Regional Variations of Metabolite Concentrations in the Rat Brain Assessed with in vivo ¹H MR Spectroscopy at 16.4T

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Introduction

In vivo ¹H NMR spectroscopy provides a neurochemical profile containing invaluable information associated with energy metabolism, membrane metabolism, antioxidants and osmolytes [1]. Postnatal and regional changes in metabolite concentrations were reported in the rat [2] and the mouse brain [3], even in the very small region of the hypothalamus [4]. All these results demonstrated different metabolite concentrations in specific brain regions. The purpose of this study was 1) to demonstrate acquisitions of spectra in different brain regions at 16.4T 2) to investigate the anatomical distribution of cerebral metabolites.

Methods

Five Sprague-Dawley rats (193 ± 5.2 g) were measured under isoflurane anesthesia. All experiments were performed on a Bruker console (Bruker BioSpin GmbH, Ettlingen, Germany) interfaced to a 16.4 T/26 cm horizontal magnet (Magnex Scientific, Abingdon UK). An ultra-short TE STEAM sequence (TR = 5000 ms, TM = 20 ms, TE = 1.7 ms, 2048 complex data points) was applied to maximize observable metabolites by reducing T₂ relaxation and J-modulation. Three volumes-of-interest, hippocampus (7.0 x 2.0 x 3.0 mm³), thalamus (6.5 x 3.5 x 2.5 mm³) and striatum (7.7 x 3.0 x 3.0 mm³) were selected based on MR images acquired with a RARE sequence. Different number of averages, 320 in hippocampus and 256 in thalamus and in striatum, were applied. An automatic shimming method (FASTMAP) [5] resulted in an average linewidth (tCr methylene signals) of 20 Hz in hippocampus, 23 Hz in thalamus and 23 Hz in striatum, respectively. Measurement time was 22 min in thalamus and striatum and 27 min in hippocampus. Correction of frequency shifts was not necessary based on a prior frequency drift measurement (17 Hz/h).

Quantitative analysis was done with LCModel [6] containing a basis set composed of simulated metabolites and macromolecular components. Statistical analysis was performed with SPSS software (SPSS 15.0 for Windows, SPSS Inc., Chicago, IL USA). The MANOVA was used to determine regional differences, setting statistical significance at p < 0.05.

Results and Discussion

Representative in vivo ¹H MR spectra from different brain regions, hippocampus, thalamus and striatum, are shown in Fig. 1. All metabolites were quantified with CRLBs below 50% except one case, glycine in striatum (54%) among a total of 15 spectra (3 brain regions x 5 rats), implying stable and high data quality. Remarkable spectral differences were increased PE in striatum, increased GABA and substantially decreased Tau in thalamus, marked with arrows in Fig. 1. All metabolites except Asp and NAA showed statistically significant variations, summarized in Fig. 2. Precise measurements of metabolic variations in different brain regions were achieved by fully making use of advantages of the ultra-high field strength. Different anatomical distribution of metabolites was reflected with specific alterations of metabolites in particular regions. Accurate detection of changes in the order of below 0.5 µmol/g in the rat brain in vivo would expand possibilities of using in vivo ¹H NMR spectroscopy in pre-clinical research.

![Figure 1. In vivo ¹H NMR spectra of the hippocampus (bottom row), thalamus (middle row) and striatum (top row) of the rat brain obtained with an ultra-short STEAM sequence.](image)

Table 1 shows the concentrations of major metabolites in different brain regions. The metabolites were quantified with CRLBs below 50% except glycine in striatum (54%). The results demonstrated significant concentration differences among the three brain regions, with increases in PE and GABA and decreases in Tau in the striatum.

![Figure 2. Concentrations of cerebrospinal fluid metabolites in thalamus (white), striatum (gray) and hippocampus (black) quantified in LCModel. Error bars represent standard deviations. Statistical significance was expressed as *P < 0.05, **P < 0.005 and ***P < 0.0005.](image)

References