

Basal Ganglia High-Energy Phosphate Metabolism in Neuroleptic-Naive Patients With Schizophrenia: A 31-Phosphorus Magnetic Resonance Spectroscopic Study

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Objective: This study used 31-phosphorus magnetic resonance spectroscopy (^{31}P MRS) to investigate basal ganglia abnormalities in neuroleptic-naive patients with schizophrenia.

Method: Nineteen schizophrenia patients and 31 age- and sex-matched healthy comparison subjects underwent ^{31}P MRS.

Results: The phosphocreatine/total phosphorus and phosphocreatine/total ATP ratios in both basal ganglia were significantly lower in patients.

Conclusions: Schizophrenia patients showed features of increased metabolism in the basal ganglia consistent with impaired activity of the frontostriatal pathways.

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Several studies have implicated basal ganglia in the pathophysiology of schizophrenia (1–3). Decrease in caudate volumes has been reported in neuroleptic-naive patients with schizophrenia (4). Findings from 31-phosphorus magnetic resonance spectroscopy (^{31}P MRS) studies have been inconclusive, perhaps due to differences in MRS methodology and medication status of the patients (5, 6).

We conducted a ^{31}P MRS study of the basal ganglia in neuroleptic-naive patients with schizophrenia and matched healthy comparison subjects. Considering that dopaminergic activity is increased in schizophrenia in subcortical structures (7), we hypothesized that basal ganglia metabolism would be increased in the schizophrenia patients.

Method

Subjects

The study group consisted of 19 right-handed inpatients and 31 healthy comparison subjects. Patients and comparison subjects did not significantly differ in terms of age (patients: mean=27 years [SD=7.6]; healthy subjects: mean=29 years [SD=6.1]) or sex (15 male and four female patients and 21 male and 10 female healthy comparison subjects). Diagnosis of DSM-IV schizophrenia was determined by a psychiatrist with the Structured Clinical Interview for DSM-IV (paranoid: N=8; catatonic: N=3; disorganized: N=2; undifferentiated: N=6). Illness duration ranged between 6 and 120 months (mean=44, SD=35). No patient was ever previously treated for psychiatric illness. Mean age at onset of psychosis was 23.6 years (SD=6.4, range=15–39). Their mean Pos-

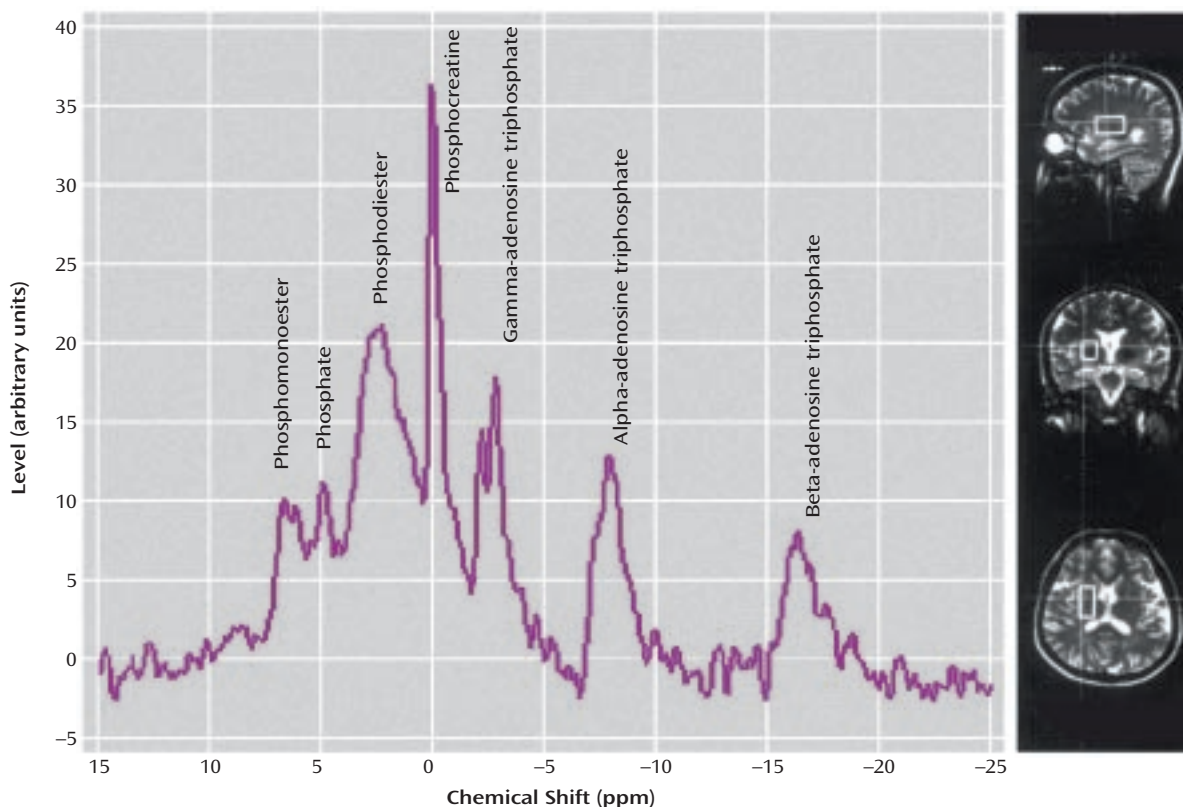
itive and Negative Syndrome Scale (8) score was 84 (SD=18, range=53–119). None had involuntary movements. MRS studies were conducted before starting antipsychotic treatment. Agitation was treated, where necessary, with lorazepam 2–6 mg/day in divided doses.

Healthy comparison subjects were screened using the 12-item General Health Questionnaire (9). None of the patients or healthy comparison subjects had a history of recent alcohol use (previous week) or scored positive on the CAGE questionnaire (10), and none used stimulants or opiate drugs. No subject had a history of epilepsy or any other neurological or medical disorder. All subjects provided written informed consent. The Institute's ethics committee approved the study.

Spectroscopy

^{31}P MRS was done on a 1.5 T scanner. Two-dimensional chemical shift imaging with image-guided in vivo spectroscopic localization and volume-selective adiabatic high-frequency pulses were used. The volume of interest was placed on representative slices of the brain in all three orthogonal planes interactively and simultaneously to avoid the ventricles. The volume of interest was localized to the basal ganglia with a mean size of $25 \times 25 \times 50 \text{ mm}^3$ (Figure 1). The magnetic field shimming for homogeneity was done to achieve a line width less than 0.15 ppm. The technical parameters were repetition time of 1500 msec, free induction decay (FID) sampling rate of 1500 Hz, sampling points of 1024, and 12 measurements.

The average FID signal in the spectra was processed using proprietary software by the rater (P.N.J.) blind to clinical data, with phosphocreatine as the reference marker. The spectra were quantified as integral values by an inbuilt program of fitting curves. The integrated area of phosphocreatine, inorganic phosphate, αATP , βATP , and γATP were measured. Phosphocreatine/total phosphorus and phosphocreatine/total ATP ratios in right and

FIGURE 1. Basal Ganglia Phosphate Metabolism as Measured With ^{31}P MRS^a

^a The volume of interest in representative slices of the brain in all three orthogonal planes is shown in the images on the right.

left basal ganglia were computed. The ratios were compared between the two groups using independent sample *t* tests and between the right and left basal ganglia within each group using paired *t* tests. Significance was set at $p < 0.05$.

Results

No significant differences were seen in phosphocreatine ratios between the right and left basal ganglia in patients or healthy comparison subjects. The average of the two sides was therefore used for analyses. Patients had lower mean phosphocreatine ratios than healthy comparison subjects (phosphocreatine/total phosphorus ratio: mean=0.25 [SD=0.064] versus 0.31 [SD=0.082], respectively [$t=2.62$, $df=48$, $p < 0.02$]; phosphocreatine/ATP ratio: mean=0.70 [SD=0.18] versus 0.94 [SD=0.25] [$t=3.64$, $df=48$, $p=0.001$]; phosphocreatine/ β ATP ratio: mean=18.85 [SD=23.75] versus 40.26 [SD=48.86] [$t=2.1$, $df=46.2$, $p=0.04$], with correction for unequal variance). The ATP/inorganic phosphate ratio was not different between patients (mean=70.02, SD=52.79) and healthy comparison subjects (mean=75.53, SD=44.88). After Bonferroni correction, phosphocreatine/total phosphorus and phosphocreatine/ATP ratios remained significantly different between patients and healthy comparison subjects. Phosphocreatine ratios of the patients not receiving lorazepam ($N=5$) did not differ from the rest ($N=14$) (phosphocreatine/total phosphorus ratio: mean=0.24 [SD=0.058] and 0.28 [SD=0.078], respectively; phosphocreatine/ATP

ratio: mean=0.68 [SD=0.16] and 0.75 [SD=0.23]). Illness duration did not correlate with the phosphocreatine/total phosphorus ratio ($r=0.22$, $df=17$, $p=0.36$) or the phosphocreatine/ATP ratio ($r=0.07$, $df=17$, $p=0.77$).

Discussion

The main findings of this study were decreased phosphocreatine/total phosphorus, phosphocreatine/ATP, and phosphocreatine/ β ATP ratios in basal ganglia of the patients relative to healthy comparison subjects. When ATP is consumed during metabolism, phosphocreatine is converted to ATP to maintain energy balance. Hence, in metabolically more active tissues, the phosphocreatine would be lower. It suggests that basal ganglia metabolism is elevated in schizophrenia. This finding in neuroleptic-naïve schizophrenia patients excludes medication effects. The lack of correlation with illness duration is consistent with the possibility of a nonprogressive (possibly developmental) dysfunction in schizophrenia (11). The cortical atrophy seen in schizophrenia patients (12) could result in reduced inhibitory corticostriatal transmission leading to hypermetabolism in basal ganglia (13). Alternatively, lower phosphocreatine may also be due to reduced synthesis, perhaps related to mitochondrial dysfunction in basal ganglia reported in schizophrenia (14, 15). The metabolic dysfunction of the basal ganglia is also corrobo-

rated by the membrane phospholipid abnormalities in this sample reported elsewhere (16).

The strength of the study is the use of neuroleptic-naïve schizophrenia patients. Although some patients received lorazepam, phosphocreatine ratios of patients receiving lorazepam (N=5) were not different from the rest (N=14). Interassay reliabilities were not available. Some tissue heterogeneity (gray and white matter) is inevitable in the voxels, and intravoxel segmentation to separate tissue classes would have been useful. Finally, absolute values of metabolites were not measured. Nevertheless, ratio measures compare favorably with absolute measures (17).

In summary, neuroleptic-naïve schizophrenia patients demonstrated increased high-energy phosphate metabolism in basal ganglia. The finding is consistent with impaired activity of corticostriatal pathways in schizophrenia.

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