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High-field MRS study of GABA, glutamate and glutamine in social anxiety disorder: Response to treatment with levetiracetam

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Abstract

Objective: Abnormalities in brain gamma-aminobutyric acid (GABA) and glutamate may be relevant to the underlying pathophysiology of anxiety disorders including social anxiety disorder (SAD).
Methods: We used proton magnetic resonance spectroscopy (pMRS) to examine whole brain and regional GABA, glutamate and glutamine in patients ($N=10$) with SAD at baseline compared to a matched group of healthy controls (HC), and changes following 8 weeks of pharmacotherapy with levetiracetam.
Results: For SAD subjects, there were significantly higher whole brain levels of glutamate and glutamine, though no significant differences in GABA. In the thalamus, glutamine was higher and GABA lower for SAD subjects. There was a significant reduction in thalamic glutamine with levetiracetam treatment.
Conclusion: Our findings provide preliminary support for impaired GABAergic and overactive glutamatergic function in social anxiety disorder and the potential relevance of changes in these systems for the anxiolytic response to levetiracetam.

Keywords: GABA; Glutamate; Levetiracetam; MRS; Social anxiety

1. Introduction

Converging lines of evidence suggest that abnormalities in brain gamma-aminobutyric acid (GABA) and glutamate may be relevant to the underlying pathophysiology of anxiety disorders, including social anxiety disorder. Data from animal studies suggest that a decrease over time in brain GABA levels is associated with anxiety like behavior (Dalvi and Rodgers 2001; Shekhar et al., 2006) and elevated GABA levels with decreased anxiety (Sherif and Oreland 1995). Recent evidence also implicates overactivity in the central glutamatergic system as relevant for the pathophysiology of anxiety (Cortese and Phan 2005). Rats with inhibited GABA synthesis and associated increased glutamatergic excitation in the dorsomedial hypothalamus (DMH) developed panic-like responses in response to a social interaction test after intravenous sodium lactate infusion (Johnson and Shekhar 2006).

Recent work has employed MRS technology to examine the association of GABA (Goddard et al., 2001; Goddard et al., 2004), and glutamate (Phan et al., 2005) with anxiety in general (Grachev and Apkarian 2000), and in patients with anxiety disorders such as panic, social and generalized anxiety disorders (Goddard et al., 2001; Goddard et al., 2004). There has, however, been little systematic inquiry regarding the impact of

Abbreviations: ACC, anterior cingulate cortex; CNS, central nervous system; DMH, dorsomedial hypothalamus; GABA, gamma-aminobutyric acid; HC, healthy controls; LSAS, Liebowitz Social Anxiety Scale; MDD, major depressive disorder; pMRS, proton magnetic resonance spectroscopy; SAD, social anxiety disorder; SCID-IV, structured clinical interview for DSM-IV; SSRI, serotonin selective reuptake inhibitor.

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treatment on brain GABA and glutamate among patients with anxiety disorders in general, and social anxiety disorder (SAD) in particular.

Levetiracetam is a novel anticonvulsant agent which reduces currents through high-voltage-activated calcium channels and has effects at a unique CNS binding site (Niespodziany et al., 2001; Noyer et al., 1995). Recent evidence also suggests that levetiracetam enhances GABAergic activity, perhaps through its binding to the synaptic vesicle protein SV2A (Crowder et al., 1999; Safdieh and Harden 2006) which may have direct relevance for its potential anti-anxiety effects (Poulain and Margineanu 2002; Rigo et al., 2002). Levetiracetam demonstrated potential anxiolytic effects in animal models of anxiety (Gower et al., 2003) and in small open and controlled trials in humans with SAD (Simon et al., 2004; Zhang et al., 2005), as well as posttraumatic stress disorder (Kinrys et al., 2006) and panic disorder (Papp 2006).

In the present study we used proton magnetic resonance spectroscopy (pMRS) to examine whole brain and regional GABA, glutamate, and glutamine (an amino acid associated with glutamate (Rothman et al., 2003)) in patients with social anxiety disorder (SAD) compared to a matched group of healthy controls. In what is one of the first attempts to examine changes in central neurochemistry associated with treatment of social anxiety disorder, we examined changes in these neurotransmitters as assessed by repeated pMRS following 8 weeks of pharmacotherapy with levetiracetam. We hypothesized that levels of GABA would be lower and glutamate (and associated glutamine) elevated at baseline compared to healthy controls and would increase and decrease respectively with treatment.

2. Methods

2.1. Subjects

Participants were men or women ages 18–75 with a primary diagnosis of generalized social anxiety disorder as established by structured clinical interview for DSM-IV (SCID-IV: First et al., 1994), who were eligible to participate in an 8-week treatment study of levetiracetam for SAD; results of the treatment study have been published (Simon et al., 2004). After subjects underwent initial proton (1H)-MRS, levetiracetam was initiated at 250 mg/day for the first week and flexibly titrated up to a maximum of 3000 mg/day (1500 mg b.i.d.); 1H-MRS was repeated at week 8. Comorbid anxiety disorders and major depressive disorder (MDD) were allowed as long as the SAD was judged to be primary (i.e., causing the patient the most distress), but those with a current or past history of bipolar disorder, schizophrenia or other psychotic conditions, head trauma, loss of consciousness, seizures, metallic implants, unstable medical conditions, psychotropic medication use within the past 2 weeks or history of alcohol or substance abuse or dependence within the last six months were excluded. The institutional review board approved the study, and all subjects received and signed informed consent, and were compensated for study participation.

The study population comprised 10 patients (2 female; mean ± SD age 37.2 ± 11.8 years) with SAD, with a mean (±SD) duration of illness of 26.9 (±14.1) years and a mean (±SD) age at onset of 10.3 (±5.0) years. Comorbidity was as follows: current generalized anxiety disorder ($n=3$), past MDD ($n=5$), past alcohol abuse ($n=5$). Age and gender matched healthy control participants ($n=9$; 2 female) had a mean ± SD age of 33.2 ± 11.6 years.

2.2. Healthy controls

Age and gender matched controls were recruited by advertisement to undergo an identical neuroimaging protocol to patients on one occasion. Control subjects were required to be free of current and past psychiatric disorders as established by the SCID-IV (First et al., 1994). Additional exclusions were identical to subjects with SAD.

2.3. Image acquisition and analysis

All subjects underwent 1H-MRS scans at rest to assess whole brain and regional GABA, glutamate, and glutamine ratios to creatine. SAD subjects repeated resting scans approximately 8 weeks after initiation of levetiracetam.

2.4. Proton-MRSI processing and analysis

All in vivo data were collected on a 4-Tesla Varian, Unity-INOVA, whole-body MR system running VNMRj 1.1b (Varian Inc, Palo Alto, CA), using a volumetric TEM design (Bioengineering Inc, Minneapolis, MN) RF head coil operating at 170.3 MHz for proton imaging. A detailed description of our methods using different acquisition parameters can be found in Jensen et al. (2005a,b). Briefly, the parameters used for this study were: TE-steps = 48 (30–490 ms, 10 ms increments), sampling matrix = 44 circular, sparsely-sampled *k*-space points (zero-filled to 8 × 8 grid), TR = 1.4 s, spectral bandwidth = 4 kHz, complex time-points = 2048, FOV = 16 × 16 cm, slab thickness = 2 cm, NEX = 1, nominal voxel volume = 8.0 cm^3 (effective voxel size ~ 16 cm^3), total scan duration = 48 min. The raw matrix of voxels used in each subject was 6 × 6, with voxels anterior to the ventricles omitted due to problems arising from susceptibility and off-resonance effects from the sinus-cavity in the frontal regions. A 4 × 3 sub-matrix of voxels was also placed over the sub-cortical regions, encompassing such structures as the thalamus. An automated software package developed on site filtered out all MRSI voxels deemed "unsatisfactory" based on aspects of the residual water resonance for each voxel, including line width, frequency-offset, as well as excessive lipid signal contamination. Once filtered, all remaining high-quality spectra were automatically first-order phased, using the residual water peak as a phase reference. For each voxel, two spectra were extracted from the *J*-resolved data: one at $J=7.5$ Hz (GABA) and $J=0.0$ Hz (Creatine and glutamate). All spectra were then fitted using the LC Model spectral analysis tool. All metabolites are expressed as ratios to creatine, derived from the 3.03 ppm creatine peak area at $J=0.0$ Hz. As an additional methodological note, we must mention that the units in which we report our metabolite-to-creatine ratios have not been corrected to represent