Simultaneous Detection of GABA, Glutamate and NAA using MEGA editing and PRESS localization

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Introduction

γ– Aminobutyric acid (GABA), glutamate (Glu) and glutamine (Gln) are major inhibitory and excitatory neourotransmitters, respectively. In vivo measurement of changes in the concentrations of these chemicals is of great interest in the treatment and management of neurological and psychiatric illnesses including depression, epilepsy and schizophrenia. Several methods have been developed for the editing and measurement of GABA and Glu individually [1,2,3]. However, the ability to obtain an edited spectrum from more than one metabolite could be very useful, especially when concentration changes are expected in multiple metabolites as a consequence of disease. Such a measurement could provide a useful marker for disease presence or progression, and would have the practical value of making the MRS study more time efficient. Recently, simultaneous detection of GABA and Glu has been reported using a multi-quantum filter [4], with other resonances eliminated.

Here, we report an approach derived from the MEGA editing technique [5] based on J difference spectroscopy, to simultaneously detect GABA and Glu (in fact Glu+Gln as they are not resolved, referred to as Glu). This approach allows us to also retain NAA in the edited spectrum, hence enabling it to be used as a reference peak for incorporation into a user independent (automatic) spectral analysis fitting routine, such as LCModel [6], as described previously for GABA edited spectra [7].

Methods

Simultaneous editing of GABA, Glu and Gln makes use of the similarities in their molecular structure, and hence their similar J coupling patterns and chemical shift values in 1H MRS spectra. For editing we used a pulse sequence based on the previously described MEGA-PRESS sequence [5] with TE=71ms. One band of the selective double-banded 180˚ pulse was created from a 20 ms Gaussian pulse centred at 4.7 ppm (to suppress water). The second band was an optimised inversion pulse with a slightly wider bandwidth, designed to affect simultaneously the β-CH_2 on GABA at 1.9 ppm, and the CH_2 on Glu at 2.09 ppm. These are the coupling partners to the edited GABA at 3 ppm, and Glu at 3.76 ppm. The frequencies of this pulse were alternated between a) 2.0 ppm (to edit GABA and Glu) and b) symmetric about water. For the in vivo spectra the inverted signal from NAA at 2 ppm can be used as a chemical shift reference. Additionally, its amplitude and phase provide a quality control for the inversion, or allow the monitoring of possible frequency drifts.

In order to reduce the contribution from macromolecules (MM) a metabolite-nulled spectrum was also acquired [8] (with the pre-inversion pulse and inversion recovery delay adjusted to minimise the Cr peak; TI=0.85 s on our system). This was then subtracted from the edited spectrum and analysed as described above.

All MRS experiments were performed on a 3T Varian –Inova spectrometer fitted with a standard birdcage coil. Phantom studies were performed to evaluate editing efficiency. Additionally, 5 healthy control subjects were studied, each having provided informed consent. 1H spectra were acquired from an 18 ml (3×3×2 cm) localised volume in the occipital region. Standard PRESS spectra with the same TE=71 ms were also and Cr was used as an internal concentration reference for estimation of GABA/Glu levels.

Results Fig. 1 shows the inversion profiles for the double banded pulse described above. Fig. 2 shows spectra from the phantom containing solutions of GABA, Glu, NAA, and Cr :from a non-edited standard PRESS sequence (top), and edited with the proposed technique (bottom). Fig. 3 shows an example of a MEGA-edited GABA/Glu spectrum. The concentrations of GABA and Glu obtained were, respectively, 1.36 (0.41) and 13.34 (1.50) mM, similar to values published elsewhere [1, 9].

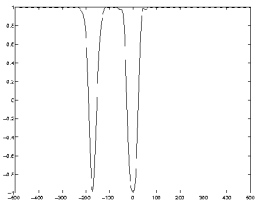

FIG.1

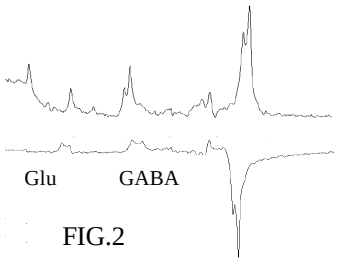

FIG.2

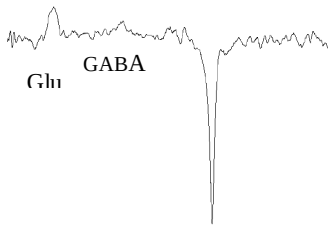

FIG3

Conclusions

The protocol described above allows simultaneous monitoring of GABA, Glu+Gln and NAA, with the possibility of incorporating user independent LCM data analysis. The NAA signal can also be used to control for editing efficiency. Estimated values for GABA and Glu concentrations (for N=5 subjects) are close to the published values.

References:1 Rothman Proc. Natl. Acad Sci USA: 90:5662-5666 (1993); 2 Keltner et al. MRM 37:366-371 (1997); 3 Thomson et al Magn. Reson.Med. 39: 762-771 (1998); 4 Shungu et al. Proc. Intl. Soc. Magn. Reson. Med. 11:1140 (2003); 5 Terpstra et al. Magn.Reson.Med. 47:1009-1012 (2002); 6.Provencher .Magn.Reson.Med.30:672- 679 (1993);7 Wylezinska et al Proc. Intl.Soc Magn.Reson.Med .11 (2003); 8 Shen et al Proc.Intl.Soc.Magn.Reson.Med 9:964,(2001); 9 McLean et al Magn.Reson.Med 44:401-411(2000).