In Vivo Measurement of Cerebral GABA in Patients with Schizophrenia Using Chemical Shift Imaging of GABA

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INTRODUCTION

GABA, the primary inhibitory neurotransmitter in the human brain, plays a pivotal role in normal brain function and energy metabolism [1]. Increasing evidence suggests that altered GABAergic function is involved in many neurological and psychiatric disorders, including schizophrenia. However, the clinical applications of *in vivo* measurement of GABA have been very limited due to high technical challenges. *In vivo* GABA CSI using selective multiple quantum (MQ) filtering methods [2, 3] enables us to investigate the regional alterations of cerebral GABA content in patients with schizophrenia, where the etiologic role of GABA has been proposed but no *in vivo* GABA measurement has been reported to date.

METHODS

Ten patients with a DSM-IV diagnosis of schizophrenia (32 ± 10 years old, mean ± SD) and ten closely age-matched healthy control subjects (32 ± 10 years old) were studied on a 3 T SMIS system using a circularly polarized ^{1}H RF coil. All patients were without any antipsychotics or antiepilepic medication or mood stabilizers, and no lifetime history of substance dependence that can influence endogenous GABA contents in the brain. The ^{1}H GABA CSI sequence is based on a single shot selective MQ filtering method [3]. During MQ preparation period, a double-band spectrally selective 180^o pulse was used for improved selection of GABA-4 (3.0 ppm) and GABA-3 (1.9 ppm). For *in vivo* studies, T_1-weighted images were acquired using an MPRAGE sequence as shown in Fig. 1. The CSI slice was positioned across the prefrontal to parietal regions. The MR parameters for GABA CSI were FOV = 18 cm × 18 cm, Slice thickness = 3 cm, 6 × 6 PE steps, nt = 10 – 12. Spectra from regions of interest ($3.5 \times 7 \times 3$ cm^3 in the frontal and parietal lobes) were reconstructed from the CSI data sets using a SLIM reconstruction method [4]. *In vivo* GABA concentration was estimated by the external reference method using a phantom with known concentration of GABA.

RESULTS AND DISCUSSION

The T_1-weighted anatomical MPRAGE image of a patient with schizophrenia (Fig. 1 left) shows the regions of interest where GABA spectra were reconstructed. *In vivo* GABA doublets were observed in both patient and control groups (Fig. 1 right), indicating excellent suppression of overlapping creatine and glutathione as also demonstrated in our single-voxel measurements [5, 6].

A preliminary quantitative analysis of the GABA distribution in both frontal and parietal regions showed a significant decrease of GABA contents in patients with schizophrenia, 38% in frontal region and 36% in parietal region, respectively. The results reported here is the first *in vivo* measurement of GABA in schizophrenia patients. The importance of this study can be appreciated in the context of the large body of evidence implicating GABAergic dysfunction is in the pathophysiology and etiology of schizophrenia. Currently, most studies of GABAergic function in schizophrenia have been performed on postmortem tissues, which have found a selective reduction of GABAergic neurons in limbic and prefrontal cortical regions of schizophrenic brains. Since GABA anabolism is known to produce abnormal GABA levels during ischemia, GABA concentrations measured postmortem are significantly distorted. The value of measuring GABA level per se in postmortem studies to assess GABAergic dysfunction is therefore quite limited. In contrast, our method, as demonstrated here, make it possible to assess the GABAergic function through the measurement of GABA levels in vivo. The concentration of GABA reflects the viability of GABAergic function and GAD, the GABA-synthesizing enzyme. The total concentration of GABA has also been found to correlate with GABA release. The noninvasive spectroscopy method also allows longitudinal study of GABAergic response to treatment. The observed reduction in GABA levels in the frontal regions of the schizophrenic brains is consistent with the loss of GABAergic neurons in that region found in postmortem studies. Interestingly, we also found reduced GABA concentration in the parietal region, which may need further investigation.

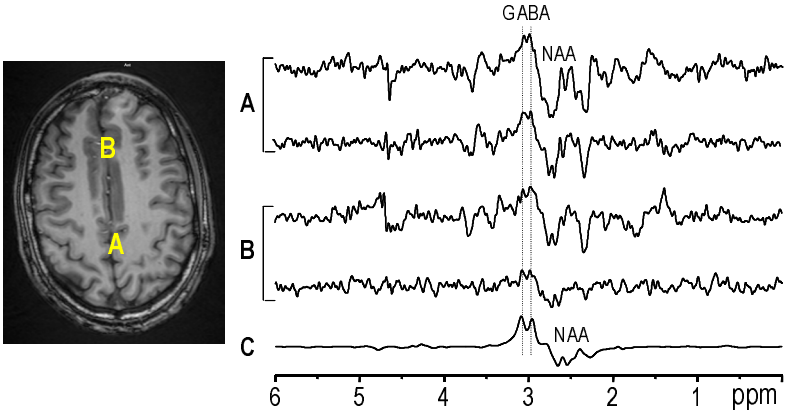

Fig. 1 GABA measurements of the human brain *in vivo* using MQ GABACSI at 3 T. GABA spectra were acquired from the parietal region (A) and the frontal region (B). Spectra of the normal control are on the top and those of patients with schizophrenia are on the bottom for both (A) and (B). (C) Spectrum of a solution phantom containing GABA, NAA and Cr. MRI of the patient with schizophrenia (left) shows regions of interest (A: parietal, B: frontal).

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