Multi-exponential characteristics of acetate diffusion-weighted MRS signal in the in vivo rat brain at 14.1T

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Target audience: *In vivo* NMR Spectroscopists and Neuroscience Researchers.

Purpose: Acetate (Ace) is a well-known glial-specific substrate that has been used extensively to study glial metabolism [1-3]. Mathematical modeling of Ace oxidative metabolism during Ace infusion requires information about uptake and distribution of Ace in brain tissue. It has been demonstrated that diffusion MR is able to investigate the compartmentalization of molecules inside the brain [4]. The aim of this study is to address the diffusion characteristics of Ace in the rat brain *in vivo*, combining large diffusion weighting and ^{1}H MRS methods. The current study is based on the assumption that metabolites in intracellular and extracellular compartments experience different diffusion behaviors.

Methods: All experimental procedures involving animals were approved by the local veterinary authorities. Three adult rats (male, 200-225g) have been prepared for intravenous infusion of α-chloralose as anesthesia and Ace according to our previous protocol [5]. All experiments were performed on a 14.1T/26cm horizontal magnet with a 12-cm gradient coil insert (400mT/m, 120μs) using a home-built quadrature transceiver. ^{1}H-MRS data were acquired using localized diffusion weighed STEAM-based spectroscopic pulse sequence [6] with optimum parameters (echo time of 50 ms and a mixing time of 49 ms) to suppress GABA resonance which has overlap with Ace at 1.89 ppm [5]. Diffusion weighting was applied simultaneously along three orthogonal diffusion gradient directions (i.e. x, y and z) to cover the wide b range of 0 to 18 ms/ μm^2. *In vivo* data was acquired with gradient duration of δ=5 ms, gradient separation of Δ=75 ms and gradient strength of 0, 2.8, 4.9, 6.5, 9.1, 13.7, 15.9 and 19.1 G/cm in a voxel of 240 μl enabling sufficient sensitivity to correct the phase of single scan metabolite spectra at all b values. Metabolite concentrations were quantified with LCModel. The basis sets for LCModel were simulated by NMRScope-B plugin to JMRUI software. To compare with previous *in vivo* studies of metabolite diffusion, data for NAA and Ace at b range of 0 to 5 ms/ μm^2 was fitted with a monoexponential diffusion model to estimate the apparent diffusion coefficient (D_{mono}^{App}). Furthermore, data for whole b range in Fig 1 was fitted using following bi-exponential equation where (D_{fast}^{App}, D_{slow}^{App}) represent apparent diffusion coefficients of the fast and slow decaying signal components of each metabolite and P_{fast}^{App} reflects the relative contribution of the fast component in the metabolite signal. S and S_0 are signal intensity with and without diffusion gradients [4]. Diffusion behavior of Ace was compared with NAA, known as a primarily intracellular metabolite.

$$\frac{S}{S_0} = P_{fast}^{App}.\exp\left(-b.D_{fast}^{App}\right) + \left(1 - P_{fast}^{App}\right).\exp\left(-b.D_{slow}^{App}\right)$$

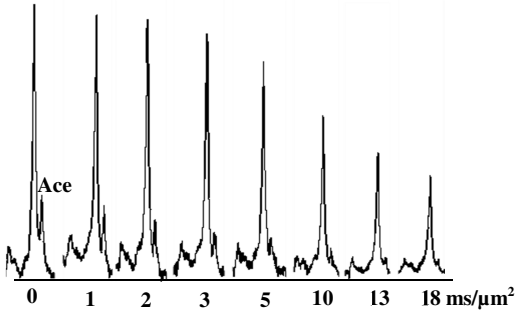

Fig 1. Series of ^{1}H NMR spectra for NAA and Ace at increasing diffusion weighting.

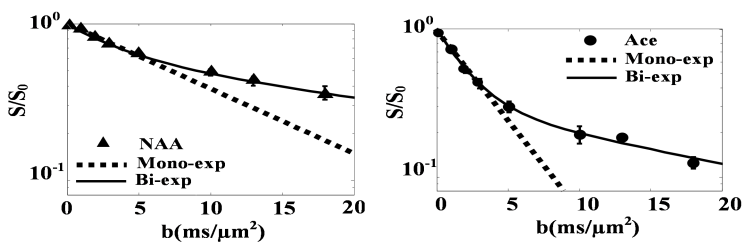

Fig 2. The normalized Diffusion-attenuated ^{1}H MRS signal intensities of NAA and Ace in the rat brain *in vivo* with mono-exponential fit (b≤5ms/μm^2) and bi-exponential fit (0 ≤b≤ 18 ms/μm^2) in logarithmic plot. The error bars indicate the standard deviation of data averaged over three animals.

Results and discussion: The remarkable sensitivity and spectral resolution of localized ^{1}H MRS at 14T allowed a precise measurement of the diffusion properties of NAA and Ace in the rat brain *in vivo* at very high diffusion weighting (Fig 1), under previously used Ace infusion protocol. Our D_{mono}^{App} values for NAA in Table 1, fitted in the b range of 0 to 5 ms/μm^2, are comparable with previous studies [4, 7]. Strong attenuation of Ace in the b range of 0-5ms/μm^2 in Fig 2 results in three times faster diffusion for Ace compared to NAA. This result is in good agreement with our previous report [5]. In addition, the present study shows clear deviation from mon-exponential attenuation for Ace and NAA (Fig 2) when extending the diffusion weighting by a factor of 3.5. The increased D_{mono}^{App}, D_{fast}^{App} and P_{fast}^{App} of Ace relative to NAA in table 1 point out the smaller molecule size of Ace and furthermore suggest that a significant concentration of Ace could be distributed in the extracellular space. The slow diffusion component of Ace is in the same range as for NAA; however Ace has slightly higher D_{slow}^{App} than NAA. This supports the distribution of Ace in a larger compartment than NAA, which is consistent with the different localization of Ace (glial compartment) and NAA (neuronal compartment) [1, 4].

Table 1. Apparent diffusion coefficients of metabolites estimated by mono-exponential and bi-exponential fitting of ^{1}H MRS data in the rat brain *in vivo*.

Metabolite	D_{mono}^{App} (μm^2/ms)	P_{fast}^{App} (%)	D_{fast}^{App} (μm^2/ms)	D_{slow}^{App} (μm^2/ms)
NAA	0.09 ±0.01	37 ±5	0.27 ±0.06	0.031 ±0.005
Ace	0.26 ±0.02	68 ±10	0.52 ±0.11	0.051 ±0.013

Conclusion

The increased diffusion of Ace reflects its smaller molecule size and indicates different *in vivo* diffusion barriers and cellular restrictions compared to NAA. This result suggests different intracellular distribution space for Ace in the rat brain.

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