Prefrontal Cortex GABA Concentrations by Double-Quantum Filtering Pre- and Post-Administration of Vigabatrin

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Introduction

The development of in-vivo GABA measurements has considerable potential for the investigation of neuropsychiatric disorders, such as epilepsy, anxiety and mood disorders, or substance abuse, and of the mechanisms of anticonvulsant and psychotropic drug actions. It is well known that the concentration of GABA in occipital cortex increases with administration of the GABA transaminase inhibitor vigabatrin. However, in-vivo studies of GABA have rarely reported values for prefrontal cortex, a region with particular relevance for psychiatric disease [1]. Here, we present the response of GABA to vigabatrin administration for the human prefrontal cortex, measured by an optimized ^{1}H double-quantum filter.

Experimental

A double-quantum filtering (DQF) sequence was used for the GABA measurement. Following a slice-selection 90° excitation, a 28.6-ms long dual-resonance spectrally-selective 180° pulse, tuned to 3.01 and 1.89 ppm, was used to prepare the target antiphase coherences. The echo time was set at 49.4 ms, which returned the maximal GABA doublet at the acquisition. A yield of 43%, obtained from a phantom test, was used for assessment of the observed GABA signal. A pair of adiabatic pulses (T_p = 5ms, BW = 4.6 kHz) was used for localization during the second echo period. Eight healthy volunteers (male) were recruited and screened to exclude neuropsychiatric disorders. Subjects were given vigabatrin 50 mg/kg immediately following the first scan, and returned 24 hours later for the second scan. A 2.5×3×3 cm^3 voxel was selected in prefrontal cortex, as shown in Fig. 1. Spectral acquisition parameters were TR 2.4 s, NEX 512 (for GABA), spectral width 5 kHz, acquisition time 820 ms. While the 512 DQF scans were recorded individually, the PRESS sequence with TE of 82 ms (identical to the DQF echo time) was applied (four scans) between every 64 DQF scans. Adjustment of the transmitter frequency against the B_0 drift was made, if necessary, while monitoring the PRESS NAA peak. In the post-data processing, the DQF and PRESS FIDs were averaged separately and apodized with a 3-Hz exponential and a 6-Hz Gaussian function, and a 1-Hz exponential function, respectively, before Fourier transformation. Only zero-order phase correction was used for the DQF data. FASTMAP was used for shimming. The linewidth of the PRESS water signal at TE = 82 ms was typically ~6 Hz. The r.f. pulses were phase cycled with 512 steps, to minimize unwanted signals. The phase optimization of the second 90° pulse (slice-selective) was accomplished using the water signal. Water distribution (grey matter, white matter and CSF) within the voxel was obtained by recording the 1-D projection following the STEAM sequence. Double-inversion recovery was used to discriminate the water signals between the three compartments [2]. Several pairs of the recovery delays were used to separate GM and WM. Separation of the CSF water from GM and WM was achieved with a long TE (800 ms). For a metabolite-nulled DQF test, an inversion recovery following an adiabatic 180° pulse (T_p = 5 ms) was used with delay of 740 ms (TR = 2.4 s). Experiments were carried out at 3.0 T in an 80-cm bore magnet (Magnex Scientific PLC), interfaced to a SMIS console. A 28-cm diameter quadrature birdcage coil was used for r.f. transmission and reception.

Results and Discussion

Fig. 1 presents the typical water composition for the prefrontal cortex voxel (2.5×3×3 cm^3), as displayed in the sagittal image. The percentage for GM, WM and CSF for all tests is within 10% variation from the values shown in Fig. 1. For estimation of MM contamination in vivo, both ordinary and metabolite-nulled DQF tests were carried out, Fig. 2. At 3 T, for TR = 2.4 s, following a 740-ms long inversion recovery delay, the PRESS Cr 3.03 ppm singlet is suppressed >100-fold. This will also be the case for the GABA signal, assuming a similar T_1 to Cr. No discernible signal is observed at ~3 ppm in the metabolite-nulled DQF spectrum, indicating that MM contamination is negligible. Therefore, the signal detected at 3 ppm must be from free GABA and the GABA moiety of homocarnosine. Three selected pairs of the DQF spectra following the pre- and post-administration of vigabatrin are shown in Fig. 3. Fig. 4 presents the individual pre- and post- vigabatrin administration GABA concentrations for the eight subjects. The total baseline GABA+homocarnosine concentration in the prefrontal voxel was estimated to be 0.96±0.17 µmol/g, with respect to Cr at 9 µmol/g. The mean post-administration GABA+homocarnosine concentration was 1.3±0.15 µmol/g, an increase of ~40% by 24 hours following vigabatrin administration.

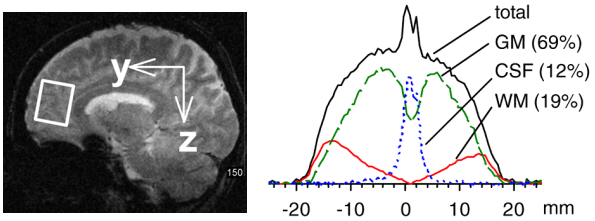

FIG 1. (left) Voxel positioning in the human prefrontal cortex selected for the vigabatrin test. (right) Decomposition, along the x direction, of the brain water within the selected volume. A one-dimensional gradient-echo imaging sequence was appended to the STEAM sequence to obtain the 1-D water profiles. Separation of the water signals between gray-matter, white matter and CSF was achieved with a double-inversion recovery.

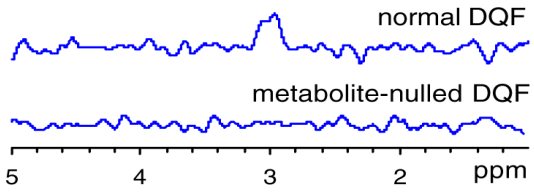

FIG 2. DQF GABA spectra without and with metabolite-nulling inversion recovery indicate that the macromolecule contamination is negligible.

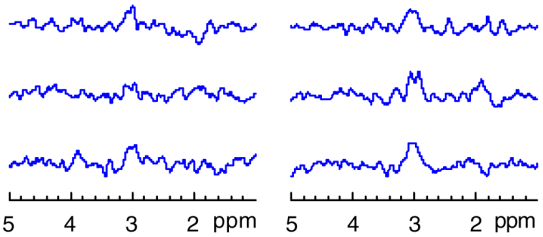

FIG 3. Three pairs of DQF spectra obtained before and after the administration of vigabatrin are displayed on the left and right, respectively. The pairs correspond, from the top, to test number 4, 5 and 8 in Fig. 5, respectively.

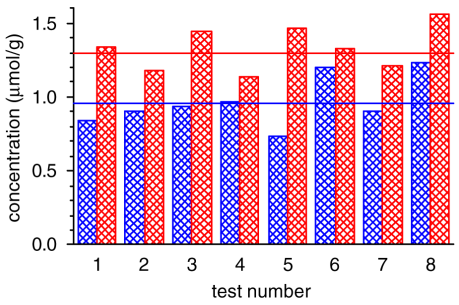

FIG 4. A bar graph for the GABA level changes in the eight sets of the vigabatrin tests. The results for the pre- and post-administration are drawn on the left and right for each test number, respectively. The horizontal lines indicate the mean value for the pre- and post-administration.

References

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Acknowledgments

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