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Haloperidol Improves Membrane Phospholipid Abnormalities in Temporal Lobes of Schizophrenic Patients

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Using ^{31}P magnetic resonance spectroscopy, we examined changes in the levels of phosphorus metabolites in the temporal lobes of 13 schizophrenic patients before and 12 weeks after initiating haloperidol treatment. Spectra were obtained from a volume of interest positioned in each temporal lobe. Findings were compared with those in 13 age- and gender-matched healthy subjects. Prior to treatment the patients showed higher levels of phosphodiesters (PDE) in both temporal lobes than healthy subjects. Haloperidol administration significantly reduced the excess of PDE in the left temporal lobe, although the PDE concentration remained somewhat higher bilaterally than in controls. Treatment was associated with a decline in the total symptom score according to the Brief Psychiatric Rating Scale and the score for positive symptoms showed a relatively high correlation with reduction in PDE level in the left temporal lobe. These preliminary results suggest that haloperidol may partially normalize disturbed metabolism or abnormalities in components of membrane phospholipids in the left temporal lobe of untreated schizophrenic patients, paralleling symptom alleviation.
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KEY WORDS: *Schizophrenia; Magnetic resonance spectroscopy; Haloperidol; Temporal lobe; Phosphorus metabolites*

Functional neuroimaging studies have revealed abnormalities in the brains of schizophrenic patients, especially in the frontal and temporal lobes, basal ganglia, and thalamus (Bertolino et al. 1996; Andreasen et al. 1997; Egan and Weinberger 1997; McClure et al. 1998). Frontal lobe dysfunction generally has been associated with "negative" symptoms and the disorganization syndrome (Liddle et al. 1992; Kaplan et al. 1993; Shioiri et al. 1994; Deicken et al. 1995), whereas temporal lobe dysfunction may be related to "positive" symptoms (Fukuzako et al. 1996; Klemm et al. 1996; Nordahl et al. 1996; Sabri et al. 1997). The effects of neuroleptic treatment on regional cerebral blood flow (rCBF) and metabolism are not yet clear (Miller et al. 1997). Several researchers have found, however, that neuroleptic treatment produced changes in rCBF in the frontal and temporal lobes of schizophrenic patients. Nilsson et al. (1977) demonstrated a widespread reduction in cortical perfusion, especially in frontotemporal regions, after several weeks of treatment with haloperidol. Changes in positive symptom scores correlated well with changes in both frontal and temporal CBF (Berman et al. 1996). Single-dose haloperidol administration in schizophrenic patients ameliorated hypoactivity in the frontal lobes and suppressed hyperactivity in the temporal lobe and adjacent occipital and parietal areas (Matsuda et al. 1991). These CBF changes were not de-

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tected when the drug was administered to normal volunteers. These observations suggest that neuroleptics alleviate schizophrenic symptoms by actions in the frontal and temporal lobes.

Phospholipase A_2 (PLA_2) is a key enzyme in the metabolism of phospholipids that also affects receptor function and signal transduction (Farooqui et al. 1992). In a biochemical study, Gattaz et al. (1995) found platelet PLA_2 activity to be greater in schizophrenic patients than in healthy controls; this elevation was reduced by neuroleptic treatment. Neuroleptics may alter brain phospholipid metabolism and composition by regulating PLA_2 activity in a manner similar to that seen in platelets and red blood cells. Possible effects of neuroleptics like haloperidol on membrane phospholipid metabolism and composition are under investigation. In one study, haloperidol was found to reduce synthesis of various phospholipids in rat brain (Singh and Shankar 1996).

Disturbed phospholipid metabolism has been proposed as a neurodevelopmental pathogenesis of schizophrenia (Horrobin 1998). *In vivo* ^{31}phosphorus magnetic resonance spectroscopy (^{31}P-MRS) is able to quantitate membrane phospholipids and high-energy phosphate metabolism in the brain (Maier 1995; McClure et al. 1998). Therefore, ^{31}P-MRS may represent a direct test for such a hypothesis. With ^{31}P-MRS, increased levels of phosphodiesters (PDE) and decreased levels of phosphomonoesters (PME) have been observed in the frontal lobes of drug-naive schizophrenic patients compared with levels in healthy subjects (Pettegrew et al. 1991; Stanley et al. 1995). Increased β-phosphates of 5′-adenosine triphosphate (β-ATP) and decreased inorganic orthophosphate (Pi) also have been reported (Pettegrew et al. 1991). Evidence of changes in phosphorus metabolites has been sought after treatment with neuroleptic medication only in the study of Keshavan et al. (1995), with negative results. However, no previous report has investigated metabolite changes in the temporal lobes of drug-naive schizophrenic patients and subsequent alterations in metabolite levels with neuroleptic treatment. In our previous study, the association between membrane phospholipid abnormality in the temporal lobe and positive symptoms was reported in medicated schizophrenic patients (Fukuzako et al. 1996). In the present study, we performed ^{31}P-MRS to investigate metabolite changes in the temporal lobes of schizophrenic patients induced by the administration of haloperidol for 12 weeks and its relations to specific symptoms.

MATERIALS AND METHODS

Twenty-five first-episode, drug-naive Japanese patients (14 men and 11 women aged 16 to 32 years; mean 23.1) who met DSM-III-R diagnostic criteria for schizophrenia or schizophreniform disorder (American Psychiatric Association 1987) and were right-handed according to the Edinburgh Handedness Inventory (Oldfield 1971; Schachter et al. 1987) were recruited from the outpatient clinics of Fujimoto Hospital and Kagoshima University Hospital between 1991 and 1996. All patients gave their written informed consent for participation in the study. None had a recent history of alcohol or drug abuse.

Sixteen patients of the 25 completed adequate MRS studies before and after 12 weeks of treatment with haloperidol. The dose of haloperidol given each patient was determined by the treating psychiatrist. The average total dose of haloperidol administered during the 12-week period was 470 ± 223 mg. All patients were treated in the two institutions, and their diagnoses were reevaluated one year following the first scan. Three patients were excluded from data analysis because their diagnosis remained schizophreniform disorder at this follow-up estimation. As a result, data from the 13 patients (7 men and 6 women aged 16 to 32 years; mean 22.6), who were diagnosed with schizophrenia, were analyzed. They had been ill for 7.4 ± 6.5 months at the time of the first scan. A neuropsychiatrist (T. Fukuzako) evaluated the patients using the Oxford version of the Brief Psychiatric Rating Scale (BPRS, range 0 to 6) (Kolakowska 1976) before and after treatment. The sum of scores for conceptual disorganization, suspiciousness, hallucinatory behavior, mannerisms and posturing, and unusual thought content was taken as the subscale score for positive symptoms. Negative symptom scores were estimated based on emotional withdrawal, motor retardation, uncooperativeness, and blunted affect. This selection criteria was based on the results of Kitamura et al. (1990).

Thirteen age- and gender-matched healthy subjects who served as controls (ages 15 to 31 years; mean 22.2) were relatives of hospital staff members and students at the University. They underwent MRS twice, with the same interval between scans as in the patient group. All subjects were right-handed according to the Edinburgh inventory (Oldfield 1971); a laterality score greater than 80 was considered evidence of right-handedness (Schachter et al. 1987).

The method of MRS data acquisition and processing has been described in our earlier report (Fukuzako et al. 1996). Spectroscopy was performed on a Siemens-Asahi Meditec MR system (Erlangen, Germany) with a magnetic field strength of 2.0 tesla. A circular polarizing head coil was tuned to 84.5 MHz for proton imaging and to 34.2 MHz for in vivo multivoxel ^{31}P-MRS (two-dimensional chemical shift imaging; 2DCSI). T_1-weighted spin-echo images with a repetition time of 500 msec and an echo time of 15 msec were acquired for the voxel placement. The field of view was 24 cm with an 8 x 8 data matrix and a 4-cm section thickness. The volume of

each voxel was 36 ml. We sought to make the location of the voxels investigated as near to identical as possible between the two MRS scans. On the midsagittal slice, placement of voxels was determined as the posterior limit of the volume of interest (VOI) passing through the superior and inferior colliculus. On the coronal slice, the placement of the voxels was determined as the midline of voxels passing through the interhemispheric fissure and third ventricle. In addition, the inferior limit of the VOIs was placed on a line passing through the inferior aspect of both temporal lobes. The spectra from the two VOIs, each consisting of two voxels, were produced by recalculating the signals already obtained. These VOIs contained mainly the temporal lobes and small part of the frontal and parietal lobes. The time of repetition was 2 sec; the number of sample points was 1024; and the acquisition delay was 1.72 msec. Twelve measurements were obtained for each spectrum. Data were processed with Fourier transformation and exponential multiplication (16 Hz) and then phase-corrected for the constant phase and linear frequency dependent phase.

Spectral peaks were obtained for PME, Pi, PDE, phosphocreatine (PCr), and γ-, α-, and β-ATP. The spectra were quantified by peak area measurements. An automated baseline correction technique removed the sinc-wiggle-like distortion from the baseline of the spectra. The technique minimized the square error between the theoretically derived spectrum and the corrected spectrum. After baseline correction, peak parameters such as height, position, and width were obtained by a Lorentzian curve-fitting procedure. This process was performed automatically after the number of peaks was determined. For each spectrum, the integrated areas for PME, Pi, PDE, and PCr, and for γ-, α-, and β-ATP were measured, and percentages of total phosphorus signal (mole percentages) were calculated. The β-ATP peak was adopted as an ATP reference because γ- and α-ATP peaks contain other phosphate metabolites such as adenosine diphosphate and dinucleotide phosphate. Coefficients of variation (CVs) for controls in this study for each metabolite ranged from 6.5% to 17.6% (PME, lt 12.0%, rt 14.8%; Pi, lt 15.4%, rt 17.6%; PDE, lt 6.5%, rt 6.6%; PCr, lt 15.0%, rt 12.4%; β-ATP, lt 10.5%, rt 10.7%; γ-ATP, lt 11.1%, rt 16.2%; and α-ATP, lt 10.2%, rt 10.1%). These CVs were less than those we had previously calculated based on one voxel (36 ml, range 8.7% to 27.9%) (Fukuzako et al. 1996). We investigated changes between two scans performed one to two weeks apart in five schizophrenic patients who underwent long-term medication and five healthy volunteers. No significant metabolite changes were demonstrated between the two scans by a paired t test, although the sample size was very small. In addition, the CVs in the patients and controls in the previous study of small sample were comparable to those in the present one.

Repeated-measures analysis of variance (ANOVA) was performed separately for patients and controls, with scan (pre- and posttreatment) analyzed and side (left and right) as within-subject factors. Subsequently, two-way ANOVA with a between-subject factor of diagnosis and a within-subject factor of side was performed on data obtained before and after haloperidol treatment, and was followed by Scheffé multiple-comparison method to establish statistically significant differences ($p < .05$). Pairwise comparisons were made: the second scan to the first scan in each patient or control group; patient to control at the time of the first scan or the second scan; and left to right for the first scan or the second scan in each group. Phosphorus metabolites were analyzed in an exploratory manner without correction for multiple comparison, in spite of the increased risk of a Type I error. Pearson's product moment correlation coefficient (r) was used to test relationships between the two types of values.

RESULTS

No obvious morphologic abnormalities were detected on magnetic resonance images of patients or healthy subjects. Mole percentages of metabolites in controls, in the drug-naive patients, and in patients after 12 weeks of haloperidol treatment are shown in Table 1. In the patient group, ANOVA revealed significant effects of scan (pre- vs. post-treatment) and side for levels of PME ($F_{3, 36} = 3.42$; $p = .028$) and PDE ($F_{3, 36} = 5.21$; $p = .004$). In the control group, no significant effects were observed for any metabolite.

Subsequent repeated-measures ANOVA showed a significant effect of diagnosis for levels of PME ($F_{1, 24} = 4.75$; $p = .039$) and PDE ($F_{1, 24} = 20.0$; $p < .001$) in drug-naive patients compared with healthy subjects. A significant diagnosis-by-side interaction was observed for PCr ($F_{1, 24} = 5.05$; $p = .034$). Post hoc multiple comparison revealed a significant elevation of PDE on both sides in drug-naive patients compared to the control group (left, $p < .001$; right, $p = .004$) (Table 1). Haloperidol administration significantly reduced the excess of PDE in the left temporal lobe of schizophrenic patients ($p = .028$) (Table 1, Figure 1).

The total BPRS score declined with haloperidol treatment, from an average of 35.3 to 13.4 (paired *t*-test: $t = 9.79$, $p < .001$). After 12 weeks of treatment with haloperidol, only the PDE level showed a remaining trend toward an excess in comparison to levels in healthy subjects (lt, $p = .065$; rt, $p = .073$). Relationships between changes in symptom score and metabolite level were tested for PME and PDE on both sides separately because the level of PDE in the left temporal lobe was changed significantly by haloperidol treatment, whereas both levels of PME on the left ($p = .061$) and of

Table 1. Phosphorus Metabolites in Temporal Lobes before and after Haloperidol Treatment

Metabolite		Schizophrenic Patients (N = 13)		Controls (N = 13)	
		Before Treatment	After Treatment	First Scan	Second Scan
PME	lt	9.4 ± 1.7	10.5 ± 1.2	10.7 ± 1.7	10.3 ± 1.3
	rt	9.5 ± 1.7	10.3 ± 1.2	10.6 ± 2.0	10.3 ± 1.6
Pi	lt	5.6 ± 1.5	5.9 ± 1.0	6.3 ± 1.0	5.6 ± 1.1
	rt	5.3 ± 1.3	5.6 ± 0.8	5.9 ± 1.5	5.9 ± 1.1
PDE	lt	41.8 ± 2.7[a]	39.9 ± 1.5[b]	37.8 ± 2.3	38.6 ± 1.9
	rt	41.1 ± 2.4[a]	39.7 ± 1.8	37.7 ± 2.6	37.8 ± 3.5
PCr	lt	11.5 ± 1.3	10.7 ± 1.2	10.5 ± 1.5	11.0 ± 1.4
	rt	10.4 ± 1.2	10.9 ± 1.0	10.9 ± 1.3	11.1 ± 1.9
β-ATP	lt	10.1 ± 1.5	9.6 ± 2.0	11.0 ± 1.3	10.9 ± 1.4
	rt	10.6 ± 1.5	10.5 ± 1.3	11.0 ± 1.3	10.6 ± 1.2
γ-ATP	lt	9.5 ± 1.9	10.4 ± 2.8	11.0 ± 1.3	10.5 ± 1.9
	rt	10.5 ± 2.1	10.5 ± 1.9	10.9 ± 2.3	11.0 ± 2.1
α-ATP	lt	12.0 ± 1.8	12.9 ± 2.3	12.8 ± 2.1	13.2 ± 1.8
	rt	12.7 ± 2.6	12.6 ± 2.9	13.0 ± 2.0	13.4 ± 1.9

[a] $p < .005$; post-hoc Scheffé test (compared to control under untreated condition).
[b] $p < .05$; post-hoc Scheffé test (compared to the condition before haloperidol treatment).

PDE on the right ($p = .095$) tended to be altered by the medication. Reduction in PDE level in the left temporal lobe correlated well with decline of total BPRS score (r = 0.69, $p = .007$) and the score for positive symptoms (r = 0.73, $p = .003$) (Figure 2). The PDE reduction in the right temporal lobe showed a weak correlation with the decline in positive symptom score (r = 0.59, $p = .031$). The total amount of haloperidol did not correlate significantly with changes in the level of any metabolite. The decline in BPRS score did not correlate with levels of any metabolite prior to haloperidol treatment.

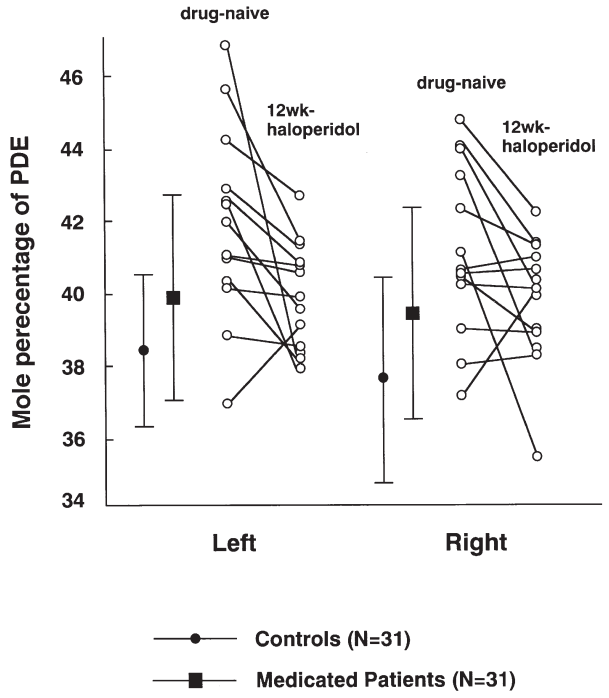

Figure 1. Mole percentages of phosphodiesters (PDE) in the left and right temporal region of schizophrenic patients before (drug-naive) and after (12-week haloperidol) receiving haloperidol for 12 weeks. Mean values (± SD) in healthy controls and long-term medicated patients also are shown (data from our previous study: Fukuzako et al. 1996).

DISCUSSION

In this study, ^{31}P-MRS detected an elevation of PDE in the temporal lobes of drug-naive schizophrenic patients compared with healthy subjects. These results are in part consistent with previous observations reported in the prefrontal cortex of schizophrenic patients (Pettegrew et al. 1991; Stanley et al. 1995). A recent preliminary study of ^{31}P-MRS in the temporal lobes of postmortem brains has shown a nonsignificant decrease in phosphoethanolamine (PE) and increases in glycerophosphoethanolamine (GPE) and glycerophosphocholine (GPC) in schizophrenic subjects, changes smaller but otherwise similar to our own findings (Williamson et al. 1996). Pettegrew et al. (1991) have speculated that increased PDE in the frontal lobes of schizophrenic patients may reflect increased breakdown of membrane phospholipids. The pre-acquisition delay time of 1.72 msec in our study makes interpretation of increased PDE difficult. The PDE resonance obtained from our ^{31}P-MRS method arises from free mobile PDE (GPC, GPE) and mobile PDE moieties (small membrane phospholipid structures such as micelles and vesicles) (Murphy et al. 1989; McNamara et al. 1994; Stanley et al. 1997; McClure et al. 1998). The longer pre-acquisition

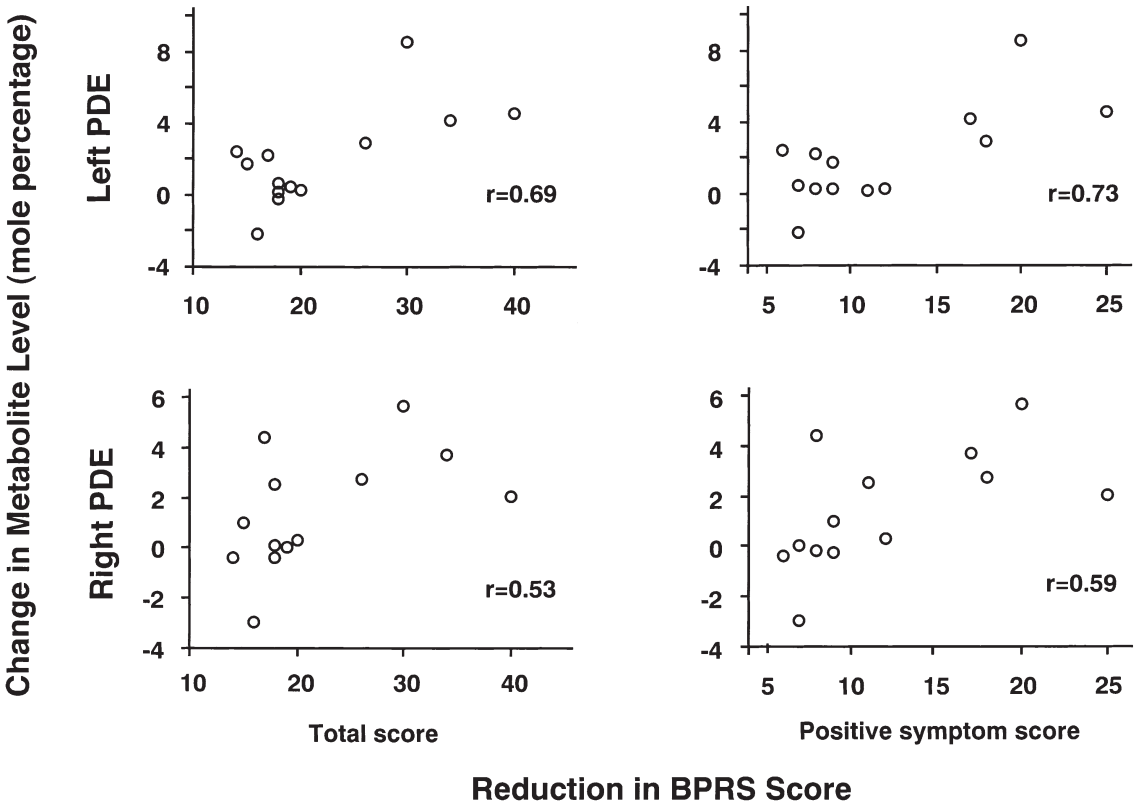

Figure 2. Correlations between changes in phosphodiesters (PDE) and changes in total Brief Psychiatric Rating Scale (BPRS) score and score for positive symptoms after 12 weeks of haloperidol treatment.

delay time might yield different results (Stanley et al. 1997). PDE are more concentrated in white matter than in gray (Kilby et al. 1990). However, a decreased gray-to-white matter ratio would be an unlikely cause of increased PDE level, since haloperidol treatment for 10 months does not alter volumes of gray and white matter (Keshavan et al. 1994). Therefore, the increase in PDE may reflect an increase in GPC, GPE, and/or small membrane phospholipid structures (McClure et al. 1998).

Several recent studies have used ^{1}H-decoupled ^{31}P-MRS to try to determine which PDE components contribute to the changes in PDE resonance observed in schizophrenic patients (Potwarka et al. 1996; Blüml et al. 1998). A preliminary study has shown that membrane or mobile phospholipids are increased in the frontal lobes of medicated schizophrenic patients, suggesting abnormal membrane structures (Potwarka et al. 1996). Recent reports suggest that schizophrenia is associated with a deficiency of arachidonic acid and docosahexaenoic acid in cell membranes (Horrobin 1998; Puri and Richardson 1998). On the other hand, Blüml et al. (1998) have demonstrated elevation of GPC and GPE concentrations in the parietal lobes of young medicated schizophrenic patients compared with healthy controls and elderly schizophrenic patients. Although definitive determination of the origins of increased PDE is difficult, disturbed metabolism or abnormalities in components of membrane phospholipids may not be restricted to the frontal lobe in the manner of the gray matter volume reduction observed in first-episode and long-term medicated schizophrenic patients (Lawrie and Abukmeil 1998; Zipursky et al. 1998).

In the present study an elevated level of PDE, especially in the left temporal lobe, was decreased by treatment with haloperidol, in contrast to the report of Keshavan et al. (1995), who reported increased levels of PDE on pretreatment imaging but no significant changes after four weeks of haloperidol treatment. The discrepancy between their results and ours may have resulted from differences in patient characteristics, location of the VOI, or the MRS techniques. Only nine of the 15 patients studied by Keshavan group were diagnosed with schizophrenia, while the remaining six had other psychotic disorders. The VOI was located in the prefrontal cortex in their study; in ours the VOI was placed in the temporal lobe, which has been associated with positive symptoms representing reality distortion that are alleviated substantially by administration of neuroleptics (Fukuzako et al. 1996; Klemm et al. 1996; Nordahl et al. 1996; Sabri et al. 1997). In contrast, the frontal lobe reportedly has been associated with negative

symptoms (psychomotor poverty) and disorganization syndromes that often resist neuroleptic treatment (Liddle et al. 1992; Kaplan et al. 1993; Shioiri et al. 1994; Deicken et al. 1995). A relatively high correlation between reductions in PDE level and in scores for positive symptoms lends support to VOI location as the reason for interstudy differences. Also, the depth-resolved surface coil spectroscopy used by the Keshavan group did not eliminate signals originating from the skull and cranial muscles, while our method of 2DCSI was virtually free of such artifacts. Finally, the period of haloperidol administration between the two scans was three times longer in our study than in theirs.

Administration of haloperidol for 12 weeks reduced the level of PDE to that found in patients receiving neuroleptic medication over long periods. However, the resonance representing PDE in the medicated patients still had a trend toward increase, compared with those in healthy subjects. These *in vivo* results may be consistent with biochemical findings demonstrating that increased PLA_2 activity was reduced by administration of neuroleptics (Gattaz et al. 1987, 1995), while remaining higher in treated schizophrenic patients than in healthy subjects (Ross et al. 1997). Our results suggest that neuroleptic medication may partially normalize the disturbed metabolism or abnormalities in components of membrane phospholipids in the temporal lobe of schizophrenic patients, especially on the left side.

Several limitations of this study need to be addressed. First, absolute metabolite quantitation, although preferable to assessment by percentage, was not feasible with our preliminary protocol. Second, alterations in T_1 or T_2 of phosphorus metabolites in the temporal lobe of schizophrenic patients could have influenced the differences detected between groups. Third, the size of the voxel was large (72 ml) because of the lower sensitivity of the ^{31}P-MRS and reducing the CVs between the scans; the voxels contained small portions of the frontal and parietal lobes besides temporal lobe. Fourth, the voxels contained varing percentages of gray matter, white matter, and CSF, which also may have altered group differences in metabolites. More sophisticated software that collects signals from these tissues separately may be better able to determine how subtle morphologic abnormalities in schizophrenic patients might interact with phosphorus MRS findings *in vivo.* Fifth, we investigated rest-retest reliability in five medicated schizophrenic patients and five healthy subjects, without any significant metabolite changes between the two scans. However, the sample size may not be sufficient for comparing results with this study. Finally, our MRS method may not be sufficiently sensitive to detect other subtle changes caused by haloperidol treatment.

In conclusion, our preliminary findings suggest that *in vivo* ^{31}P-MRS shows promise as one way to monitor the effect of the treatment of schizophrenia using neuroleptics and other therapies. Further studies regarding changes in metabolites with treatment using recently developed *in vivo* ^{31}P- and ^{1}H-MRS techniques (Bertolino et al. 1996; Stanley et al. 1997; Blüml et al. 1998; Deicken et al. 1998) will help to assess such possibilities.

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