Altered levels of GABA and Glutamate in patients with depression detected with MEGA-PRESS editing and LCM analysis.

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Introduction

γ–Aminobutyric acid (GABA) and glutamate (Glu) are major inhibitory and excitatory neourotransmitters, respectively. There is evidence suggesting that abnormalities of neurotransmitter systems are associated with major depression. Reduced GABA levels have been shown in acutely depressed unipolar patients [1]. Increased and decreased Glu levels have been reported [1,2] in depressed subjects.

Here, we present results from simultaneous measurement of GABA and Glu (in fact Glu + glutamine (Gln), referred to as Glx), using the MEGA-PRESS editing technique as described in [3,4]. 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.

Methods

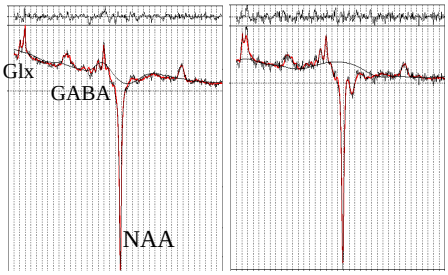
All MRS experiments were performed on a 3T Varian –Inova spectrometer fitted with a standard birdcage coil.

We studied 12 patients with a history of major depression (UNI) (off medication and symptom free for at least three months), and 12 age and gender matched controls (CON).

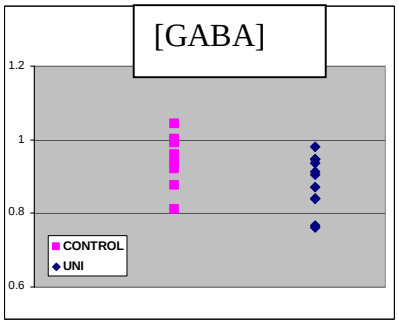
1H spectra were acquired from an 18 ml (3×3×2 cm) localised volume of interest (VOI) in the occipital region. Standard PRESS spectra with echo time TE=26ms were acquired, along with an additional acquisition at TE=68 ms. The creatine (Cr) signal was used as an internal concentration reference for estimation of GABA/Glx levels. Cr concentration in the occipital VOI, containing a mixture of white and grey matter, was estimated for 6 subjects in each group using brain water as a reference.

Simultaneous editing of GABA, and Glu+Gln was possible due to 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 [3] with TE=68s. 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 affecting simultaneously the β-CH_2 on GABA at 1.9 ppm, and the CH_2 on Glu at 2.04 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) 1.95 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, and allow the monitoring of possible frequency drifts. All spectra were analysed using the LC model [5].

In order to account for the macromolecular (MM) contribution, metabolite-nulled spectra were also acquired and used to simulate a MM model spectrum in the LC model analysis.



A B



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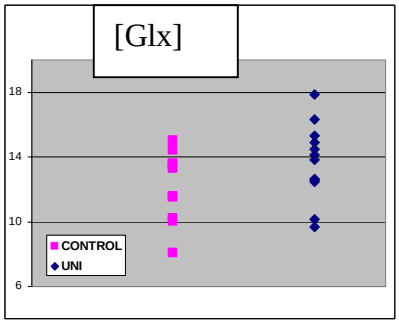

D

Results

Fig. A and B show examples of MEGA-edited GABA/Glx spectra for a subject in the CON group (A), and the UNI group (B). Concentration of Cr was estimated to be 6 (± 0.96) mM and was not significantly different between CON and UNI groups. The values of GABA and Glx obtained here for the CON group were: 1.07 (±0.19) and 11.96 (±2.35) mM, respectively, similar to published values [6,7]. Levels of GABA were significantly lower for the patient group : 0.87 (±0.17) mM, (p(t-test) < 0.01), while the levels of Glx were increased in the UNI group: 13.69 (± 2.35) mM (p< 0.04) (see Fig. C and D).

Conclusions

Using MEGA-PRESS editing we measured simultaneously the levels of GABA and Glx. Values for controls were similar to those published elsewhere. For the patients we observed decreased concentrations of GABA and increased concentrations of Glx, supporting previous reports in acutely depressed subjects. The protocol described here can be of practical value in this type of MRS study, providing an improved time efficiency when identifying possible markers for disease presence and/or progression.

References:1.Sanacora G et al.*Arch Gen Psych*, 61:705-713,2004;2.Auer D et al. *Biol.Psych*,47:305-313,2000;3.Mesher et al. *NMR Biomed*.11,266-272,1998;4. Wylezinska et al. Proc. *Intl.Soc.Magn.Reson.Med* 12:2427,2004;5.Provencher S *MRM* 30:672-679,1993,6.Tepstra M et al.*MRM* 47: 1009-1012, 2002,7.McLean et al. *MRM* 44: 401-411, 2000.