Lower Levels of Nucleoside Triphosphate in the Basal Ganglia of Depressed Subjects: A Phosporous-31 Magnetic Resonance Spectroscopy Study

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Objective: *The purpose of this study was to evaluate whether the concentration of β-nucleoside triphosphate is lower in the basal ganglia of depressed subjects.* *Method:* *In vivo ^{31}P magnetic resonance spectra were acquired from a 45-cm^3 region surrounding the basal ganglia of 35 unmedicated depressed subjects and 18 comparison subjects.* *Results:* *β-Nucleoside triphosphate, which arises primarily from β-ATP, was 16% lower in the depressed subjects than in the comparison subjects.* *Conclusions:* *The low level of β-nucleoside triphosphate is consistent with an abnormality of high-energy phosphate metabolism in the basal ganglia of subjects with major depression.*

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Phosphorous magnetic resonance spectroscopy (^{31}P MRS) provides a means to noninvasively determine cerebral levels of a number of metabolites including the high-energy phosphates phosphocreatine and γ, α, and β-nucleoside triphosphate; inorganic phosphate; and the phosphomonoesters and phosphodiesters that are involved in phospholipid metabolism.

Positron emission tomography (PET) (1) and single photon emission tomography (2) studies have shown lower fluorodeoxyglucose metabolic rates and blood flow, respectively, in the basal ganglia of patients with major depression than in comparison subjects. PET studies have also documented lower rates of glucose utilization in the basal ganglia of medicated subjects with schizophrenia (3). More recently, Deicken et al. (4) have used ^{31}P MRS to demonstrate that β-nucleoside triphosphate levels are lower in the basal ganglia of medicated patients with schizophrenia.

Since patients with schizophrenia and major depression both appear to show lower rates of glucose utilization in the basal ganglia, we wished to investigate the hypothesis that there would also be lower levels of high-energy phosphate metabolites, in particular β-nucleoside triphosphate, in the basal ganglia of depressed subjects than in comparison subjects without psychiatric illnesses.

METHOD

After approval of the study by the institutional review board, written informed consent was obtained from all subjects. Unmedicated depressed patients were recruited from those participating in ongoing treatment trials (N=35); the mean age was 37.2 years (SD=8.5). There were 16 men and 19 women in the group; mean number of years of education was 14.8 (SD=2.5). The comparison subjects were recruited by newspaper advertisement (N=18); the mean age was 38.2 (SD=9.9). There were nine men and nine women; mean number of years of education was 15.5 (SD=1).

All depressed patients met criteria for major depressive disorder, determined by the Structured Clinical Interview for DSM-III-R—Patient Version (SCID-P), and had a baseline score of 16 or higher on the 17-item Hamilton Depression Rating Scale (mean=20.7, SD=3.4). Both of these instruments were administered by trained raters with an interrater reliability (kappa) of >0.80. Exclusion criteria for participation included a history of neurological illness, serious medical illness, substance abuse, and age less than 18 or greater than 60. Patients were medication free for 1–3 weeks (N=9) or for more than 1 year (N=10) or had never received treatment (N=16).

The comparison subjects were screened with the SCID-P, which was administered by the same interviewers. Exclusion criteria were the same as for the depressed subjects, except that the comparison subjects could not have any axis I diagnosis. The group's mean Hamilton depression score was 1.3 (SD=1.3).

Spectra were acquired on a 1.5-T scanner through use of a double-tuned, linear proton, quadrature phosphorous volume coil. Scout images were used to prescribe an image selective in vivo spectroscopy (5) voxel with dimensions of 3 cm (anterior/posterior) × 3 cm (supe-

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rior/inferior) × 5 cm (left/right) (45 cm^3) encompassing the bilateral basal ganglia. The acquisition parameters were as follows: flip angle=90°, TR=3 seconds, acquisition delay=350 μsec, number of points=1,024, spectral width=2500 Hz, averages=512; total acquisition time=26 minutes. Within this volume signal was derived from caudate (mean=14%, SD=7%), lenticular nucleus (mean=24%, SD=6%), lateral ventricles (mean=11%, SD=3%), and adjacent white matter (mean=51%, SD=14%) (segmentation of voxel images from five comparison subjects) (6).

The free induction decay was processed by using a convolution difference with a 100-Hz exponential filter. The resultant free induction decay was zero filled to 2,048 data points and exponentially filtered to produce 15 Hz line broadening after Fourier transformation. The spectrum was manually phase corrected (zero and first order) and fit to a spline baseline. The peak areas of the following metabolites—phosphomonoesters, inorganic phosphate, phosphodiesters, phosphocreatine, and γ, α, and β-nucleoside triphosphate—were then fit to Gaussian line shapes through use of an iterative Marquardt algorithm. The γ, α, and β-nucleoside triphosphate peaks consist primarily of ionized ends (γ-ATP + β-ADP), esterified ends (α-ATP + α-ADP + dinucleotides), and middles (β-ATP), respectively (7).

For each metabolite, the peak area was normalized by the total phosphorous signal, yielding the mole percent metabolite value, which is the percentage of total ^{31}P signal intensity contributed by the metabolite (8). Statistical analysis was performed by using single factor analysis of variance (ANOVA) (alpha=0.05).

RESULTS

The mole percent β-nucleoside triphosphate was significantly lower ($F=5.06$, df=1, 51, $p<0.03$) in the basal ganglia of the unmedicated depressed subjects than in the comparison subjects. None of the other metabolites varied significantly (table 1).

TABLE 1. Concentration of the Phosphate Metabolites and pH in the Basal Ganglia of Patients With Major Depression and Comparison Subjects

	Comparison Subjects (N=18)		Depressed Patients (N=35)		ANOVA (df=1, 51)	
Metabolite	Mean	SD	Mean	SD	F	p
Concentration (%)						
Phosphomonoesters	7.2	3.8	7.5	3.7	0.09	<0.76
Inorganic phosphate	6.8	1.4	6.9	2.0	0.06	<0.80
Phosphodiesters	26.8	5.3	28.4	4.9	1.15	<0.29
Phosphocreatine	16.0	4.9	16.7	4.5	0.26	<0.61
Nucleoside triphosphate						
γ	12.1	3.1	11.9	3.2	0.04	<0.84
α	16.1	2.9	15.9	2.5	0.02	<0.87
β	15.0	3.7	12.6	3.8	5.07	<0.03
pH	6.99	0.08	6.96	0.08	1.19	<0.28

DISCUSSION

The lower mole percent β-nucleoside triphosphate in the depressed subjects, in the presence of a constant ratio of mole percent phosphocreatine to mole percent inorganic phosphate, is consistent with the presence of metabolic abnormalities within neurons or glial cells. This profile of metabolite changes is unusual, since nucleoside triphosphate concentration is usually maintained at the expense of phosphocreatine because of the higher phosphate group transfer potential of phosphocreatine. The brain nucleoside triphosphate resonance is derived primarily from ATP. Since the creatine kinase reaction is near equilibrium in human brain (9), lower concentrations of ATP are most likely associated with lower concentrations of ADP, thus maintaining a constant ratio of ATP to ADP, as well as with lower concentrations of the total adenosine pool.

Observed changes in cerebral metabolites, as determined by ^{31}P MRS, may result from different contributions of gray and white matter to the volume of interest (10). However, the concentration of nucleoside triphosphate is similar in both gray and white matter (11), and it is unlikely that the lower mole percent β-nucleoside triphosphate reported here is due to different quantities of gray and white matter in the volume of interest.

Because of the relatively low sensitivity of the ^{31}P nucleus for MRS, our ^{31}P MRS signal is derived from a 45-cm^3 voxel in which the basal ganglia make up approximately 40%, the lateral ventricles 11%, and adjacent white matter 51% of the overall tissue. The observed changes in mole percent β-nucleoside triphosphate may therefore not be confined to the basal ganglia. However, studies by other workers, using a number of modalities, have shown abnormal metabolic rates in a number of brain regions, and there have been no reported changes in cerebral white matter (1, 2). Therefore, we believe that the lower mole percent β-nucleoside triphosphate observed in this study probably originates in the basal ganglia.

In summary, we report a lower concentration of β-nucleoside triphosphate within the basal ganglia of unmedicated subjects with major depression than in comparison subjects. Further studies will be necessary in order to determine whether this biochemical anomaly is trait or state dependent. Moreover, the fact that similar biochemical findings have been demonstrated for individuals with schizophrenia suggests that these two divergent disorders may share some common pathophysiological features.

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