Quantitation of GABA in Human Brain Using MEGA-PRESS Editing and LCM Analysis

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Synopsis

We describe a protocol that allows the Linear Combination Model (LCM) routine to be applied to the analysis of GABA edited spectra. The editing sequence is based on the MEGA-PRESS editing method, and has been adjusted to use the formate peak as an internal chemical shift reference in order to generate model spectra. Our results show an *in vivo* GABA to Cr ratio of 0.19 (±0.04) and a GABA concentration of 1.52 mmol/kg (±0.32), that are in agreement with values published elsewhere.

Introduction

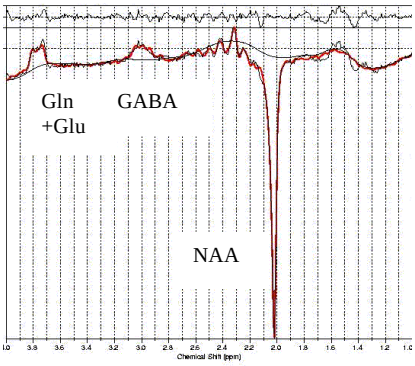
γ– Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the human brain. Dysfunction of the GABAergic system has been implicated in the pathology of a wide range of neurological and psychiatric disorders. The measurement of GABA *in vivo* is hence of great interest in the treatment and management of these diseases. Several spectral editing methods have been developed that enable GABA spectra to be obtained. However, in order for quantitative comparison to be made across study sessions and across research centres there is a need for a user-independent automatic fitting routine to be applied. Such an automated approach is the LC-Model [1]. The main problem with the LCM approach is the difficulty of including reference chemical shift and intensity standards in the acquisition of phantom calibration spectra, since such standards will in general fail to pass through the spectral editing process. In this work we investigated the possibility of incorporating the LCM routine into the analysis of GABA editing using the MEGA-PRESS sequence [2]. This uses a double-banded pulse that retains the formate as a reference peak in the edited spectrum and hence allows its use as a reference for generation of the model spectral data.

Methods

MRS experiments were performed on a 3T Varian Inova spectrometer fitted with a standard birdcage coil. We studied 5 healthy control subjects. 1-H spectra were acquired from a 27 ml (3×3×3 cm) localised volume in the occipital region of the brain containing mainly grey matter. For GABA editing we implemented a pulse sequence based on the previously described MEGA-PRESS sequence [2]. A TR of 3s was used, along with selective double-banded 180^o pulses derived from a 20ms Gausian pulse. The frequencies of this hybrid pulse were set to 4.7 ppm (to suppress water), and alternated between a) 1.9 ppm (to edit γ -CH2 GABA) and b) 8.44 ppm (to suppress formate in the phantom acquisition). As a result the model spectra contained a formate peak that was used as a chemical shift reference. For scaling of the model spectra we used locally measured values proportional to the voltage required for a 90^o square pulse, using methods similar to [3]. In order to determine the zero and first order phase corrections of the edited spectra, we used the subspectra from the model solutions. For the *in vivo* spectra the inverted signal from NAA (present due to the finite bandwidth of the Gaussian pulse applied at 1.9 pmm) can be used as the *in vivo* chemical shift reference. In order to be able to express the GABA concentration relative to Cr (since NAA is less ideal as a concentration reference), we used a standard PRESS spectrum acquired from the same volume and with the same TR, and TE=68 ms to calibrate the NAA to Cr ratio. The GABA concentration was then estimated relative to Cr (which was set to 8 mmol/kg, and assumed that the relaxation times of GABA and Cr are similar). In order to reduce the contribution from macromolecules (MM) a metabolite-nulled spectrum was acquired (with a pre-inversion pulse and inversion recovery time adjusted to minimise the Cr peak; TI=0.720 s). This was then subtracted from the edited spectrum and analysed as above.

Results

Fig 1 presents an example of the LCM analysis output from a MEGA-edited GABA spectrum. The SDs for GABA to NAA ratio ranged from (7%–18%) across the subjects. Table 1 shows GABA/Cr relative concentrations measured in this study and compared with other published results.



		GABA/Cr ratio		[GABA]mmol/kg
This study		**0.19**	**(0.04)**	**1.52 (0.32)**
Rothman	[4]	0.13	(0.01)	1.10 (0.10)
Keltner	[5]	0.20	(0.05)	1.60 (0.40)
Hetherington	[6]	0.14	(0.02)	1.15 (0.13)
Tepstra	[2]	0.09	(0.02)	0.75 (0.14)

Table1. Mean and SD of GABA concentrations in this study and comparison with the literature.

Figure 1: LCM fit of MEGA-PRESS GABA edited spectrum. Fit and residuals are shown.

Discussion

We demonstrated the incorporation of the LCM routine into the analysis of MEGA-PRESS edited spectra. This allows a more reproducible, user independent quantitation. The GABA concentrations obtained here are similar to those published elsewhere. Note that the MM contribution is not fully eliminated by the metabolite-nulling. This is due to different levels of MM T1 saturation in metabolite-nulled spectra as compared to non-nulled spectra. This effect could be improved by considering saturation correction of the metabolite-nulled spectrum.

References:

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