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ORIGINAL INVESTIGATION

Nikolaus Michael · Andreas Erfurth · Patricia Ohrmann · Michael Gössling · Volker Arolt · Walter Heindel · Bettina Pfleiderer

Acute mania is accompanied by elevated glutamate/glutamine levels within the left dorsolateral prefrontal cortex

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Abstract *Rationale:* The dorsolateral prefrontal cortex (DLPFC) participates in the pathophysiology of mania. In particular, left-sided structural and metabolic abnormalities have been described. *Objectives:* Clinical symptoms may be due to hyperactivity of cortical glutamatergic neurons, resulting in increased excitatory neurotransmitter flux and thus enhanced Glx levels. *Methods:* Glutamate/glutamine (Glx) levels were assessed by proton magnetic resonance spectroscopy (^{1}H-MRS) in eight acute manic patients compared with age- and gender-matched controls. *Results:* Manic patients had significantly elevated Glx levels (*t*-test; t=–3.1, P=0.008) within the left DLPFC. *Conclusions:* Our results indicate that the prefrontal cortical glutamatergic system is involved in the pathophysiology of acute mania. This may have implications for the treatment of mania.

Keywords Acute mania · Bipolar disorder · Glutamate · Glutamine · Proton magnetic resonance spectroscopy

Introduction

Surprisingly little is known about the pathophysiology of mania. Clinically, mania presents with symptoms contrary to those of depression, i.e. elevated versus depressed mood, inflated versus low self-esteem, or increased versus decreased activity. Pharmacologically, mood stabilizing drugs such as antiepileptics are known to inhibit glutamate activity (Krystal et al. 2002) and lithium robustly protects neurons against excitotoxicity, probably by reducing gluamatergic overstimulation (Nonaka et al. 1998). Neuroanatomically, the dorsolateral prefrontal cortex (DLPFC) is likely to be involved in acute mania (Clark et al. 2001). Postmortem studies found reduced neuronal and glial density (Rajkowska et al. 2001), while molecular research revealed abnormalities of markers pertaining to glutamatergic neurotransmission (Knable et al. 2002). Since glutamate is the most abundant excitatory neurotransmitter of the cerebral cortex (Fuster 1997), glutamate metabolism is likely to be involved in diseases affecting the DLPFC (Krystal et al. 2002). Functional imaging showed hypometabolism within frontal cortex areas occurring with depression, while, in contrast, hypermetabolism with mania (Baxter et al. 1985; de Asis et al. 2001; Drevets et al. 1997) was observed. Hypermetabolism as revealed by positron emission tomography (PET) probably reflects increased glutamate neurotransmitter flux (Shulman 2001).

Thus we postulated that acute mania is accompanied by altered glutamate metabolism within the left DLPFC. We assessed glutamate/glutamine (Glx) levels as well as *N*-acetyl-aspartate (NAA), creatine/phosphocreatine (Cr) and choline-containing compounds (Cho) in acute manic patients by proton magnetic resonance spectroscopy (^{1}H-MRS).

N. Michael · A. Erfurth · P. Ohrmann · M. Gössling · V. Arolt · W. Heindel · B. Pfleiderer
University of Muenster, 48129 Münster, Germany

N. Michael (✉) · A. Erfurth · P. Ohrmann · M. Gössling · V. Arolt
Department of Psychiatry, University of Muenster,
Albert Schweitzer Strasse 11, 48129 Münster, Germany
e-mail: nikmich@uni-muenster.de
Tel.: +49-251-8356626
Fax: +49-251-8356612

M. Gössling · W. Heindel · B. Pfleiderer
Department of Clinical Radiology, University of Muenster,
Albert Schweitzer Strasse 33, 48129 Münster, Germany

Materials and methods

Patients

Eight patients (mean age: 40.1±13.9 years; two female, all right-handed) hospitalized for treatment of manic episode and eight age- and gender-matched healthy controls (mean age: 40.7±14.7 years; two female; all right-handed) were enrolled. Patients and controls were also matched for educational level, and all except one had a college degree (master). One patient and one control finished high school, but had no further education. Diagnosis was made independently by two experienced psychiatrists employing the Munich checklist for DSM-IV (Hiller et al. 2000). Patients, as well

as controls with a medical history of alcohol/drug abuse or brain damage were excluded. Six patients were drug-naive, one patient was on lithium, and another switched into mania after cessation of electroconvulsive therapy [mean mania score: Bech-Rafaelsen Mania Scale=24±8 (moderate-severe) (Bech et al. 1978)].

A standardized interview (Hiller et al. 2000) was performed to rule out any underlying psychiatric or neurologic condition in healthy subjects. After detailed briefing, written informed consent was obtained from all participants. The protocol was approved by the Ethics Committee, University of Münster, Germany, based on the guideline of the Declaration of Helsinki.

MRS measurements

The MRI protocol included T1-weighted 3D-spoiled-gradient-echo acquisition of the whole brain and T2- and proton-density-weighted fast-spin-echo sequences in transaxial and coronal orientation. The image parameters for the images used for voxel segmentation were as follows: TE=15 ms, NS=2, FOV=250, matrix size: 256×196, slice thickness: 4 mm. Single voxel STEAM spectroscopy [TE=20 ms, TR=2.5 s, TM=15 ms, voxel size (VOI)=3.375 cm^3, number of scans=128] at 1.5 T (Magnetom SP, Siemens, Erlangen, Germany) was used. The voxel was positioned in the left DLPFC based on readily identifiable anatomical landmarks (Rajkowska and Goldman-Rakic 1995). For a more detailed description of voxel position and spectra quality see Michael et al. (2003).

Postprocessing and data analysis

To account for variations in voxel composition (cerebral spinal fluid (CSF), gray matter (GM) and white matter), voxels were segmented by one investigator using a semiautomatic interactive alogorithm (M. Fiebich, Department of Biomedical Engineering, University of Applied Sciences, Giessen, Germany). The voxel was placed in the corresponding image slices automatically, but the boundaries of each tissue type were outlined manually in each slice. The program then calculated the total amount of CSF, GM and white matter in the voxel. Even though this method is not ideal, the results obtained are very reproducible (Pfleiderer et al. 2003).

Structurally, the gray matter fraction in patient voxels was increased compared to controls (*t*-test; t=–2.3, P=0.035) and white matter reduced accordingly (*t*-test; t=2.3, P=0.036). Even though the results are still somewhat inconclusive regarding higher or lower metabolite levels in gray and white matter, respectively, it is accepted that relative metabolite levels are different (Wang and Li 1998). Normalization to gray matter fraction was performed to reduce the potential confounding effect of a higher gray matter fraction in patients on our results.

Metabolite concentrations were calculated using a time domain fitting program by using a basis model set of metabolite spectra acquired previously (Provencher 1993). Cho (GPC and PCh), Cr, NAA, NAAG, glutamine, glutamate (Glx), myo-inositol, GABA, lactate, taurine and aspartate were included in this basic set. However, only metabolite information with the fitting error (percent standard deviation) of <20% SD were included in the final analysis. Postprocessing was standardized using a linear combination (LC) model program package with zero filling, Fourier transformation, automated phase, baseline and eddy current correction (Provencher 1993). Raw values as obtained from the LC model (scaled to water) were corrected for CSF, coil loading (multiplication with the transmitter reference voltage) (Michaelis et al. 1993) and then corrected for gray matter fraction [multiplication with GM (volume % voxel) divided by the sum of GM+WM (volume % voxel)] and expressed in institutional units (IU). Due to overlapping resonances of glutamate/glutamine and GABA at a field strength of 1.5 T, these compounds were fitted together (Glx). The contribution of altered GABA levels may still have influenced our data. However, the GABA concentration in general is much lower (about 1 mmol/kg brain tissue (Sanacora et al. 1999); than combined Glu/Gln (about 12–14 mmol/kg brain tissue). In addition, the Glx signal is mostly dominated by glutamate (Glu) (Auer et al., 2000). Remeasurement of six healthy volunteers after 5.2±0.8 months for assessment of reproducibilty showed stable Glx levels (repeated measure ANCOVA; F=0.39, P=0.56).

Statistical analysis was performed with SPSS software (SPSS 10.0 for Windows, SPSS Inc. Chicago, Ill., USA). A *t*-test was used for assessing group effects for Glx, NAA, Cho and Cr levels.

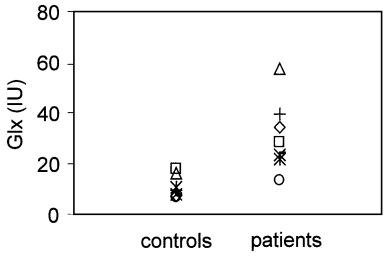

Fig. 1 Glx levels [institutional units (IU)] within the left DLPFC in manic patients compared to controls. In patients (n=8), Glx was significantly increased (*t*-test; t=–3.1, P=0.008)

Results

Manic patients showed significantly increased Glx levels (27.2±14.9 (IU), Fig. 1) (*t*-test; t=–3.1, P=0.008), compared to controls [10±4.3 (IU)]. Since electroconvulsive therapy (ECT) can also increase Glx, the manic patient after ECT was excluded. Still Glx was significantly higher in patients (*t*-test; t=–2.96, P=0.011), indicating that this patient does not influence the outcome of our result. NAA (*t*-test; t=–1.6, P=0.12), Cho (*t*-test; t=–0.99, P=0.34) and Cr (*t*-test; t=–1.8, P=0.095) levels were not significantly different from controls.

Discussion

The results of the present study show that mania is accompanied by significantly elevated Glx concentrations within the left DLPFC. This may well reflect an overregulation of the cortical glutamatergic system. It is known from positron emission tomography (PET)-based studies that mania is associated with metabolic hyperactivity of the prefrontal (Baxter et al. 1985) and the anterior cingulate cortex (de Asis et al. 2001), among other areas. In contrast, decreased metabolic activity of the same regions occurs in depression (Baxter et al. 1985). Both abnormalities seem to normalize with recovery (Baxter et al. 1985; Drevets et al. 1997). Since about 80% of cerebral energy consumption depends on glutamate/glutamine neurotransmitter signaling, it would appear that glutamatergic activity is the main contributor to the metabolic alterations observed with PET (Shulman 2001). Interestingly, low Glx levels were reported in the anterior cingulum of depressed patients (Auer et al. 2000), whereas higher levels within the frontal lobe were seen in children hospitalized for bipolar disorder (severity of manic symptoms not reported) (Castillo et al. 2000).

Thus, it is conceivable that both phenomena, altered metabolism observed with PET and Glx abnormalities with H-MRS, may reflect the functionality of the frontal lobe glutamatergic system, in this case an over-regulation associated with manic symptomatology. Dysfunction of the glutamatergic system may also contribute to structural as well as to neuropsychological abnormalities (Sax et al. 1999).

The following limitations to the present study should be borne in mind: First, the small patient number requires duplication of the results in a larger population. Second, due to the low field strength (1.5 T) glutamate/glutamine and GABA could not be separated, though glutamate is known to dominate the measured signal. In particular, the contribution of altered GABA levels may still have influenced our data. However, the GABA concentration in general is much lower (about 1 mmol/kg brain tissue; (Sanacora et al. 1999) than combined Glu/Gln (about 12–14 mmol/kg brain tissue), and under the assumption that this relation will not change dramatically in manic patients, we feel confident that changes are mainly attributed to alterations in Glx levels. A higher field strength would allow for better spectral resolution and discrimination of these metabolites. Nevertheless, our data indicate that dysregulation of the cortical glutamatergic system is involved in the pathophysiology of acute mania. This may have implications for treatment of mania, e.g. pharmacological strategies influencing glutamergic neurotransmission, such as antiepileptic drugs.

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