Abnormal Frontal Lobe Phosphorous Metabolism in Bipolar Disorder

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Objective: Abnormalities in frontal lobe phosphorous metabolism in patients with bipolar disorder have been reported, but many of the patients studied were receiving lithium. In this study, medication-free bipolar patients were examined to determine abnormalities in frontal lobe high-energy phosphorous metabolism. Method: In vivo phosphorous-31 magnetic resonance spectroscopic imaging was performed on 12 unmedicated, euthymic bipolar patients and 16 healthy comparison subjects. The percentages of total phosphorous signal for phosphomonoesters, inorganic phosphate, phosphodiesters, phosphocreatine, and β-ATP were calculated. Results: In relation to the comparison group, the patients with bipolar disorder had significantly lower phosphomonoester values and higher phosphodiester values in both the left and right frontal lobes. The patients also had a significantly higher right-to-left ratio of frontal lobe phosphocreatine. No other differences in phosphorous metabolites or lateralized asymmetries were noted. Conclusions: This preliminary study provides support for abnormal frontal lobe phosphorous metabolism in bipolar disorder.

(Am J Psychiatry 1995; 152:915–918)

Preliminary in vivo phosphorous-31 magnetic resonance spectroscopy (^{31}P MRS) studies of patients with bipolar disorder have shown lower than normal frontal lobe phosphomonoester values and pH in the euthymic state and higher than normal frontal lobe phosphomonoester values and pH in the depressed and manic states (1–3). A confounding factor in these studies, however, was the lithium treatment of many of the patients; lithium has been reported to cause substantial alterations in phosphomonoesters in animal studies, presumably due to effects on phosphatidylinositol, phosphatidylethanolamine, and phosphatidylcholine (4–6).

Given these findings, we conducted a pilot study using ^{31}P MRS to determine whether there are differences in frontal lobe phosphorous metabolism between medication-free patients with bipolar disorder and healthy comparison subjects.

METHOD

Twelve men who met the DSM-III-R criteria for bipolar disorder (nine Caucasian, two black, one Asian; mean age=40.3 years, SD=8.7) and 16 male comparison subjects (nine Caucasian, three black, two Asian, two Hispanic; mean age=39.9 years, SD=11.1) gave informed consent for participation in the study. The diagnosis of bipolar disorder was confirmed by using the Structured Clinical Interview for DSM-III-R—Patient Version (7). The comparison subjects were assessed by using the Structured Clinical Interview for DSM-III-R—Non-Patient Edition (8). 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 of less than 5 on both the Young Mania Rating Scale (9) and the Hamilton

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Supported by a 1992 National Alliance for Research on Schizophrenia and Depression Young Investigator Award (Dr. Deicken), Biomedical Research Support Grant RR-05755 from the NIH Division of Research Resources (Dr. Deicken), a University of California, San Francisco, Academic Senate Individual Investigator Grant (Dr. Deicken), a VA Research Associate Career Development Award (Dr. Deicken), a VA Research Career Scientist Award (Dr. Fein), the VA Medical Research Service (Dr. Weiner), and Philips Medical Systems (Dr. Weiner).

FIGURE 1. Magnetic Resonance Image From a Normal Subject, Showing Location of Selected Voxels in Right and Left Frontal Lobes

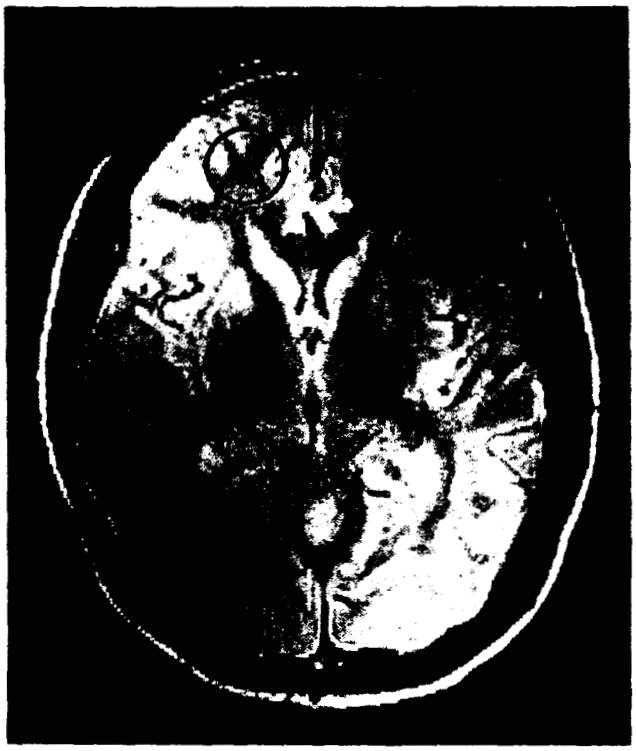

TABLE 1. Frontal Lobe Phosphorous Metabolism of 12 Patients With Bipolar Disorder and 16 Healthy Comparison Subjects

Variable and Hemisphere	Bipolar Group Mean	Bipolar Group SD	Comparison Group Mean	Comparison Group SD
Phosphorous metabolites (percent of total phosphorous signal)				
Phosphomonoesters[a]				
Right	11.2	3.2	13.0	3.9
Left	10.4	1.7	13.8	3.2
Inorganic phosphate				
Right	5.7	2.5	6.6	2.5
Left	6.6	2.6	6.4	3.3
Phosphodiesters[b]				
Right	29.8	3.1	27.1	3.7
Left	31.3	3.4	28.0	5.3
Phosphocreatine[c]				
Right	24.2	4.3	21.4	3.2
Left	20.1	2.5	20.6	3.4
β-ATP				
Right	8.3	1.4	9.4	2.6
Left	8.8	1.9	9.8	2.7
pH				
Right	7.07	0.11	6.97	0.28
Left	7.03	0.06	7.03	0.12

[a]Significant group effect ($F=7.82$, df=1, 26, $p=0.009$; repeated measures ANOVA).
[b]Significant group effect ($F=5.70$, df=1, 26, $p=0.03$).
[c]Significant Side by Group interaction ($F=5.72$, df=1, 26, $p=0.02$).

Depression Rating Scale (10) on the day of the MRS study. The average duration of illness was 17.5 years (SD=9.4).

All patients had agreed to discontinue any medications 1 week before the examination and were carefully monitored for reemergence of symptoms. None of the selected patients had any history of rapid decompensation after discontinuation of medication. A 1-week medication-free period was chosen because it was felt that this time period would not pose a substantial risk of relapse for this group of patients. One patient had never taken medication, five patients had been taking lithium only, two patients 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 had clinically significant alcohol or substance abuse in the 12 months before the study. None of the comparison subjects had any history of major medical illness, head injury, neurological disorder, psychiatric disorder, or clinically significant alcohol or substance abuse. There were no significant group differences between patients and comparison subjects in age or education.

All MRS studies were performed on a Philips Gyroscan S15 MRI/MRS system operating at 2 T. A standard imaging saddle-type proton head coil was used for magnetic resonance imaging (MRI). For each subject, T_1-weighted sagittal multislice images (seven slices, 7.1 mm thick, 1.2-mm gap, TR=600 msec, TE=30 msec) and T_2-weighted axial multislice images (16 slices, 7.1 mm thick, 1.2-mm gap, TR=2000 msec, TE=30 and 80 msec) were obtained. A neuroradiologist blind to each subject's clinical status evaluated the MRI scans from both the comparison subjects and patients to determine whether 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 of the patients and healthy subjects. For ^{31}P MRS, an inductively coupled, high-pass, quadrature birdcage head coil was used to provide homogeneous radiofrequency excitation and detection. The MRS procedures and experimental variables were identical to those previously described for studies on the frontal and parietal lobes of schizophrenic patients (11). A spin-echo sequence (TR=350 msec, TE=3.5 msec) was used.

MRS data volumes were reconstructed, and the effective voxel size was 25 cm^3. A reference image of the total ^{31}P signal was generated, and the higher resolution of the spatially registered magnetic resonance images was used to select two voxels in comparable locations for each subject in the right and left frontal lobes (figure 1). ^{31}P spectra from these voxels were fit by using NMR-1 data processing software (New Methods Research, Inc., Syracuse, N.Y.). The percentages of total phosphorous signal for phosphomonoesters, inorganic phosphate, phosphodiesters, phosphocreatine, and β-ATP were calculated. The β-ATP resonance was selected to best represent the ATP concentration in tissue because, unlike the g-ATP and α-ATP resonances (which were also fit by NMR-1 software and included in the normalization of the ratios), it is free from signal contribution from other phosphate-containing metabolites, such as ADP and nicotinamide adenine dinucleotide phosphates. The spectra were coded for blind processing by a single operator to eliminate interoperator variance.

Repeated measures analysis of variance (ANOVA) was used for data analysis. The dependent variable was the percentage of the total phosphorous signal for each metabolite, group was the between-subjects factor, and side (left versus right) was the within-subjects repeated measures factor. The ANOVAs were performed in an exploratory fashion without correction for multiple comparisons. The significance level was set at $p<0.05$.

RESULTS

No abnormalities were noted on the MRI scans of the patients or the healthy comparison subjects. Relative to the comparison group, the bipolar patients had significantly lower phosphomonoester values (table 1) and significantly higher phosphodiester values in both the right and left frontal lobes. In addition, the right-

to-left ratio of frontal phosphocreatine was higher in the bipolar patients. No such asymmetry of phosphocreatine was noted in the comparison group. There were no group differences or lateralized asymmetries for inorganic phosphate, β-ATP, pH, or total phosphorous signal.

DISCUSSION

The primary finding of this preliminary study was significantly lower phosphomonoester values and higher phosphodiester values in both the right and left frontal lobes of unmedicated, euthymic bipolar patients than in healthy comparison subjects. The phosphomonoester findings are consistent with prior results from investigations of lithium-treated euthymic bipolar patients; however, we also noted high phosphodiester values in our patient group, which to our knowledge have not been reported before. The results are also similar to those from in vivo ^{31}P MRS studies in schizophrenia, which have shown low phosphomonoester values and high phosphodiester values in the frontal lobes (12–14). This suggests that abnormal frontal lobe phospholipid metabolism may play a role in the pathophysiology of both bipolar disorder and schizophrenia.

It appears less likely that the observed abnormalities in phosphomonoesters are related to lithium effects on phospholipids because the seven lithium-treated patients had been medication free for 1 week and four other patients had been maintained on carbamazepine and not lithium. In addition, low phosphomonoester values were reported for a group of 10 euthymic bipolar patients, seven of whom had not been treated with lithium (2). It has therefore been suggested that an abnormal frontal lobe phosphomonoester value in the euthymic state is a trait-dependent abnormality, possibly related to membrane abnormalities in bipolar disorder (2, 3). Nevertheless, chronic administration of lithium has been reported to 1) decrease both in vitro levels of phosphatidylinositol and phosphatidylethanolamine and increase phosphatidylcholine in rats (5) and 2) cause a large initial increase and subsequent decline to normal levels of in vivo phosphomonoester measurements in cats (4). To our knowledge, there is no clear evidence on the time course over which lithium effects on phospholipids resolve. Thus, it is conceivable that any underlying phospholipid changes in humans due to lithium might have persisted beyond the 7-day medication-free period in this study.

A secondary finding of this study, which to our knowledge has not been reported previously, is an asymmetry of phosphocreatine in the bipolar patients, who demonstrated higher phosphocreatine values in the right than left frontal lobe. However, because our study employed metabolite ratios (percentage of total phosphorous signal for each metabolite), it is not possible to definitively conclude whether the right or left frontal lobe has the abnormal metabolite concentration. It is also unclear whether the observed asymmetry is in part due to a difference in atrophy between the right and left frontal lobes. Although there were no qualitative differences in atrophy between the bipolar patients and comparison group or between the right and left sides, more quantitative analyses are required. Moreover, we did not observe a lateralized difference in all phosphorous metabolites or the total phosphorous signal, which would most likely follow from a significant difference in size or atrophy between the right and left frontal lobes. Future studies with larger subject groups, absolute quantitation of phosphorous metabolites, and tissue segmentation techniques (to assess the relative contributions of gray matter, white matter, and CSF in selected voxels) will be able to determine whether the phosphocreatine asymmetry reflects a true concentration difference.

With regard to the limitations of the present study, our study group was small and it is not clear whether the 7-day medication-free period was sufficient to completely exclude lithium-induced effects on phosphomonoesters. Future studies will be able to address this question by examining whether the observed changes are present in patients who either have been maintained without lithium for a longer period of time or are taking mood stabilizers that are not known to affect phosphomonoesters, such as carbamazepine and valproic acid. Second, abnormalities in the T_1 or T_2 of phosphorous metabolites in the frontal lobes of the bipolar patients might also have contributed to the observed group differences. In other words, the differences observed here may have reflected differences in metabolite variability (as a consequence of relaxation time differences) rather than metabolite concentration differences. Third, a recognized limitation of in vivo spectroscopy is the low sensitivity of ^{31}P MRS and the low concentrations of ^{31}P metabolites, which limit the spatial resolution of ^{31}P MRS. Fourth, 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 ^{31}P MRS to determine the exact percentages of gray matter, white matter, and CSF in selected voxels.

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