Proton MR Spectroscopy of the Brain in 14 Patients with Parkinson Disease

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PURPOSE: To determine whether the proton spectra from patients with clinically diagnosed Parkinson disease differ from the spectra of age-matched healthy subjects with respect to the major cerebral metabolite resonances as well as lactate. **METHODS:** Fourteen patients with Parkinson disease (38 to 81 years of age) and 13 healthy control subjects (37 to 81 years of age) were studied using image-guided, single-voxel (27-cm^3 volume) proton MR spectroscopy of the occipital lobe. **RESULTS:** The peak area ratios of *N*-acetyl aspartate to creatine and *N*-acetyl aspartate to choline for Parkinson patients did not show a statistically significant difference from the corresponding ratios for control subjects. There was a very significant increase in the ratio of lactate to *N*-acetyl aspartate for patients with Parkinson disease, with the greatest increase (threefold) manifested by the subgroup (n = 4) with dementia. The difference in *N*-acetyl aspartate to choline between women (n = 7) with Parkinson disease and healthy women (n = 9) approached significance. No dependence of the peak ratios on age, duration of Parkinson disease, or medication (L-dopa) regimen was found. **CONCLUSION:** Preliminary results indicating an increase in cerebral lactate in patients with Parkinson disease support the hypothesis that Parkinson disease is a systemic disorder characterized by an impairment of oxidative energy metabolism. The larger increases for Parkinson patients with dementia may be diagnostically useful in assessing clinical course and in differentiating Parkinson disease from other causes of dementia. Additional studies are needed, though, to quantitate lactate changes and identify potential contributions from lipid resonances better.

Index terms: Parkinson disease; Magnetic resonance, spectroscopy; Brain, metabolism

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Although the cause of Parkinson disease is unknown, there is accumulating evidence that a disorder of the mitochondrial electron transport chain plays an important role in its pathogenesis (1). Postmortem studies of brains from patients with Parkinson disease demonstrate reduced activity of complex I of the electron transport chain in the substantia nigra (2–4) and possibly the striatum (5). Defects in complex I in platelets (6) and muscle (7, 8) from living Parkinson patients have also been described. A metabolite, 1-methyl-4-phenyl pyridinium, of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine inhibits complex I and produces a parkinsonian syndrome in humans similar to idiopathic Parkinson disease (9). These findings have led to the hypothesis that Parkinson disease is a systemic disease characterized by dysfunction of the mitochondrial electron transport chain, primarily as a result of a defect in complex I.

In animal models of Parkinson disease and in isolated mitochondria, studies of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine–induced toxicity have demonstrated that one consequence of complex I inhibition is increased lactic acid production (10), with lactate levels increased as much as twofold to threefold when there is complete inhibition of complex I (11). These results

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Peak ratios from occipital lobe spectra

Group	NAA/Cho	NAA/Cr	La/NAA
Control subjects (n = 13)	3.19 ± 1.65	2.60 ± 0.95	0.05 ± 0.05
Parkinson patients (n = 14)	3.76 ± 1.50 (0.36)*	3.06 ± 0.93 (0.22)*	0.11 ± 0.06 (0.009)*
Nondemented (n = 10)	3.91 ± 1.77 (0.58)	2.84 ± 0.69 (0.17)	0.09 ± 0.04 (0.05)
Demented (n = 4)	3.39 ± 0.31 (0.81)	3.61 ± 1.31 (0.11)	0.16 ± 0.08 (0.004)
Percent change for Parkinson disease compared with control group	+18	+18	+120

Note.—Ratios are expressed as means ± SD.

* *P* values given in parentheses are those obtained with the unpaired Student's *t* test applied to comparisons between each of the Parkinson groups and the control group. $P < 0.05$ is considered significant.

raise the question of whether there are increased levels of lactate in Parkinson patients, in the nigrostriatal system and/or in other cell populations. Recently, preliminary results showing elevated levels of lactate in the occipital cortex of patients with Huntington disease have been reported (Jenkins BG et al, "Evidence of an Energy Metabolism Defect in Huntington's Disease Using Localized Proton Spectroscopy," presented at the Eleventh Annual Meeting of the Society for Magnetic Resonance in Medicine, Berlin, 1992). The lactate elevations have been attributed to an impairment of oxidative metabolism in Huntington patients. These results must be interpreted cautiously, though, because basal lactate levels in healthy persons are variable (12).

The purpose of this study is to determine whether the proton spectra obtained from patients with Parkinson disease differ from those obtained from healthy control subjects, with respect to the major metabolic species—*N*-acetyl aspartate (NAA), choline (Cho), and creatine/phosphocreatine (Cr)—and whether differences in lactate (La) levels between the two groups are present.

Methods

Fourteen patients (seven men and seven women) with Parkinson disease diagnosed by a neurologist (J.S.-R.) in a movement disorders clinic participated in the study. The age range was 38 to 81 years (mean age, 64 ± 15 years [SD]); the duration of disease was 2 to 12 years (mean duration, 7 ± 4 years). Each patient met the following criteria for clinical diagnosis: (*a*) presence of two of the four cardinal signs (bradykinesia, rigidity, tremor, and postural instability) of Parkinson disease; and (*b*) improvement of these after L-dopa therapy. Patients with scores below 20 on the Folstein minimental test (13) were considered demented. Thirteen healthy control subjects ranging in age from 37 to 81 years (mean age, 58 ± 13 years) were also studied (Table).

All studies were conducted using a 1.5-T magnetic resonance (MR) whole-body imager with standard quadrature head coil. A set of T2-weighted axial images of the brain was acquired first. An image at the level of the trigone of the lateral ventricles was chosen as a reference for voxel location (Fig 1A). The voxel included primarily occipital lobe parenchyma, encompassing both gray matter and white matter. Spectra were obtained using the single-voxel version of the multiple-echo spectral-acquisition technique (14) for water-suppressed proton spectra. In this technique, excitation with a $1\text{-}\overline{3}\text{-}3\text{-}\overline{1}$ composite pulse (centered at the water resonance frequency) is followed by three 180° pulses, each accompanied by a section-select gradient along one of the three major axes. An echo is produced from the selected voxel at the intersection of the three (orthogonal) sections.

The occipital lobe spectra were obtained using 1500/270/640 (repetition time (TR)/echo time (TE)/excitations) and a voxel size of $3 \times 3 \times 3$ cm. Field homogeneity was shimmed to give a localized water-proton spectral line width of 4 to 6 Hz before data acquisition. Raw data were zero filled to 4096 data points, and an exponential line-broadening factor of 2 Hz was applied before Fourier transformation of the time domain data. After spectra were phased, an iterative computer program (spectroVISTA, Picker International, Cleveland, Ohio) was used to fit the spectral data using seven peak assignments and a six-parameter baseline fit, with a user first estimate of peak positions, line widths, and intensities. The peak positions for the curve-fitting program were chosen as follows: three peaks with locations corresponding to the primary resonances of Cho, Cr, and NAA were always selected. A peak or peaks, if present, in the 1.27- to 1.40-ppm region (see below) was (were) then selected. The remaining peaks (making up the total of seven assignments) were selected from the highest amplitude resonances in the 1.0- to 2.0-ppm region, to have optimal fitting in this region of the spectrum.

Normalized peak areas, determined from the computer fits of the spectra, were tabulated and area ratios calculated. Chemical shifts were determined by comparing peak positions to that of NAA, taken as 2.01 ppm, and using the published values (15–17) for the main resonances of the other metabolites of interest—Cr (3.0 ppm), Cho (3.2 ppm), and La (1.33 ppm). Because the lactate

Fig 1. Image-guided, single-voxel proton MR spectroscopy.
A, T2-weighted axial image (2800/80/1) from a patient with Parkinson disease indicates typical location of a 27-cm^3 voxel (*square*).
B and *C*, Localized proton MR spectra from a healthy elderly subject (*B*) and a patient with Parkinson disease (*C*) using the multiple-echo spectral-acquisition technique (1500/270).

doublet may be only partially resolved or distorted because of adjacent resonances, the integrated area for La was determined from the area under the peak(s) within the spectral region from 1.27 to 1.40 ppm. This "lactate region" corresponded to the width of the lactate doublet at half-maximum amplitude in preliminary studies on a 20 mmol/L lactate solution. Analysis of the MR spectral data, as described above, was performed by one of the authors (R.E.B.) blinded to the clinical diagnosis.

To correct for spectral distortion introduced by the 1-$\bar{3}$-3-$\bar{1}$ pulse (18), the water excitation profile of the pulse was determined, using the same parameters as for the in vivo acquisitions (Fig 2). From this profile, signal intensity ratios were calculated and used to correct for the partial suppression of signal at the peak locations of interest.

The signal-to-noise ratio for in vivo spectra was determined from the ratio of NAA peak intensity to baseline signal intensity in the 0- to 3.6-ppm region. The signal-to-noise ratio was usually greater than 40, and a mean value of 50 $\pm$ 7 was obtained for six spectra acquired from one control subject.

Statistical Methods

Two-tailed, unpaired Student's *t* tests were applied. To evaluate for correlations, linear regressions with the F test were used.

Results

Spectra from a healthy subject and from a patient with Parkinson disease and dementia are shown in Figures 1B and C, respectively. The ratios of peak areas for the computer fit of the spectrum in Figure 1B were: NAA/Cho, 5.02; NAA/Cr, 4.02; and La/NAA, 0. In Figure 1C, there is a slightly distorted doublet centered at 1.33 ppm, corresponding to the La resonance. The ratios calculated from this spectrum were: NAA/Cho, 5.40; NAA/Cr, 3.81; and La/NAA, 0.19.

The peak ratios for each subject in the study were corrected using the water-excitation pro-

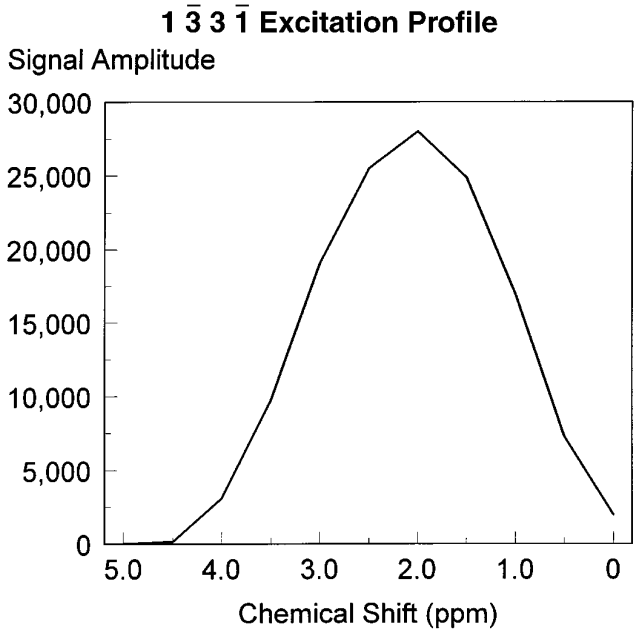

Fig 2. Water excitation profile of the 1-$\bar{3}$-3-$\bar{1}$ binomial pulse optimized for the NAA resonance (2.01 ppm).

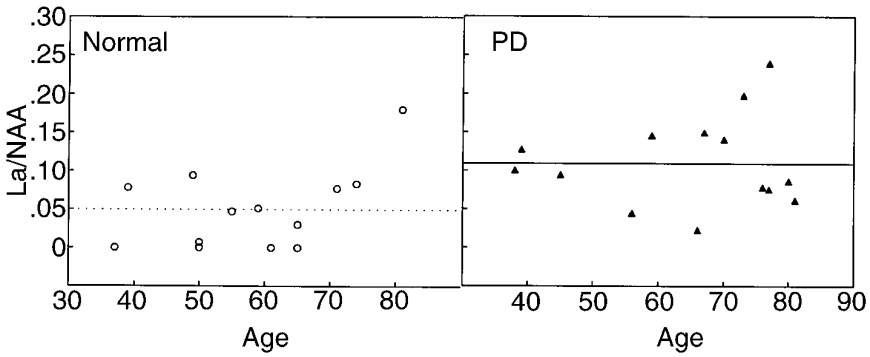

Fig 3. Distribution of La/NAA for healthy subjects (○) and for patients with Parkinson disease (▲) as a function of age. Each point corresponds to one subject. The mean value of La/NAA for healthy subjects (*dotted line*; SD, 0.05) and that for patients with Parkinson disease (*solid line*; SD, 0.06) are shown.

file of the 1-$\bar{3}$-3-$\bar{1}$ pulse (Fig 2). The correction factors were 1.73, 1.49, 1.0, and 1.24 for the Cho, Cr, NAA, and La resonances, respectively. Thus, for example, the corrected peak ratios were: NAA/Cho, 2.90; NAA/Cr, 2.70; and La/NAA, 0 for the control spectrum (Fig 1B) and 3.12, 2.56, and 0.24, respectively, for the Parkinson spectrum (Fig 1C).

The Table shows the statistical comparisons of the NAA/Cho, NAA/Cr, and La/NAA ratios in all Parkinson patients and control subjects. Each mean was determined from the corrected peak ratios of the individual subjects, and not from the means of the corrected peak areas of all control or Parkinson subjects taken together. No statistically significant difference was found between the Parkinson and control values for NAA/Cho and NAA/Cr, although the Parkinson subjects had slightly larger values for each.

Reproducibility of the peak ratio measurements was evaluated by repeated examination (n = 6) of a single control subject. The coefficients of variation (SD divided by mean value) for NAA/Cho and NAA/Cr were each about 0.25. This value may account for much of the statistical variation in the ratios for the control subjects and the Parkinson patients (n = 14) in the Table, in which the coefficients of variation range from 0.30 to 0.52.

For La/NAA the difference between the Parkinson and control groups was very significant (P = .009; Table), and for La/Cr the difference was significant (P = .01). Figure 3 shows the La/NAA results for individual examinations and indicates the scatter of the data. The horizontal lines represent the mean values for each group. There is some overlap of the two groups at 1 SD (σ).

In addition to the mean peak ratios, the mean value of the percentage area under each of the main peaks was tabulated. For NAA, the value was 59.75 ± 8.12% for the control group compared with 59.66 ± 6.71% for the Parkinson group. For La, mean values of 3.01 ± 3.07% (control) and 6.52 ± 3.21% (Parkinson) were obtained. These data support the notion that the La/NAA differences are caused by variation in La between the control and Parkinson groups.

The spectral data were also evaluated for evidence of certain trends, such as dependence of peak ratios on age, or on medication regimen, duration of disorder, or dementia for the Parkinson group. No age dependence was found for the NAA/Cho, NAA/Cr, or La/NAA ratios of the control or Parkinson subjects. No statistically significant relationship between peak ratios and medication regimen was demonstrated in the 14 Parkinson patients, 11 of whom received L-dopa (300 to 750 mg/day). The 3 Parkinson subjects who were receiving no medications had corrected La/NAA ratios of 0.20, 0.15, and 0.10; however, their mean was not significantly different (P = .20) from that of the remaining Parkinson group. No correlation between duration of Parkinson disease and La/NAA was found.

In the four Parkinson subjects (age 74 ± 6 years) with dementia, the mean La/NAA ratio was 0.16 ± 0.08. For the remaining, nondemented Parkinson subjects (age 62 ± 16 years), the ratio was 0.09 ± 0.04. The difference between the demented and nondemented Parkinson groups was significant (P = .04), whereas the difference between the demented Parkinson group and the control group was very significant (P = .004). The mean values for NAA/Cho and for NAA/Cr were not significantly different between the demented and nondemented Parkinson subgroups, nor was there a significant difference between each of these subgroups and the control group (Table).

Discussion

Neurodegenerative and psychiatric disorders often have cranial MR findings that are nonspecific and/or indistinguishable from those seen in normal aging (19). Clinical MR spectroscopy shows promise as a tool to improve diagnostic accuracy (20) and monitor therapy (21) in these conditions, in addition to elucidating underlying biochemical changes. In vivo proton spectroscopy of Parkinson disease has received little attention compared with Alzheimer disease (20), despite evidence that Parkinson disease is a systemic biochemical disorder involving energy metabolism, specifically complex I of the electron transport chain (1). Comparison of regional brain spectra from Parkinson patients with those from healthy controls is needed, and this was the purpose of our study. An increase in cerebral lactate associated with complex I inhibition, as occurs in mouse striatal slices (11), should be looked for in human spectra and, if present, correlated with clinical variables. This topic is addressed preliminarily in our study.

The NAA/Cr and NAA/Cho results for healthy subjects can be compared with published values, derived from spectra acquired with a TE of 270 milliseconds. Menon et al (22) used the single-voxel version of the multiple-echo spectral-acquisition technique and obtained NAA/Cr of 3.3 ± 0.7 for the parietal lobe in healthy control subjects (n = 11) at 1.6 T and a TR of 2000 milliseconds. No attempt was made to correct for spectral distortion, nor was an excitation profile presented. Their mean NAA/Cr is not significantly different from our uncorrected result of 3.88 ± 1.41. Our corrected NAA/Cr of 2.60 ± 0.95 (Table) compares favorably with the value of 2.51 ± 0.37 (n = 12) obtained by Jenkins et al ("Evidence of an Energy Metabolism Defect") for the occipital lobe, using a stimulated-echo acquisition mode sequence at 1.5 T with 2000/272. NAA/Cr as high as 3.45 ± 0.24 (n = 6) has been reported by Duijn et al (23), who used a point resolved spectroscopy sequence at 2.0 T and 2000/272. The difference in TR between these previous studies and our own (1500 milliseconds) should have minimal effect on NAA/Cr, based on the similarity in published in vivo T1 relaxation times for NAA (1450 milliseconds) and Cr (1550 milliseconds) (24).

NAA/Cr values of 2.2 ± 0.5 (25), 2.44 ± 0.38 (26), and 2.20 + 0.42 (Sauter R, "Clinical MR Spectroscopy of the Brain with Single Voxel Techniques: Volunteer Baseline Study," presented at the Eleventh Annual Meeting of the Society for Magnetic Resonance Imaging, San Francisco, 1993), have been obtained using a point resolved spectroscopy sequence at 1.5 T and 2000/135. Our result is expected to be larger than these values derived from TE-135 spectra, because the in vivo T2 relaxation time for NAA (370 milliseconds) is reportedly longer than that for Cr (220 milliseconds) (24, 27).

The corrected NAA/Cho (Table) is within the range of 2.33 ± 0.16 (23) to 3.68 ± 0.45 (Jenkins et al, "Evidence of an Energy Metabolism Defect") reported for healthy subjects. In a multicenter study (Sauter, "Clinical MR Spectroscopy"), NAA/Cho was found to be 2.75 ± 0.61 for the occipital lobe. Although obtained at a TE of 135, this ratio should not be appreciably different from its value obtained at a TE of 270, other factors being equal, because the T2 for Cho (360 milliseconds) is similar to that for NAA (24, 27). These reference values, though, may be slightly less at a TR of 1500, given the shorter T1 of Cho (1150 milliseconds) than of NAA (24).

The mean values of NAA/Cr and NAA/Cho for control subjects presented in the Table are thus within the range of published values. However, the SDs, or coefficients of variation, we obtained were larger. Much of this error is likely caused by the variation in calculated ratios from exam to exam independent of the subject, (ie, reproducibility). This conclusion is supported by our finding that the coefficient of variation for each ratio was about 0.25, that is, 25%, for the six spectra obtained from a single healthy subject, compared with 0.37 and 0.52 (NAA/Cr and NAA/Cho, respectively) for the control group, and 0.30 and 0.40 for the total Parkinson group (Table).

Over the age range we investigated, no dependence of mean NAA/Cr or NAA/Cho ratios on age could be demonstrated for the control or the Parkinson group. Kreis and Ross (28) have also reported that values of NAA/Cr and Cho/Cr for occipital lobe in healthy subjects were constant over an age range of 22 to 89 years.

Although NAA/Cr and NAA/Cho mean values for the total Parkinson group were slightly greater than those for healthy control subjects, the difference was not statistically significant (Table). For Parkinson patients, the subgroup

with dementia showed a nonsignificant (P = .58) decrease in NAA/Cho compared with the subgroup without dementia. This trend is in the same direction as that reported for in vivo studies of Alzheimer patients (Meyerhoff DJ et al, "Increased Cerebral Choline in Alzheimer Disease Support Theory of Membrane Defect," presented at the Eleventh Annual Meeting of the Society for Magnetic Resonance Imaging, San Francisco, 1993). However, relative to the control group, the Parkinson subgroup with dementia had NAA/Cho and NAA/Cr mean values that tended to be increased rather than decreased (Table). Additional studies of this subgroup are needed to determine whether there are significant differences from control values, as have sometimes been reported for other causes of dementia (21) (Meyerhoff et al, "Effects of Normal Aging and Alzheimer's Disease on Cerebral ^{1}H Metabolites," presented at the Eleventh Annual Meeting of the Society for Magnetic Resonance in Medicine, Berlin, 1992; Jungling FD et al, "Localized ^{1}H-Spectroscopy in the Hippocampus of Normals and Patients with Alzheimer's Disease," presented at the Twelfth Annual Meeting of the Society for Magnetic Resonance in Medicine, New York, 1993).

Because NAA is considered a neuronal marker, the lack of a difference in NAA/Cr values between the control and total Parkinson groups argues against any preferential loss of neurons in the occipital region in our overall Parkinson patient population. Although NAA/Cho for the total Parkinson group did not differ significantly from the control value (Table), the difference between Parkinson women (4.50 ± 1.80) and healthy women (3.02 ± 1.09) and between Parkinson women and Parkinson men (3.02 ± 0.61) approached significance (P = .06 for each comparison). The possibility that Parkinson women have relatively less choline than other groups has not been reported previously, to our knowledge, and would require further study to determine whether a significant difference in NAA/Cho or Cho/Cr values exists. The findings are of interest because one model of Parkinson disease, based on animal studies, attributes the biochemical changes of Parkinson disease to an excess of cerebral *S*-adenosyl methionine, which methylates and depletes dopamine yet also has the ability to alter choline metabolism by its reaction with phospholipids (29).

A very significant difference (P = .009) was found between La/NAA values for control and Parkinson subjects in general, and an even greater difference for control and demented Parkinson subjects in particular. These results support the hypothesis that there is an impairment of oxidative energy metabolism in vivo in Parkinson disease, not limited to the substantia nigra. The impairment is thought to result from a defect in complex I (reduced nicotinamide adenine dinucleotide ubiquinone oxidoreductase), which is composed of 26 subunits, 7 of which are encoded by mitochondrial deoxyribonucleic acid. The cause of this defect is unclear, although a genetic cause has been invoked (8). Damage to dopaminergic neurons, resulting in parkinsonism, is thought to be mediated by inhibition of adenosine triphosphate production and generation of oxyradicals (10), which are produced at relatively high levels in these neurons (30).

Huntington disease, a movement disorder involving the basal ganglia and inherited as an autosomal dominant trait, has also been hypothesized to result from an impairment of oxidative energy metabolism via a defect in one of the autosomal mitochondrial enzymatic complexes, allowing slow excitotoxic neuronal degeneration (31). Recently, Jenkins et al ("Evidence of an Energy Metabolism Defect") reported mean La/NAA values of 0.127 ± 0.04 for symptomatic Huntington patients (n = 15) compared with 0.038 ± 0.01 for control subjects (n = 12). Measurements were obtained from the occipital lobe. Although the elevation in La/NAA in Parkinson patients is not as large as in Huntington patients, there is a significant increase. Symptomatic Huntington patients are considered to have some degree of dementia; thus, it may be more appropriate to compare La/NAA in controls with the Parkinson subgroup with dementia. For this subgroup, there is a threefold increase in La/NAA, similar to the increase observed in Huntington patients.

The pitfalls inherent in La measurements have been well documented (12, 18) (Merboldt KD et al, "Variability of Lactate in Normal Human Brain *In Vivo*: Localized Proton MRS during Rest and Photic Stimulation," presented at the Tenth Annual Meeting of the Society for Magnetic Resonance in Medicine, San Francisco, 1991). Interindividual differences in the basal lactate levels of normal young adults (n = 48; age, 20 to 43 years; mean, 27.5 years), ranging from less than 0.3 to 1 mmol/L, in the occipital lobe (visual cortex) have been reported by Merboldt

et al (12). Also, these authors were unable to confirm the results of Pritchard et al (17), who found that the mean basal level for adult men (n = 5; age, 22 to 55 years) of 0.71 mmol/L increased by 50% to 150% in the first 6 minutes after photic stimulation. Merboldt et al (12) found no consistent alteration in La level during photic stimulation and concluded that there is a rapid efflux of lactate from brain tissue under activated conditions, rather than a transient, measurable excess of glycolysis over respiration, as proposed by Pritchard and colleagues (17).

The interindividual variability in La concentration would contribute to the error in our La/NAA results but should not produce a significant difference between the normal and Parkinson groups. Photic stimulation is unlikely to cause any differences between the two groups, because all individuals were studied in the same manner, and the spectral acquisition time was 16 minutes. The relatively large SD for La/NAA (Table) within each group, though, may reflect true interindividual differences, in addition to the variability inherent in our measurements (reproducibility) and the error associated with curve fitting of a minor resonance such as La in the presence of background noise approaching 2% of the NAA signal intensity.

A spurious difference in La/NAA between the control and Parkinson groups could result from the spectral analysis method. Because there are seven user-designated peaks, and the area under each peak is a percentage of the total seven-peak area, errors could result if the peaks not assigned to NAA, Cho, Cr, and La varied markedly, causing a decrease or increase in La relative to NAA for one group versus the other. Such variation was not present, though, and the percentage area encompassed by the combined NAA, Cr, Cho, and La region peaks was approximately the same for control and Parkinson groups, being 91.5% and 89.8%, respectively.

A pitfall in the characterization and quantitation of resonances in the 1.27 to 1.40 region of the spectrum as La is the potential presence of lipid resonances, whether spurious from "out of voxel" or genuine. Previous authors (23) have integrated over the same spectral region as we did to obtain lactate values and found them not to be contaminated with scalp lipid signal, as long as the margins of the volume of interest did not encompass the calvarium. As shown in Figure 1A, our voxel was well within the occipitoparietal region of the brain, and this intracerebral location was confirmed on the two adjacent 5-mm-thick axial images on either side of the image displaying the voxel position. Because voxel location was similar in all subjects, it is very unlikely that the Parkinson group would have a significantly higher La/NAA ratio because of "out-of-voxel" lipid contamination.

The possibility that cerebral lipid resonances present in Parkinson patients, and absent or reduced in controls, are responsible for at least some of the differences in the integrated area in the La region, though, cannot be excluded. In a preliminary study, Heerschap et al ("Proton MR Spectroscopy of the Striatum in Patients with Parkinson's Disease," presented at the Eleventh Annual Meeting of the Society for Magnetic Resonance in Medicine, Berlin 1992) have acquired proton spectra (point resolved spectroscopy sequence with 2500/135) from the striatum of Parkinson patients (n = 9). Some, but not all, patients showed additional resonance intensity in the range of 1.3 to 1.7 ppm attributed to "triglyceride protons." Otherwise, the spectra resembled control spectra, and no significant difference in NAA/Cho, Cho/Cr, and NAA/Cr mean values between the two groups was observed. We have obtained a spectrum at a TE of 135 in one Parkinson patient and observed a shallow inverted doublet at 1.33 ppm, but no resonances comparable to those reported by Heerschap et al (unpublished). The acquisition of occipital lobe spectra at a TE of 135 may help to clarify the question of lipid resonance contributions; however, the identification of small quantities of lactate is made more difficult because the amplitude of the inverted lactate doublet is approximately 40% of that for the noninverted doublet at a TE of 270 (32).

Our preliminary spectral data from the occipital (and parietal) region for Parkinson subjects have striking similarities to those obtained for Huntington subjects by Jenkins et al ("Evidence of an Energy Metabolism Defect"). The Parkinson results are consistent with the hypothesis that mitochondrial electron transport chain deficits are present in brain tissue in each disorder and that the associated lactate elevation is a sign of metabolic (oxidative) stress (31). Because the primary area of the brain affected symptomatically in Parkinson disease is the nigrostriatal pathway, and because postmortem studies have demonstrated reduced activity of complex I in substantia nigra (4), local-

ized spectra from this area should be the focus of future studies. Modifications of current techniques, such as the use of cardiac gating (Pattany PM et al, "Improvement of Signal-to-Noise Ratio of Proton MR Spectra of the Brain with Cardiac Gating," presented at the 79th Annual Meeting of the Radiological Society of North America, Chicago, 1993) and hardware improvements, such as the use of self-shielded gradients, may be necessary to obtain reliable spectra from the substantia nigra and basal ganglia on clinical scanners. If the presence of elevated lactate is confirmed, then therapeutic clinical trials of drugs (eg, coenzyme Q) that lower La levels could be undertaken, as is now being done for Huntington patients (W. J. Koroshetz, personal communication 1993), with MR spectroscopy used to monitor changes in cerebral lactate in vivo.

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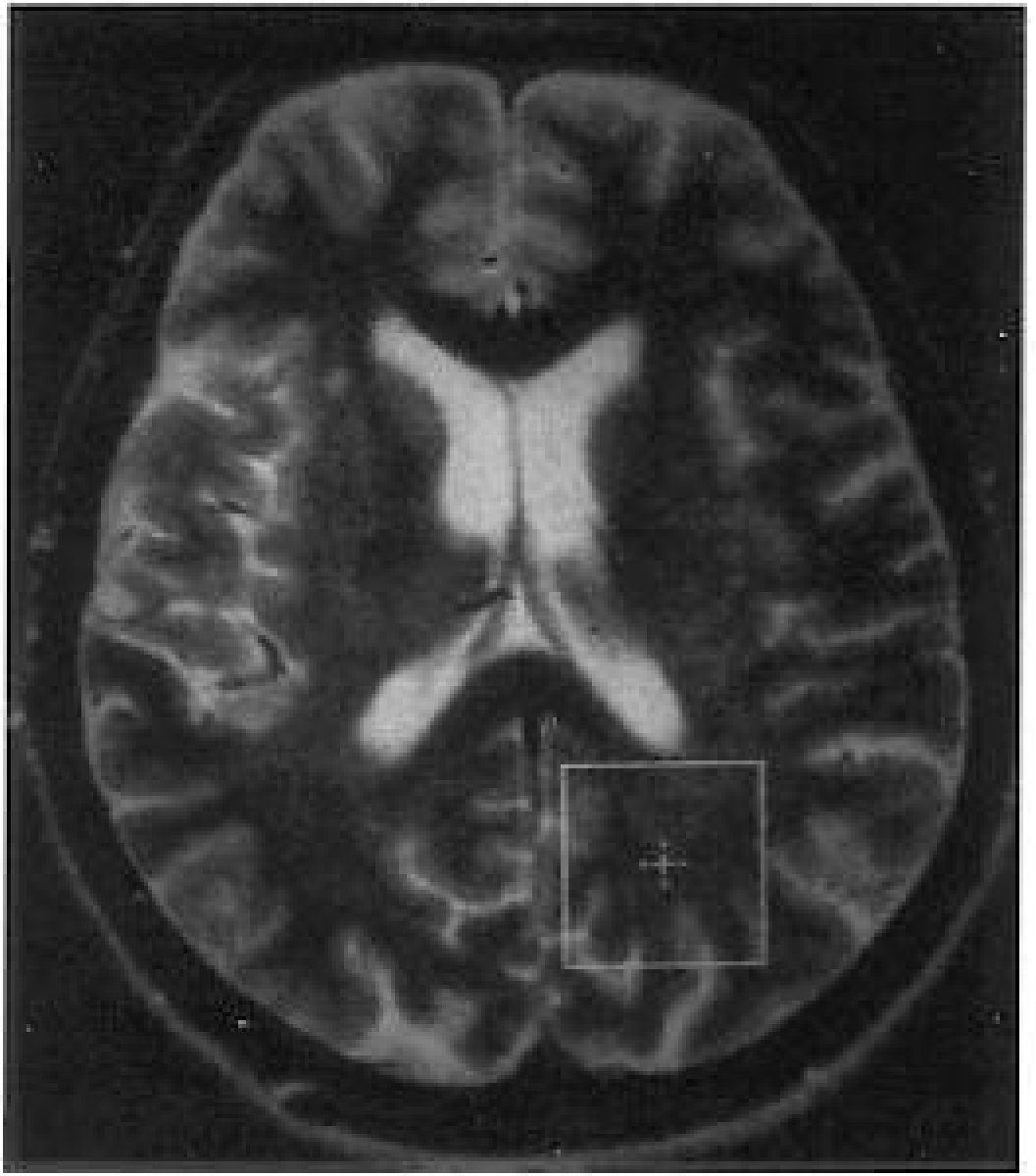
References

1. Boyson JJ. Parkinson's disease and the electron transport chain (editorial). *Ann Neurol* 1991;30:330–331
2. Schapira AHV, Cooper JM, Dexter D, Jenner P, Clark JB, Marsden CD. Mitochondrial complex I deficiency in Parkinson's disease. *Lancet* 1989;1:1269
3. Schapira AHV, Cooper JM, Dexter D, et al. Mitochondrial complex I deficiency in Parkinson's disease. *J Neurochem* 1990;54:823–827
4. Schapira AHV, Mann VM, Cooper JM, et al. Anatomic and disease specificity of NADH CoQ_1 reductase (complex I) deficiency in Parkinson's disease. *J Neurochem* 1990;55:2142–2145
5. Mizuno U, Ohta S, Tanaka M, et al. Deficiencies in complex I submits of the respiratory chain in Parkinson's disease. *Biochem Biophys Res Commun* 1989;163:1450–1455
6. Parker WD Jr, Boyson SJ, Parks JK. Abnormalities of the electron transport chain in idiopathic Parkinson's disease. *Ann Neurol* 1989;26:719–723
7. Bindoff LA, Birch-Machin M, Cartlidge NEF, et al. Mitochondrial function in Parkinson's disease. *Lancet* 1989;2:49
8. Shoffner JM, Watts RL, Juncos JL, Torroni A, Wallace DC. Mitochondrial oxidative phosphorylation defects in Parkinson's disease. *Ann Neurol* 1991;30:332–339
9. Nicklas WJ, Vyas I, Keikkila RE. Inhibition of NADH-linked oxidation in brain mitochondria by 1-methyl-4-phenyl-pyridine, a metabolite of the neurotoxin, 1-methyl-4-phenyl-1,2,5,6 tetrahydropyridine. *Life Sci* 1985;36:2503–2508
10. Sanchez-Ramos JR, Hefti F, Hollinden GE, Sick T, Rosenthal M. Mechanisms of MPP+ neurotoxicity: oxyradical and mitochondrial inhibition hypotheses. In: Hefti F, Weiner WE, eds. *Progress in Parkinson Research*. New York: Plenum Press, 1989:145–152
11. Vyas I, Heikkila RE, Nicklas WJ. Studies on the neurotoxicity of MPTP; inhibition of NAD-linked substrate oxidation by its metabolite MPP^+. *J Neurochem* 1986;46:1501–1507
12. Merboldt K, Bruhn H, Hanicke W, Michaelis T, Frahm J. Decrease of glucose in the human visual cortex during photic stimulation. *Magn Reson Med* 1992;25:187–194
13. Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–198
14. Lampman DA, Murdoch JB, Paley M. In vivo proton metabolite maps using the MESA 3D technique. *Magn Reson Med* 1991;18:169–180
15. Michaelis T, Merboldt K-D, Hanicke W, et al. On the identification of cerebral metabolites in localized ^{1}H NMR spectra of human brain *in vivo*. *NMR Biomed* 1991;4:90–98
16. Kreis R, Ross BD, Farrow NA, Ackerman Z. Metabolic disorders of the brain in chronic hepatic encephalopathy detected with H-1 spectroscopy. *Radiology* 1992;182:19–27
17. Prichard J, Rothman D, Novotny E, et al. Lactate rise detected by ^{1}H NMR in human visual cortex during physiologic stimulation. *Proc Natl Acad Sci* 1991;88:5829–5831
18. Bottomley PA. The trouble with spectroscopy papers. *Radiology* 1991;181:344–350
19. Braffman BA, Trojanowski JQ, Atlas SW. The aging brain and neurodegenerative disorders. In: Atlas SW, ed. *Magnetic Resonance Imaging of the Brain and Spine*. New York: Raven Press, 1991:567–624
20. Miller BL, Moats RA, Shonk T, Ernst T, Wooley S, Ross BD. Alzheimer disease: depiction of increased cerebral myo-inositol with proton MR spectroscopy. *Radiology* 1993;187:433–437
21. Gonzalez RF, Guimaraes AR, Sachs GS, Rosenbaum JF, Garwood M, Renshaw PF. Measurement of human brain lithium in vivo by MR spectroscopy. *AJNR Am J Neuroradiol* 1993;14:1027–1037
22. Menon DK, Baudouin CJ, Tomlinson D, Hoyle C. Proton MR spectroscopy and imaging of the brain in AIDS: evidence of neuronal loss in regions that appear normal with imaging. *J Comput Assist Tomogr* 1990;14:882–885
23. Duijn JH, Matson GB, Maudsley AA, Hugg JW, Weiner MW. Human brain infarction: proton MR spectroscopy. *Radiology* 1992;183:711–718
24. Frahn J, Bruhn H, Gynell ML, Merboldt KD, Hanicke W, Sauter R. Localized proton NMR spectroscopy in different regions of the human brain *in vivo*: relaxation times and concentrations of cerebral metabolites. *Magn Reson Med* 1989;11:47–63
25. Kugel H, Heindel W, Ernestus RI, Bunke J, deMesnil R, Friedman G. Human brain tumors: spectral patterns detected with localized H-1 MR spectroscopy. *Radiology* 1992;183:701–709
26. Chong WK, Sweeney B, Wilkinson ID, et al. Proton spectroscopy of the brain in HIV infection: correlation with clinical, immunologic, and MR imaging findings. *Radiology* 1993;188:119–124
27. Michaelis T, Merboldt K-D, Bruhn H, Hanicke W, Frahm J. Absolute concentrations of metabolites in the adult human brain in vivo: quantification of localized proton MR spectra. *Radiology* 1993;187:219–227
28. Kreis R, Ross BD. Cerebral metabolic disturbances in patients with subacute and chronic diabetes mellitus: detection with proton MR spectroscopy. *Radiology* 1992;184:123–130
29. Charlton CG, Crowell B Jr. Parkinson's disease-like effects of *S*-adenosyl-L-methionine: effects of L-dopa. *Pharmacol Biochem Behav* 1992;43:423–431
30. Leehey M, Boyson SJ. The biochemistry of Parkinson's disease. In: Appel SH, ed. *Current Neurology*. St Louis: Mosby Year Book, 1991;11:223–286
31. Beal MF. Does impairment of energy metabolism result in excitotoxic neuronal death in neurodegenerative illnesses? *Ann Neurol* 1992;31:119–130
32. Ernst T, Hennig J. Coupling effects in volume selective ^{1}H spectroscopy of major brain metabolites. *Magn Reson Med* 1991;21:82–96



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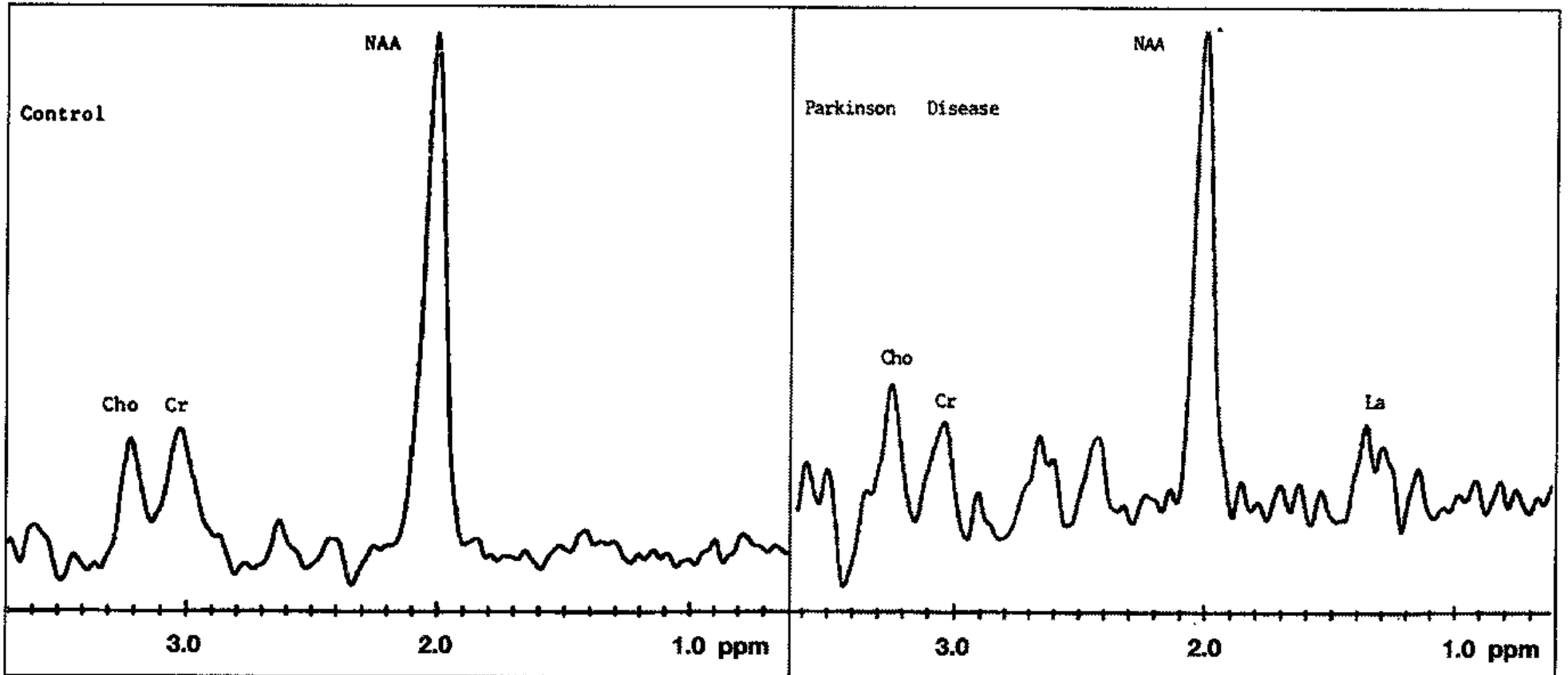
Control
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Parkinson Disease
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