^{1}H NMR quantitation of 11 metabolites in the brain at 3 Tesla

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Introduction

^{1}H MRS has been widely used to investigate brain metabolism under normal and pathological conditions. A large majority of studies has been performed at long echo time in order to simplify the spectrum, generally restricting the detection to total N-acetyl-aspartate (tNAA), creatine (tCr) and choline (tCho). In contrast, a limited number of studies has taken advantage of short echo time ^{1}H MRS combined with automatic fitting procedure in order to detect J-modulated metabolites with reasonable accuracy (sd < 30%). This approach has allowed quantifying up to 5 metabolites at 1.5 T, 7 at 2 T, 16 at 4 T and 18 at 9.4 T [1-6]. The purpose of this study was to determine how many brain metabolites could be accurately quantified using this approach on a whole-body 3 T system. In order to answer this question, MR spectra were acquired under optimal experimental conditions on anaesthetized primates.
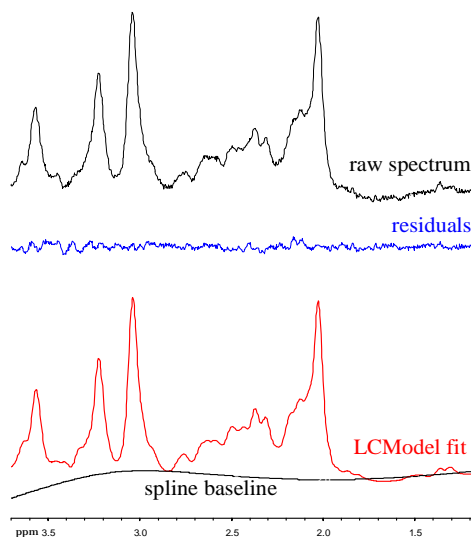

Fig. 1. *LCModel fit of a short echo time ^{1}H NMR spectrum acquired in one monkey.*
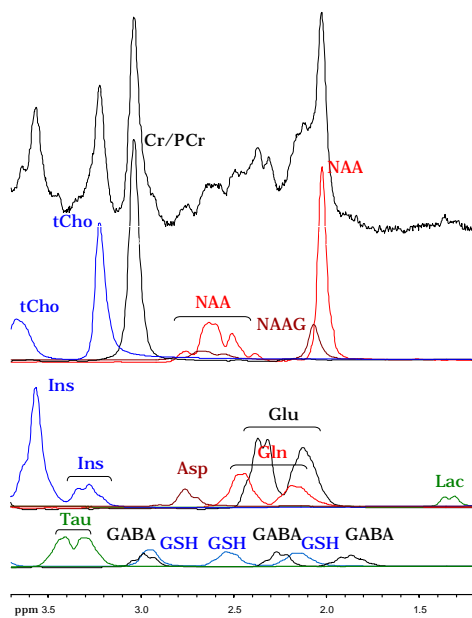

Fig. 2. *Individual contributions of brain metabolites to the in vivo ^{1}H spectrum.*

Materials and Methods

Animal preparation. NMR studies were conducted on 3 healthy macaque monkeys (*macaca fascicularis*, body weight ~8 kg, 3-4 experiments for each monkey leading to 11 different measurements). Animals were anaesthetized using i.v. infusion of propofol (~200 µg/kg/min), intubated and ventilated.

Spectra acquisition. NMR experiments were performed on a whole-body 3 Tesla system (Bruker, Ettlingen, Germany) equipped with a surface ^{1}H probe. T1-weighted images were acquired for positioning of the 3.9mL voxel in the center of the brain and for calculation of water content within the voxel [7]. An optimized 8-ms echo time PRESS sequence with BISTRO-type OVS [8] and VAPOR water suppression [9] was used. After manual shimming down to 7 Hz, 3 different spectra were acquired: (i) a raw metabolite spectrum (TR 2500, 432 scans), (ii) a macromolecule (MM) spectrum by adding an adiabatic inversion pulse to the sequence (TR 1000, 1024 scans) [10] and (iii) a water spectrum taken as an internal concentration reference (TR 5000, 8 scans) [11].

Spectra processing. After zero filling to 8k points, MM contribution was automatically subtracted from the metabolite spectrum using Matlab (The MathWorks Inc., Natick, MA, USA). The resulting spectrum was analyzed using the frequency domain LCModel software [2] in the 1.0-3.7 ppm range since signal above 3.7 ppm was partly affected by water suppression. The basis set was made of *in vitro* collected spectra of lactate (Lac), NAA, Cr, PCho, GPC, GABA, glutamate (Glu), glutamine (Gln), aspartate (Asp), taurine (Tau), myo-inositol (Ins), glucose (Glc) and alanine (Ala). The NAAG spectrum was derived from NAA by frequency shift and the glutathione (GSH) spectrum was simulated. Comparison with the water spectrum then led to absolute quantitation of the metabolites included in the basis set [7].

Results

Fig. 1 presents a raw spectrum without filtering (after MM subtraction). Residuals, best fit and spline baseline as determined by LCModel are shown. Individual metabolite contributions are shown in Fig. 2. Metabolite concentrations are presented in Table 1.

Discussion

Absolute tissue concentrations were estimated for up to 10 metabolites with Cramér-Rao (CR) lower bounds below 15%. In addition, lactate was quantified with higher CR lower bounds (11 to 30%) due to its lower level. Glu/Gln separation was achieved and confirmed *in vitro* (data not shown). Among the 11 metabolites listed in table 1, 10 were detected and quantified by LCModel in each experiment. GABA detection by LCModel failed once in the experiment presenting the lowest SNR. Metabolite concentrations are in good agreement with literature data for human brain [1-5], arguing in favor of similar neurochemical profile for both species. As shown on Fig. 1, residual peaks could be seen around 2.15 and 3.40 ppm. The approximation of NAAG basis spectrum by a shifted NAA spectrum is likely to explain the residual peak at 2.15ppm. Residuals around 3.40 ppm are probably due to the fact that glucose could not be accurately detected by LCModel in the 1.0-3.7 ppm window, so that glucose resonances around 3.40 ppm were partly ascribed to Tau. This explanation is consistent with Tau level in this study being slightly higher than in humans (Table 1). Further development will include implementation of more selective water suppression, allowing a larger analysis window for improved glucose and taurine detection.

Conclusion

This work demonstrates that combination of short echo time ^{1}H MRS with LCModel analysis allows for reproducible absolute quantitation of 11 brain metabolites at 3 Tesla with CR lower bounds below 30%. With the increasing availability of 3 T clinical MR scanners, this methodological approach should prove useful for clinical diagnosis and therapy monitoring.

	Concentration (mM)	CR range (%)	Literature data (mM)
Asp	1.8 ± 0.4	9-15	1.6-3.3[1, 4, 5]
tCho	1.7 ± 0.4	2-4	0.9-2.2[3, 4]
tCr	10.6 ± 0.9	1-3	5.5-11.6[3, 4]
GABA *	1.3 ± 0.3	9-11	1.1-3.1[4, 5]
Gln	3.1 ± 0.4	4-6	1.5-5.4[3, 4]
Glu	9.4 ± 1.3	2-3	6.0-8.8[3, 4]
GSH	1.2 ± 0.6	4-7	1.0-2.3[1, 4]
Ins	4.8 ± 0.4	2-4	3.1-5.8[3, 4]
Lac	0.5 ± 0.3	11-30	0.3-1.0[1, 4]
tNAA	9.5 ± 0.8	1-3	8.4-12.2[3, 4]
Tau	3.7 ± 0.4	4-7	2.7-2.9[4, 5]

Table 1. *Metabolite concentrations (n=11 except *n=10 , mean ±s.d.)*

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