Decreased temporal lobe phosphomonoesters in bipolar disorder

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Abstract

In vivo [31P]magnetic resonance spectroscopic imaging ([31P]MRSI) was performed on 12 unmedicated, euthymic bipolar patients and 14 control subjects to determine if there were alterations in high-energy P metabolism in the temporal lobes of bipolar patients. Compared with the control group, the patients with bipolar disorder demonstrated significantly lower phosphomonoesters (PME) in both the left and right temporal lobes. No other group differences in P metabolites or lateralized asymmetries were noted. This preliminary study provides support for altered temporal lobe phospholipid metabolism in bipolar disorder.

Keywords: Magnetic resonance spectroscopy; Phosphorous; Phosphomonoester; Brain

1. Introduction

In recent years, in vivo [31P]magnetic resonance spectroscopy studies of patients with bipolar disorder have reported decreased frontal lobe phosphomonoesters (PME) and pH in the euthymic state as well as increased frontal lobe PME and pH in the depressed and manic state (Kato et al., 1991-93). However, no studies to date have examined the temporal lobes in bipolar disorder which are implicated as having a role in the emotional responsiveness and affective states in mood disorders. Furthermore, many of the patients in the prior spectroscopy studies were medicated with lithium which has been reported to cause significant alterations in PME in animal studies, presumably due to lithium-induced effects on phosphatidylinositol, phosphatidylethanolamine and phosphatidylcholine (Renshaw et al., 1986-87; Navidi et al., 1991). Therefore, we conducted a pilot study utilizing [31P]magnetic resonance spectroscopic imaging ([31P]MRSI) to determine if there were differences in temporal lobe P metabolism between medication-free euthymic patients with bipolar disorder and healthy control subjects.
2. Methods

2.1. Subjects

10 men and two women who met DSM-III-R criteria for bipolar disorder (eight Caucasian, two Black and two Asian; mean ± SD age = 40.1 ± 8.3 years) and 12 male and two female control subjects (eight Caucasian, three Black, three Asian and two Hispanic; mean ± SD age = 39.8 ± 10.2 years) gave informed consent for participation in the study. All subjects were right-handed. The bipolar patients had all been euthymic for at least 2 months before the study as documented by clinical interview, history and scores on both the Young Mania Rating Scale and Hamilton Depression Rating Scale on the day of the MRSI study. The mean ± SD years of illness was 16.6 ± 8.4. All patients had discontinued any medication they were taking 1 week before their examination. One patient had never taken medication, six patients had been taking lithium only, one patient had been taking lithium and lorazepam, and four patients had been taking carbamazepine only. None of the bipolar patients had a history of head injury, organic mental disorder, neurological disorder, schizophrenia or other psychotic disorder or anxiety disorder. None of the patients had clinically significant alcohol or substance abuse in the 12 months before the study. None of the control subjects had any history of significant medical illness, head injury, neurological disorder, psychiatric disorder or clinically significant alcohol or substance abuse. There were no significant group differences between patients and controls for age or education.

2.2. MRSI methods

All MRSI studies were performed on a Philips Gyroscan S15 MRI/MRS system operating at 2 Tesla. A standard imaging saddle-type proton head coil was used for MRI. T1 weighed sagittal (seven slices, 7.1 mm thick, 1.2 mm gap, TR = 600 ms, TE = 30 ms) and T2 weighed axial (16 slices, 7.1 mm thick, 1.2 mm gap, TR = 2000 ms, TE = 30 and 80 ms) multi-slice images were obtained on each subject. A neuroradiologist blind to each subject’s clinical status evaluated the MRI scans from both controls and patients to determine if any structural abnormalities, white matter hyperintensities, asymmetry or atrophy were present. The axial slices were angulated parallel to the canthomeatal plane observed on the sagittal slices to give a consistent anatomical perspective, facilitating comparisons between patients and controls. For [31P]MRSI, an inductively coupled, high-pass, quadrature birdcage head coil was used to provide homogeneous RF excitation and detection. The MRSI procedures and experimental parameters are identical with those previously described for studies on the frontal and parietal lobes in schizophrenic patients (Deicken et al., in press). A spin-echo sequence (TR = 350 ms, TE = 3.5 ms) was utilized. MRSI data volumes were reconstructed and the effective voxel size was 25 cm^3. A reference image of the total 31P signal was generated and the higher resolution of the spatially registered MR images was used to select two voxels in comparable locations for each subject in the inferior medial aspect of the right and left temporal lobes (Fig. 1). Individual voxels were selected with the assistance of a neuroradiologist on the basis of anatomical features seen on axial images. The voxels contain both gray and white matter since the voxel size did not allow us to selectively sample either gray matter or white matter in the temporal lobe regions. 31P spectra from these voxels were fit by NMR-1 data-processing software (New Methods Research, Syracuse, NY). The % of total P signal for PMEs, inorganic phosphate (Pi), phosphodiesters (PDE), phosphocreatine (PCr) and β-adenosine triphosphate (β-ATP) were calculated. The β-ATP resonance was selected to best represent the ATP concentration in tissue because, unlike the γ and δ resonances, it is free from signal contribution from other phosphate-containing metabolites, such as adenosine diphosphate and nicotinamide adenine dinucleotide phosphates. Spectra were coded for blind processing by a single operator to eliminate interoperator variance. Intraoperator reliability of NMR-1 spectral fitting has been determined in our laboratory for [31P]MRSI spectra from regional white matter voxels in 16 normal controls subjects (C. Husted, unpubl. data).
The intraoperator correlation coefficients were as follows: 0.75 for PME, 0.99 for Pi, 0.86 for PDE, 0.95 for PCr and 0.95 for β-ATP.

2.3. Statistical analysis

Repeated measures ANOVA was used for data analysis. The dependent variable was the % of the total P signal for each metabolite, group was the between-subjects factor and side (left vs. right) was the within-subjects repeated measures factor. P metabolites were analysed in an exploratory fashion without correction for multiple comparisons. Significance level was set at $P < 0.05$.

3. Results

No abnormalities were noted on the MRI images of the patients or the healthy comparison group. Relative to the comparison group, PME (metabolite % of total P signal) in the bipolar patients (Table 1) was significantly lower ($F = 9.22$, df = 1,24, $P = 0.006$) in both the right and left temporal lobes. There were no group differences or lateralized asymmetries for PDE, Pi, PCr, β-ATP, pH or the total P signal. Furthermore, there were no significant differences in PME or PDE values between the seven patients who had been taking lithium and the remaining five patients who had not been taking lithium.

4. Discussion

The primary finding of this preliminary study is significantly reduced PME in both the right and left temporal lobes in unmedicated, euthymic bipolar patients compared with control subjects. These PME findings in the temporal lobe, to our knowledge, have not been reported before. They are particularly interesting in view of prior in vivo [$^{31}$P]MRS studies demonstrating: (1) reduced frontal lobe PME in euthymic bipolar patients (Kato et al., 1991–93); and (2) no significant alterations of right or left temporal lobe PME in chronic schizophrenia (O'Callaghan et al., 1991; Calabrese et al., 1992; Deicken et al., 1994). These findings taken together suggest that alter-

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### Table 1

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<th>Temporal lobe metabolite % of total P signal</th>
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<td>PME a</td>
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^a Group difference ($P = 0.006$, repeated measures ANOVA). ^b R, right temporal lobe. ^c L, left temporal lobe.
ations in temporal lobe as well as frontal lobe phospholipid metabolism may play a role in the pathophysiology of bipolar disorder. Moreover, the pattern of phospholipid abnormalities in bipolar disorder appears to be different from that in schizophrenia where decreased PME and increased PDE have been observed in the frontal lobes, but not in the parietal or temporal lobes (Pettegrew et al., 1991; Williamson et al., 1991; Deicken et al., in press).

The likelihood that the observed changes in temporal lobe PME are simply the result of lithium effects on phospholipids is diminished by the fact that the seven lithium-treated patients had been medication-free for 1 week and there was no significant difference between their PME values and the PME values for the remaining five patients who had not been taking lithium. In addition, reduced frontal lobe PME has been reported in a group of 10 euthymic bipolar patients, seven of whom had not been treated with lithium (Kato et al., 1992). The results of this study and previous reports suggests that altered frontal and temporal lobe PME in the euthymic state may represent a trait-dependent abnormality, possibly related to membrane abnormalities in bipolar disorder (Kato et al., 1992–93). Nevertheless, chronic administration of lithium has been reported to: (1) cause a large initial increase and subsequent decline to normal levels of in vivo PME measurements in cats (Renshaw et al., 1986); and (2) decrease both in vitro measurements of phosphatidylinositol and phosphatidylethanolamine and increase phosphatidylcholine in rats (Joseph et al., 1987). To our knowledge, there is no clear evidence in humans on the time course over which lithium effects on phospholipids resolve. Thus, it is conceivable that underlying phospholipid changes in humans due to lithium might have persisted beyond the 7-day medication-free period in this study.

It is unlikely that the observed changes in PME are related to atrophy of the right and left temporal lobes. There were no qualitative differences in atrophy between the bipolar patients and comparison group or between the right and left sides, however, more quantitative analyses are required. Moreover, a significant difference in size or atrophy between the bipolar and control groups would most likely result in a reduction in all P metabolites as well as the total P signal in the group demonstrating significant atrophy and we did not observe this.

The limitations of the present study include the modest sample size and whether the 7-day medication-free period was sufficient to completely exclude lithium-induced effects on PME. Future studies will be able to address this question by examining whether the observed changes are present in larger patient populations who have either been maintained off lithium for a longer period of time or are taking mood stabilizers that are not known to affect PME, such as carbamazepine or valproic acid. (2) Alterations in the T1 or T2 of P metabolites in the temporal lobes of bipolar patients might also have contributed to the observed group difference. In other words, the difference in PME may have reflected differences in metabolite variability (as a consequence of relaxation time differences) rather than metabolite concentration differences. (3) A recognized limitation of in vivo spectroscopy is the low sensitivity of [31P]MRS and the low concentrations of 31P metabolites which limit the spatial resolution of [31P]MRSI. (4) The voxels selected for each subject contain varying percentages of gray matter, white matter and CSF which also need to be quantitatively determined. In future studies, MRI segmentation software will be interfaced with [31P]MRSI to determine the exact percentages of gray matter, white matter and CSF in selected voxels.

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References


