Estimation of intrinsic relaxation parameters of human brain metabolites *in vivo*

S. Mangia[1], M. Garwood[1], P-G. Henry[1], K. Ugurbil[1], and S. Michaeli[1]
[1]Radiology, University of Minnesota, Minneapolis, MN, United States

Introduction

The measurement of metabolite concentrations by ^{1}H MRS is widely used in biomedical research to provide *indirect* information about the metabolism/function of the investigated region. However, altered metabolism can occur also in presence of unchanged concentrations of the involved metabolites, therefore a more *direct* measurement of the dynamics of metabolites is desirable. This goal can be achieved by relaxation measurements which employ adiabatic pulses, since the analysis of the rotating frame longitudinal, $R_{1\rho}$, and transverse, $R_{2\rho}$, relaxation rates allows the extraction of *fundamental* relaxation parameters of the sample [1]. These are: rotational, translational or exchange correlation times (τ_c, τ_d, τ_{ex} for dipolar interactions, diffusion, and exchange, respectively) and the populations of the sites with different apparent diffusion coefficients (ADC) or undergoing exchange. A preliminary study conducted at 4T on the human brain of eight healthy volunteers reported the $R_{1\rho}$ and $R_{2\rho}$ of the methyl groups of N-Acetylaspartate (NAA) and total-Creatine (t-Cr, i.e. creatine plus phosphocreatine) during two different adiabatic full passage (AFP) pulses of the Hyperbolic Secant (HS) family, HS1 and HS4 [2]. However, only a qualitative description of the results was provided at that time. The present study aims at estimating the intrinsic relaxation parameters characterizing the dynamics of NAA and t-Cr from the *in vivo* measurements of adiabatic $R_{1\rho}$ and $R_{2\rho}$, based on the theoretical descriptions of the relaxation channels of dipolar interactions (dd), isochronous exchange (IE) between spins with identical chemical shifts ($\delta\omega$=0), anisochronous exchange (AE) between spins with different chemical shifts ($\delta\omega\neq$0), and diffusion. The performed simulations relied on few *a-priori* assumptions based on known properties of NAA and t-Cr *in vivo*.

Methods

The relationships used to extract the fundamental relaxation parameters from the measured adiabatic relaxation rates were detailed in [1,3-6]. Briefly, relaxations during adiabatic rotation in the weak field approximation can be represented as an average of instantaneous time-dependent contributions due to the different relaxation channels:

$$\overline{R}_{1,2\rho} = \frac{1}{T_p}\int_0^{T_p} R_{1,2\rho,ex}(t)dt + \frac{1}{T_p}\int_0^{T_p} R_{1,2\rho,dd}(t)dt = \frac{1}{T_p}\int_0^{T_p} f(\omega_{eff}(t);\alpha(t))dt$$

where T_p is pulse time duration, the subscript 'dd' refers to dipolar interactions, while 'ex' relates to both isochronous and anisochronous exchange including diffusion. The time evolution of $R_{1,2,\rho}$ during the AFP pulse originates from the time-dependence of the effective frequency, $\omega_{eff}(t)$, and of the direction of the effective field relative to the *z*-axis, $\alpha(t)$. Depending on the properties of the spin motion, the measured relaxation rates can thus be modulated by different settings of the AFP pulses, for instance different modulation functions as used in the present study. The experimental methods used to measure the $R_{1\rho}$ and $R_{2\rho}$ of NAA and t-Cr during AFP pulses where described previously in [2]. Compared to the previous study [2], two additional subjects were investigated (for a total of 10 healthy volunteers); moreover, data were analyzed with LCModel with proper basis-sets [7] to guarantee optimal quantification of the metabolite signal intensities. Simulations were performed with Mathematica 5.3.

Results and discussion

		dd	IE	Diffusion	AE	total (estimated)	total (measured)
NAA	$R_{1\rho}$ (HS1)	0.73 ± 0.07	0	NA	NA	0.73 ± 0.07	0.73 ± 0.08
	$R_{1\rho}$ (HS4)	0.73 ± 0.07	0	NA	NA	0.73 ± 0.07	0.74 ± 0.04
	$R_{2\rho}$ (HS1)	0.73 ± 0.07	0	1	0	1.73 ± 0.07	1.8 ± 0.2
	$R_{2\rho}$ (HS4)	0.73 ± 0.07	0	1	0	1.73 ± 0.07	1.7 ± 0.1

		dd + IE	Diffusion	AE	total (estimated)	total (measured)
t-Cr	$R_{1\rho}$ (HS1)	1.26 ± 0.03	NA	NA	1.26 ± 0.03	1.25 ± 0.04
	$R_{1\rho}$ (HS4)	1.53 ± 0.03	NA	NA	1.51 ± 0.03	1.57 ± 0.07
	$R_{2\rho}$ (HS1)	1.66 ± 0.03	1	1.26 ± 0.17	3.9 ± 0.2	4.0 ± 0.2
	$R_{2\rho}$ (HS4)	1.66 ± 0.03	1	0.82 ± 0.11	3.5 ± 0.1	3.3 ± 0.3

- Numbers are rate contributions in s^{-1}.
- NA: not applicable (or negligible).
- Red color indicates numbers based on *a-priori* assumptions.
- Errors of measured rates are estiamted from the mono-exponential fit of the averaged signal-intensity decays obtained by summing spectra from 10 subjects.
- Errors on estimated rates are calculated by varying the intrinsic relaxation parameters to fit the experimental data.

NAA. The contribution of the exchange channels to relaxation can be neglected *a priori* in the case of NAA, because this metabolite undergoes very slow turnover, behaving in tissue mostly as a free molecule. Consistent with this simplification, the measured $R_{1\rho}$ of the methyl group of NAA could be simulated by dipolar interactions of free tumbling spins, characterized by $\tau_c = (1.1 \pm 0.1)\cdot10^{-11}$ s. As expected for dipolar interactions in this range of τ_c, the measured rotating frame relaxation rates did not exhibit any modulation due to pulse modulation functions. Diffusion contributed by ~1 s^{-1} to $R_{2\rho}$.

t-Cr. Creatine and phosphocreatine are heavily involved in metabolic processes regulated by enzymatic reactions, thus justifying the assumption of two pools of t-Cr undergoing isochronous exchange: one of free t-Cr (site A), and one of bound t-Cr (site B). Consistent with this consideration, a modulation introduced by HS1 and HS4 was observed in the measured $R_{1\rho}$ of t-Cr. The τ_c of the free tumbling site (A) was assumed to be similar to the case of NAA, $\tau_{c,A}=1.1\cdot10^{-11}$ s. In addition, the population of sites A and B were assumed as P_A=0.85 and P_B=0.15, similarly to the distribution of free and bound water in tissue [4]. Based on these assumptions, the measured $R_{1\rho}$ of t-Cr during HS1 and HS4 were found to be consistent with $\tau_{c,B}=(6 \pm 1)\cdot10^{-8}$ s and K_{ex}= (6.3 ± 0.2) s^{-1}. These values were then utilized to estimate the contribution of IE to $R_{2\rho}$. Diffusion was considered to contribute to $R_{2\rho}$ by 1 s^{-1}, as for NAA, based on the similar ADCs reported for NAA and t-Cr in the rat brain [8]. Finally, the remaining contributions to $R_{2\rho}$ during HS1 and HS4 were accounted by AE, and they were consistent with an exchange process characterized by $P_AP_b(\delta\omega*2\pi)^2\tau_{ex}$ = (1.5 ± 0.2) rad^2/s.

Water. For comparison, the intrinsic relaxation parameters of water estimated from the human cortex [3,4] are: $\tau_{c,A}=7.6\cdot10^{-11}$ s, $\tau_{c,B}=5.6\cdot10^{-9}$ s, K_{ex}=18.8 s^{-1}, $P_AP_b(\delta\omega*2\pi)^2\tau_{ex}$ = 20 rad^2/s.

Conclusion. The analysis of the rotating frame relaxations during adiabatic pulses allowed the extraction of intrinsic relaxation parameters characterizing the dynamics of metabolites in the human brain. They were found to be substantially different from the case of water. Since these parameters are supposed to be sensitive to different functional states, the adiabatic relaxation methods holds great potential to quantitatively investigate metabolic processes of interest for biomedical research.

References : [1] Michaeli et al. CAC 2008;4:8 [2] Mangia et al. Proc ISMRM 2008, abs 693 [3] Michaeli et al. JMR 2004;169:293 [4] Michaeli et al. JMR 2006;181:138 [5] Lee, Springer MRM 2003;49:450 [6] McConnell J Chem Phys 1958;28:430 [7] Deelchand et al, Proc ISMRM 2007, 1799, [8] Pfeuffer et al. JCBFM 2000;20:736. **Acknowledgments:** BTRR - P41 RR008079, P30 NS057091, R01NS061866 and R21NS059813.