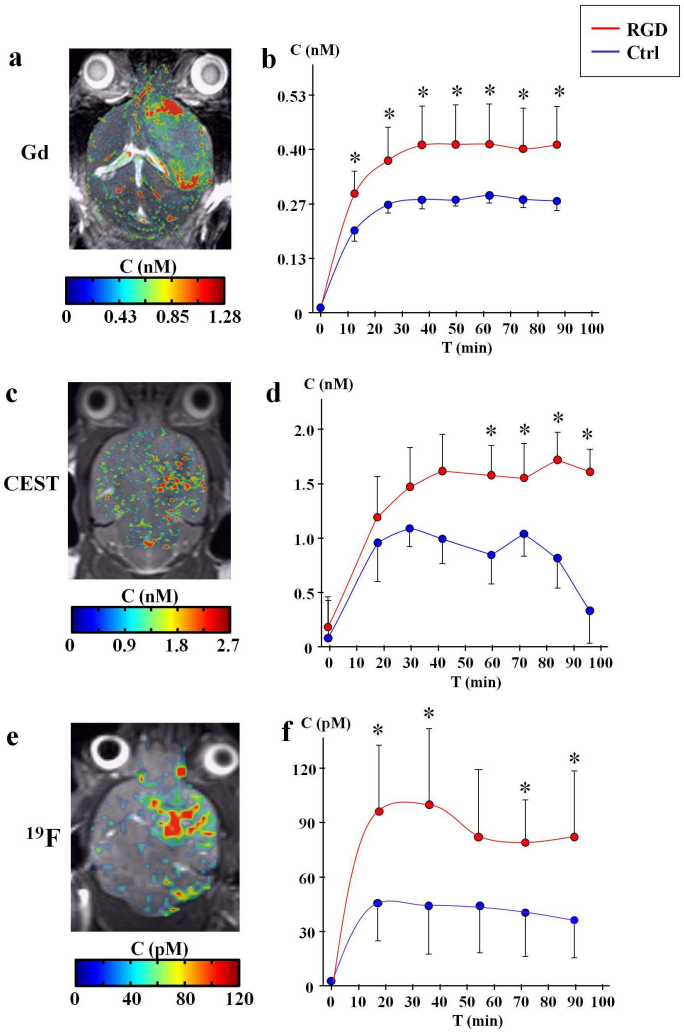

Figure 1. Example of images acquired after IV injection of RGD CA for Gd, CEST and ^{19}F modalities (a, c, e respectively). Time course obtained after IV injection of RGD and Ctrl CA (red and blue curve respectively) for Gd, CEST and ^{19}F modalities (b, d, f respectively). Signal is averaged in the tumor region and through the animal cohort (n=5/5 for Gd, n=12/12 for CEST and n=6/6 for ^{19}F).

Conclusion

To our knowledge, this study is the first comparison of functionalized CA used in similar experimental conditions. As shown by their application on a brain tumor mouse model, each modality provides additional information, promising for multimodal investigation of brain diseases.

[1] Aime et al. Angew Chem 2005
[2] Deichman et al. MRM 1999
[3] Giraudeau et al. MRM 2010