FIVE-SITE MODELING OF PROTONS CHEMICAL EXCHANGE PROCESSES FOR *IN VIVO* CEST-BASED MOLECULAR IMAGING

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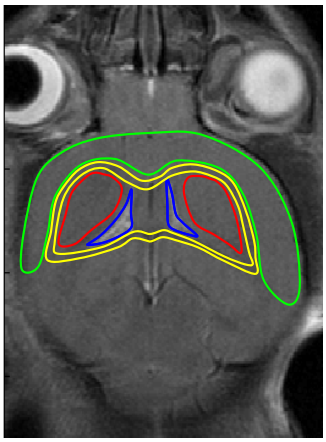

Fig.1. Anatomical image with ROI selected for *in vivo* Zspectra (green: cortex; red: sub cortex; yellow: white matter; blue: CSF)

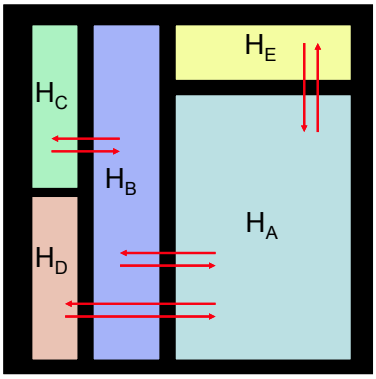

Fig.2. Five-site model for protons exchange processes. $\mathbf{H_A}$: bulk water protons; $\mathbf{H_B}$: protons dipolar-coupled to macromolecules; $\mathbf{H_C}$: macromolecular protons; $\mathbf{H_D}$: amide protons; $\mathbf{H_E}$**:** protons shifted by LipoCEST.

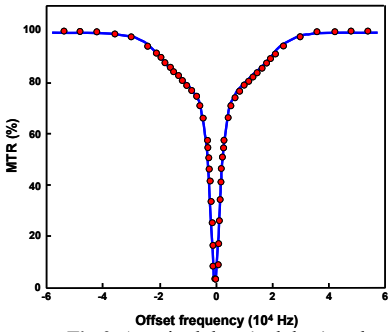

Fig.3. Acquired data (red dots) and fitted Z-spectrum (blue line) using the five-site model.

Introduction

Recently, Guerbet (WO 2006/032705) and Aime S. et al. [1] have introduced LipoCEST, a new class of contrast agent for CEST-MRI, which are lipid bilayer filled with a huge amount of lanthanide-chelate complexes. LipoCEST agents provide a tremendous amplification factor, yet they suffer from a relatively modest chemical shift (2-28 ppm). Consequently, their detection *in vivo* is hampered by a contamination of endogenous Magnetization Transfer (MT) contrast [2] coming from macromolecules and amide protons. To achieve CEST imaging, it is therefore important to separate this background endogenous MT contrast from the exogenous Contrast Agent (CA) detection. Besides, MT effect varies significantly according to tissue. Thus, we propose a five-site model to sort out endogenous and exogenous contribution to the CEST signal by calculating specific exchange parameters for each tissular compartment.

Subjects and Methods

Phantoms. *In vitro* experiments were performed on rat brain homogenates embedded in agarose matrix containing various macromolecules (0.8/1.6/3.2/6.5% wt) and LipoCEST (Guerbet, France) concentrations ($C_{lipoCEST}$=0/5/10/25 nM ; shift=9ppm).

MRI acquisition. *In vivo* Z-spectra were acquired on a mouse brain using a 7 T small animal MRI scanner (Bruker, Germany) using a home-made quadratic 2.8-cm-diameter ^{1}H coil and a MSME sequence (TE/TR=54/5000ms) preceded by a CW saturation pulse (T_{sat}=400ms, B_{1sat}~7μT, range=[-150;150]ppm). Zspectra have been acquired in the cortex, the sub-cortex, the white matter and in CSF. Figure 1 shows typical regions-of-interest.

Five-site modeling and Z-spectra analysis. The five-site model (Fig.2) is an extension of the model described by Ceckler et al. [3] with added pools accounting for amide protons (H_D) and water molecules shifted by the LipoCEST (H_E). Pool A corresponds to bulk water molecules while pool B corresponds to water protons dipolar-coupled to macromolecular protons (pool C). *In vivo* Z-spectra (Fig.3) of each cerebral structure were fitted using Bloch equations modified for chemical exchange using Matlab software (MathWorks, MA) and a simplex minimization algorithm to extract the characteristic parameters: relaxation times T_{1I} and T_{2I}, the exchange rate K_{exIJ}, as well as the relative fraction of pool J to I: f_{IJ} (I,J=A, B, C and D). LipoCEST parameters (T_{1E}, T_{2E} and k_{exAE}) were fitted using *in vitro* Zspectra. For pool D, a mean chemical shift was considered (δ_D=3.5ppm). The chemical shift of pool E was measured on Zspectra (δ_E=9ppm). A super-Lorentzian lineshape was considered for the macromolecules distribution (pool C, $1/T_{2C}$~30 kHz) [3].

Results

The fitted parameters are summarized in Table 1. They were extracted from the *in vitro* and *in vivo* fits. Overall relaxation times and rates for the endogenous and LipoCEST pools were consistent with the values reported in the literature [3,4]. The exchange rates as well as relative fractions of pools are quite similar for most of cerebral compartments excepted for CSF which contains fewer macromolecules.

Conclusion

This study allows us to establish exchange parameters for the different compartments in the mouse brain. Based on this five-site model which provides a realistic account of most possible proton exchange processes in brain tissues, we confirm that the LipoCEST technology represents a very promising approach for quantitative *in vivo* molecular imaging.

References

1. Aime S et al. Angew Chem 2005 44:5513
2. Terreno E et al. Chemistry. 2009;15:1440
3. Ceckler T et al. JMR 2001 9:27
4. Terreno E. et al. CMMI 2008 3:38

Parameter	Cortex	Sub cortex	White matter	CSF	LipoCEST
k_{exAB} (Hz)	1365	1239	1182	1596	
k_{dipBC} (Hz)	18	13	17	27	
k_{exAD} (Hz)	477	498	423	520	
k_{exAE} (Hz)					59
T_{1A} (ms)	1370	805	807	2288	
T_{2A} (ms)	61	116	98	131	
T_{1B} (ms)	191	118	151	104	
T_{2B} (ms)	3	2	1	1	
T_{1C} (ms)	13	18	61	68	
T_{2C} (μs)	45	44	44	58	
T_{1D} (ms)	6	8	10	2	
T_{2D} (ms)	2	2	1	1	
T_{2E} (ms)					306
T_{2E} (ms)					20
f_{AB}	0,02	0,03	0,03	0,0002	
f_{BC}	0,27	0,41	0,34	0,28	
f_{AD}	0,08	0,08	0,06	0,0001	

Tab.1. Fitted parameters for our five-site model obtained *in vitro*, *in vivo* and from rat brain homogenates.