Probing dynamics of human brain metabolites with ^{1}H MRS by $T_{1\rho}$ and $T_{2\rho}$ adiabatic relaxations

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Introduction

In vivo, brain metabolites undergo multiple dynamic processes which typically appear in the NMR time scale in the intermediate and slow regimes, such as chemical reactions or restricted diffusion in the cellular environment. The capability of magnetic resonance spectroscopy (MRS) to provide quantitative information on dynamics of brain metabolites enables valuable insights into biochemical processes relevant to brain function, either in healthy or diseased conditions. Simultaneous analysis of the rotating frame longitudinal, $T_{1\rho}$, and transverse, $T_{2\rho}$, relaxations during adiabatic pulses allows the extraction of fundamental relaxation parameters of the system. 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 or undergoing exchange. It has been shown that the relaxations at specific sites could be modulated using different adiabatic pulse modulation functions (1,2,3). The intrinsic relaxographic "shutter-speed" for the process can thus be tuned to different exchange or diffusion conditions (2,4). This property of adiabatic pulses was used to generate brain tissue contrast (5) and applied for the treatment monitoring of rat glioma. At high magnetic fields, the rotating frame relaxation measurements are more sensitive to slow molecular motion (with the sensitivity around $1/\tau_c \approx \omega_{eff}$, where ω_{eff} is the effective radiofrequency field in frequency units) as compared to the laboratory frame (LF) T_1 and T_2 relaxation measurements. Similar considerations are valid also in the case of metabolites. The goal of the present study was to perform $T_{1\rho}$ and $T_{2\rho}$ adiabatic relaxation measurements to probe the dynamics of human brain metabolites. In order to prove the principle of this methodological approach, we specifically focused on the methyl groups of N-acetylaspartate (NAA) and creatine/phosphocreatine (total Cr, t-Cr). These compounds are indeed intracellular metabolites, known to be involved in biochemical processes with notably different dynamics. Based on the findings presented in this work, the different dynamics of NAA and total-Cr result in different $T_{1\rho}$ and $T_{2\rho}$ adiabatic relaxations.

Methods

Eight healthy volunteers were examined on a 4T/90 cm magnet (Magnex Scientific, UK), interfaced to Varian INOVA console. LASER (TE= 39 ms, TR=7s) was used to acquire spectra from a 8ml voxel localized in the primary visual cortex. Macromolecules (MM) contribution was minimized by MM-nulling using inversion recovery (inversion time, TI=0.18s). A train of the hyperbolic secant (HS) adiabatic full passage (AFP) pulses of the HSn (n=1 and 4) family was placed prior or after the coherent excitation by adiabatic half passage (AHP) pulse, leading to $T_{1\rho}$ or $T_{2\rho}$ relaxations, respectively (5). (Pulse length=6ms; adiabaticity factor R=20; peak-power $\omega_1^{max}/(\pi)$=1.3 kHz and 800 Hz for the HS1 and HS4 pulses, respectively; phases prescribed according to MLEV-4,-8,-16,-32 with no interpulse time intervals). The signal intensity (SI) decay curves were measured when the number of AFP pulses in the pulse train was incremented from 4 to 32. After applying frequency and phase corrections on single scans, groups of 16 FIDs were summed accordingly to different decay times. SI of unsuppressed water and of the methyl groups of NAA (2.01 ppm) and t-Cr (3.03 ppm) were quantified, and then normalized to the SI corresponding to the shortest train of adiabatic pulses. The inter-subject averages of normalized SI were finally utilized to estimate $T_{1\rho}$ and $T_{2\rho}$ relaxation time constants during the HS1 and HS4 pulse trains.

Results and discussion

A representative spectrum used for the estimation of relaxation parameters is shown in Fig. 1. Our results demonstrate that both $T_{1\rho}$ and $T_{2\rho}$ adiabatic relaxations of the methyl groups of t-Cr and NAA are significantly different (Fig. 2). Specifically, $T_{1\rho}$ and $T_{2\rho}$ relaxation time constants of t-Cr were found to be shorter than NAA (see table). Shorter $T_{1\rho}$ of t-Cr is in agreement with previous findings obtained in the rat brain, where the conventional spin-lock continuous–wave $T_{1\rho}$ measurements were employed (6). The theoretical analysis which comprises the model of dipolar interaction between identical spins and the diffusion/exchange of spins between two sites coupled by the equilibrium process (e.g., MConnell relationship (7)) suggested that the rotational correlation times of NAA are τ_c=7 x 10^{-11}s. Same rotational correlation times were assumed for t-Cr, since the dipolar interactions of the methyl groups are not expected to change between t-Cr and NAA. In addition same translational correlation times characterize both t-Cr and NAA, since the apparent diffusion coefficients of NAA and t-Cr were found to be the same *in vivo* (8). Based on these observations and on the experimental data presented in this work, the spin dynamics of t-Cr appeared to be significantly different from NAA. This observation is consistent with the involvement of NAA and t-Cr in biochemical processes characterized by different rates, with the turnover of NAA being very slow compared to the energetic processes involving t-Cr. In addition, the HS1 and HS4 pulses were found to significantly modulate $T_{1\rho}$ of water, NAA and t-Cr, and $T_{2\rho}$ of t-Cr but not of water and NAA. Generally, $\Delta T_{1\rho}$ and $\Delta T_{2\rho}$ of t-Cr between HS1 and HS4 pulses were greater than for NAA. This finding suggested that the sensitivity of the shutter-speed is moving from the fast averaging regime towards the slow dynamic averaging regime, and the exchange kinetics *appear* to slow in this frame of reference. The method proposed advance conventional spectroscopic NMR techniques, which typically have restricted scopes for the relaxation analysis. The results suggest enhanced sensitivity of rotating frame relaxation measurements to metabolic processes.

Figure 1

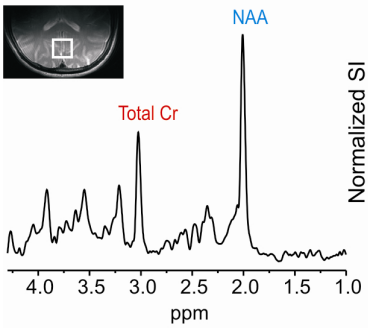
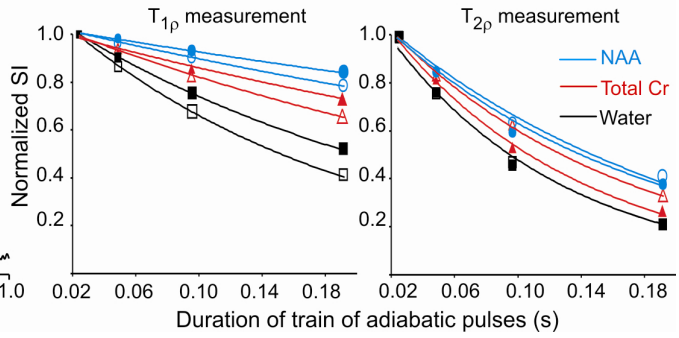


Figure 2



	Water		Total Cr		NAA	
	$T_{1\rho}$ (s)	$T_{2\rho}$ (s)	$T_{1\rho}$ (s)	$T_{2\rho}$ (s)	$T_{1\rho}$ (s)	$T_{2\rho}$ (s)
HS1	0.252 ± 0.003	0.100 ± 0.009	0.55 ± 0.06	0.118 ± 0.005	0.92 ± 0.06	0.16 ± 0.01
HS4	0.183 ± 0.004	0.100 ± 0.007	0.40 ± 0.01	0.150 ± 0.003	0.68 ± 0.03	0.18 ± 0.01

Fig. 1. Representative *in vivo* ^{1}H-NMR spectra from the human visual cortex at 4T. LASER, TE=39ms, TR=7s, NT=16. $T_{1\rho}$ configuration with four HS4 pulses.

Fig. 2. Normalized signal intensities (SI), averaged upon 8 subjects, vs. duration of train of adiabatic pulses, in $T_{1\rho}$ (left) and $T_{2\rho}$ (right) measurements. Empty and bold symbols represent data for HS1 and HS4 pulses, respectively.

References

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Aknowledgments

BTRR - P41 RR008079, P30 NS057091.