APPARENT DIFFUSION COEFFICIENT OF GD-BASED CONTAST AGENTS ASSESSED IN VIVO IN THE RAT BRAIN USING DYNAMIC T1 MAPPING

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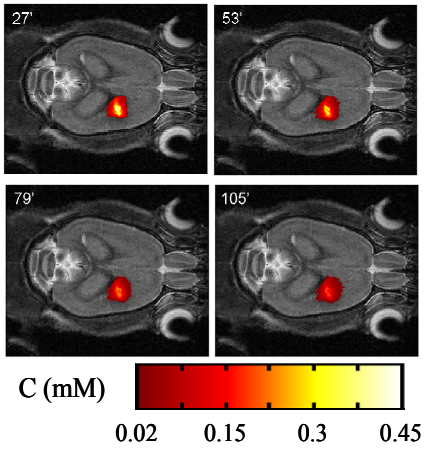

Fig.1 Concentration map of P792 27', 53', 79' and 105' after injection

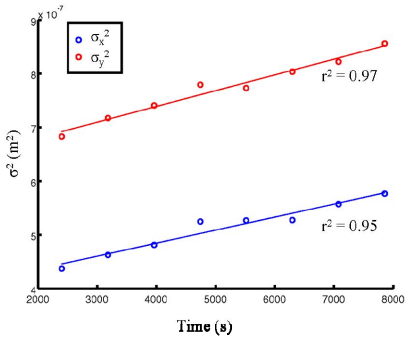

Fig.2 Estimation of the apparent diffusion coefficient of P792 in two orthogonal directions

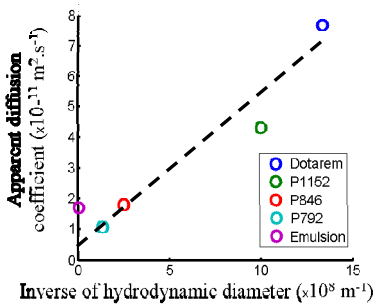

Fig.3 ADC_{mean} versus the inverse of CA size. Data for the smallest molecules have been fitted with a linear model (Stoke-Einstein law)

CA	d_H (nm)	ADC_{mean} (10^{-11} $m^2.s^{-1}$)	T_{diff} (min)	n
Dotarem	< 1	7.7	1	2
P1152	~ 1	4.3	2	2
P846	4	1.5	6	3
P792	7	1.1	8	3
Gd based emulsion	180	1.7		1

Table 1 Estimated ADC_{mean} = 1/2×(ADC_x+ADC_y) and diffusion time T_{diff} along 100µm

Introduction

Gadolinium-based contrast agents (Gd-based CA) have been used for many years for various MRI applications including more recently MR-based molecular imaging with targeted compounds. One of the most important factors to consider for brain applications is the diffusivity/transport of these probes through the blood-brain barrier and the cerebral tissue to their target. This study proposes a methodology allowing *in vivo* quantification of Gd-based CA concentration by acquiring dynamic T_1 maps. This approach has been applied to estimate *in vivo* in the rat brain the apparent diffusion coefficients (ADC) of five CA with different hydrodynamic diameters (d_H). Based on the measured ADC, the time necessary for each compound to diffuse throughout the whole brain was estimated.

Materials and Methods

Animal protocol. Anesthetized male rats were injected in the right caudate-putamen with 2µL of different Gd-based CA provided by Guerbet (Roissy Charles de Gaulle, France): Dotarem 10mM (d_H<1nm), P1152 2.5mM (d_H~1nm), P846 2.5mM (d_H~4nm), P792 10mM (d_H~7nm) and a Gd-based emulsion 2.5mM (d_H~180nm).

MRI acquisitions. MRI experiments were performed on a 7T Pharmascan scanner (Bruker, Ettlingen, Germany) using a 3-cm-diameter birdcage ^{1}H coil. Images were acquired before and every 10' after injection with an IR-TurboFLASH sequence (TE/TR=2.4/4.8ms, 30 inversion times spaced by 96.6ms). T_1 maps were generated using the approach proposed by Deichmann et al. [1]. The longitudinal relaxivities (r_1) of the five Gd-based CA were measured separately *in vitro* in an agar matrix assuming that they hardly differ from those in the brain tissue.

Data processing. Parametric T_1 maps were generated using a pixel by pixel fitting procedure written in Matlab (The MathWorks Inc, Natick, USA). Concentration maps after injection were calculated from corresponding T_1 maps using the T_1 map before injection ($T_{1,0}$) and the measured r_1: $C = 1/r_1 \times (1/T_1 - 1/T_{1,0})$. Each concentration map was adjusted with a 2D-Gaussian function, and the square of the full half width maxima in two orthogonal directions (σ_x^2 and σ_y^2) were plotted as a function of time to determine an ADC ($\sigma_{x,y}^2 \sim 2.ADC_{x,y}.t$) (Fig.2). This model is consistent with a 2D free or tortuous diffusion in a homogeneous environment.

Results and Discussion

Figure 1 shows a subset of the calculated quantitative concentration maps for one of the Gd-based CA along the 2-hrs acquisition after injection revealing its diffusion through the cerebral tissue. Mean ADC of the five Gd-based CA are given in Table 1. They are in good agreement with other studies [2] and show a consistent behavior with the inverse of hydrodynamic diameter as predicted by Stoke-Einstein law (Fig.3) at least for the four smallest molecules. For these probes, the time (T_{diff}) necessary to diffuse along a characteristic distance between two capillaries in the brain (100µm) is estimated to be less than 10 minutes (Table 1). Therefore, it is reasonable to conclude that these compounds can diffuse throughout the whole brain in a time compatible with *in vivo* molecular imaging.

Considering the composition of extracellular space, the diffusion process should be considered as hindered by brain tissue instead of occurring in obstacle-free medium. This hindrance is usually quantified introducing the tissue tortuosity: $\lambda = \sqrt{D / ADC}$ where D is the free diffusion coefficient. A first experiment was performed using the same methodology to measure the free diffusion coefficient of P792 in an agar matrix: $D = 2.6.10^{-11} m^2.s^{-1}$, leading to a tissue tortuosity of $\lambda \approx 1.5$ which is in good agreement with the literature [3]. Notice that in case of tortuous diffusion, the Stoke-Einstein law remains valid considering a correction factor of λ^2.

Interestingly, the large Gd-based emulsion (180nm diameter) exhibits a different behavior suggesting its diffusion is driven by another mechanism than free or tortuous diffusion (such as active transport by macrophages) which remains to be investigated.

Conclusion

In this study, we have demonstrated that the diffusion of Gd-based CA with sizes up to 180 nm can be investigated *in vivo* using dynamic T_1 mapping in the rat brain. An ADC could be estimated for each compound opening the way to a better understanding of the diffusion mechanisms of supra-molecular imaging probes and to characterize brain tissues in term of tortuosity.

References

[1] Deichmann et al., Mag Res in Med (1999), 42:206-209
[2] Thorne et al., PNAS (2006), 103:5567-5572
[3] Nicholson and Syková, Trends Neurosci (1998), 21:207-215